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: Guidance for Industry

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U.S. Department of Health and Human Services
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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: Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This guidance is intended for any person (you) who intends to market a food substance on the basis of a conclusion that the substance is GRAS under the conditions of its intended use (a GRAS conclusion), including a manufacturer of the food substance, a manufacturer of a food product containing the food substance, and a distributor of a food product containing the food substance.[2] We are issuing this guidance to:

- Direct you to the statutory and regulatory criteria that govern eligibility for classification of a substance as GRAS under the conditions of its intended use, and remind you of your responsibilities to comply with those criteria;
- Advise you to carefully consider whether the intended use of the food substance fully satisfies the criteria for eligibility for classification as GRAS and is lawful under sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and our regulations in Title 21 of the Code of Federal Regulations (21 CFR);

[1] This guidance has been prepared by the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition (CFSAN) and the Division of Animal Feeds in the Office of Surveillance and Compliance in the Center for Veterinary Medicine (CVM) at the U.S. Food and Drug Administration.

[2] FDA finalized the framework for the GRAS notification procedure and revised the regulatory criteria for eligibility for classification as GRAS in 2016 (81 FR 54960, Federal Register of August 17, 2016). The effective date of this rule is October 17, 2016.

- Remind you that a GRAS conclusion based upon scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of a food additive and direct you to a series of our guidance documents that address scientific issues associated with demonstrating the safety of a food substance;
- Remind you that a GRAS conclusion based on common use in food requires evidence of a substantial history of consumption prior to January 1, 1958;
- Remind you that all GRAS conclusions must be considered in context based on the knowledge and information available at a point in time, because scientific knowledge and information about a particular substance can evolve and sometimes change over time;
- Strongly encourage you to contact us and follow the available procedures for our oversight of GRAS conclusions by submitting a GRAS Notice to us in accordance with the procedures in 21 CFR part 170, subpart E (for a substance that would be used in human food) or 21 CFR part 570, subpart E (for a substance that would be used in animal food); and
- Recommend that you use the framework for a GRAS notice in documenting a GRAS conclusion if you decide to market a food substance on the basis of an independent GRAS conclusion (i.e., a GRAS conclusion that you do not submit to FDA as a GRAS notice).

We also are issuing this guidance to advise you that when a substance is not GRAS under the conditions of its intended use (or is not otherwise excepted from the definition of "food additive" in section 201(s) of the FD&C Act), that use of the substance is a food additive use subject to FDA's premarket review as mandated by the FD&C Act. Any food that is, or bears or contains, an unapproved food additive is deemed unsafe and is therefore adulterated under the FD&C Act. When a substance added to food is not GRAS (and is not otherwise excepted from the definition of a "food additive") and is not approved as a food additive under the conditions of its intended use, we can take various actions, including issuing a warning letter (which we make public on our Web site) to companies that manufacture or distribute the food additive and/or food containing the food additive; issuing a public alert; and taking enforcement action to stop distribution of the food substance and foods containing it on the grounds that such foods are or contain an unlawful food additive. As appropriate, we can issue a declaratory order determining that the substance is not GRAS under the conditions of its intended use and is a food additive subject to section 409 of the FD&C Act. As we implement the GRAS notification procedure that is established in 21 CFR part 170, subpart E and 21 CFR part 570, subpart E, we intend to continue to closely monitor and assess the ramifications of the use of substances without food additive approval or evaluation by FDA through the GRAS notification procedure. We intend to take action as appropriate, particularly when the available data and information raise a safety concern about the use of a substance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe our current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

A. What You Need to Know About the Laws and Regulations Applicable to Substances Added to Foods

In 1958, Congress enacted the Food Additives Amendment (the 1958 amendment) to the FD&C Act. The 1958 amendment requires that, before a food additive may be used in food, FDA must establish a regulation prescribing the conditions under which the additive may be safely used. The 1958 amendment defined the terms "food additive" (section 201(s) of the FD&C Act) and "unsafe food additive" (section 409(a) of the FD&C Act), established a premarket approval process for food additives section (409(b) through (g) of the FD&C Act), and amended the food adulteration provisions of the FD&C Act to deem adulterated any food that is, or bears or contains, any food additive that is unsafe within the meaning of section 409 of the FD&C Act (see section 402(a)(2)(C) of the FD&C Act).

Section 201(s) of the FD&C Act defines a "food additive" 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 characteristics of any food . . . if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use ..." [3] Under this definition, a substance that is GRAS under the conditions of its intended use is not a "food additive" and is therefore not subject to mandatory premarket review by FDA under section 409 of the FD&C Act.

We have established regulations implementing the GRAS provision of section 201(s) of the FD&C Act in part 170 (21 CFR part 170) and part 570 (21 CFR part 570) for human food and animal food, respectively. In particular, we have established criteria for eligibility for classification as GRAS (21 CFR 170.30 and 570.30), including general criteria (21 CFR 170.30(a) and 570.30(a)), specific criteria for general recognition of safety through scientific procedures (21 CFR 170.30(b) and 570.30(b)), and specific criteria for general recognition of safety through experience based on common use in food (21 CFR 170.30(c) and 570.30(c)). Although we originally established these criteria in 1971 (36 FR 12093; June 25, 1971), we revised these criteria in 1976 (41 FR 53600; December 7, 1976). In 1988, we clarified that the criteria for eligibility for classification as GRAS through experience based on common use in food for a substance intended for use in human food could be based on common use in food

[3] The definition of "food additive" in section 201(s) of the FD&C Act also excepts: (1) Pesticide chemical residues in or on a raw agricultural commodity or processed food; (2) pesticide chemicals; (3) color additives; (4) substances used in accordance with a "prior sanction" (i.e., a sanction or approval granted prior to the enactment of the Food Additives Amendment of 1958 under the FD&C Act, the Poultry Products Inspection Act, or the Meat Inspection Act); (5) new animal drugs; and (6) dietary ingredients in or intended for use in a dietary supplement. Thus, use of a substance as a dietary ingredient in a dietary supplement is not eligible for classification as GRAS. In addition, under section 201(s) of the FD&C Act, the GRAS provision applies to the definition of a food additive only; there is no corresponding provision in the definition (in section 201(t) of the FD&C Act) of a color additive.

outside, as well as in, the United States (53 FR 16544; May 10, 1988).[4] We revised these criteria in 2016 (81 FR 54869, August 17, 2016). In this document, we refer to the final rule establishing these revised GRAS criteria as "the GRAS final rule."

Immediately below, we provide the criteria for eligibility for classification as GRAS as established in 21 CFR 170.30(a) through (c) for a substance intended for use in human food. The corresponding criteria for a substance intended for use in animal food are in 21 CFR 570.30(a) through (c). See section IV.E in this document for additional information about the GRAS criteria established in 21 CFR 570.30 for a substance intended for use in animal food.

21 CFR 170.30 Eligibility for classification as generally recognized as safe (GRAS).

> (a) General recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. 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. General recognition of safety requires common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food that there is reasonable certainty that the substance is not harmful under the conditions of its intended use (see § 170.3(i)).
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> (b) General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive. General recognition of safety through scientific procedures shall be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.
>
> (c)(1) General recognition of safety through experience based on common use in food prior to January 1, 1958, may be achieved without the quantity or quality of scientific procedures required for approval of a food additive. General recognition of safety through experience based on common use in food prior to January 1, 1958, shall be based solely on food use of the substance prior to January 1, 1958, and shall ordinarily be based upon generally available data and information. An ingredient not in common use in food prior to January 1, 1958, may achieve general recognition of safety only through scientific procedures.
>
> (c)(2) A substance used in food prior to January 1, 1958, may be generally recognized as safe through experience based on its common use in food when that use occurred exclusively or primarily outside of the United States if the information about the experience establishes that the substance is safe under the conditions of its intended use within the meaning of section 201(u) of the FD&C Act (see also § 170.3(i)). Common use in food prior to January 1, 1958, that occurred outside of the United States shall be

[4] In 2016, we made a corresponding clarification to the criteria for eligibility for classification as GRAS through experience based on common use in food for a substance intended for use in animal food (81 FR 54960, August 17, 2016).

> documented by published or other information and shall be corroborated by information from a second, independent source that confirms the history and circumstances of use of the substance. The information used to document and to corroborate the history and circumstances of use of the substance must be generally available; that is, it must be widely available in the country in which the history of use has occurred and readily available to interested qualified experts in the United States. A person who concludes that a use of a substance is GRAS through experience based on its common use in food outside of the United States should notify FDA of that view in accordance with subpart E of part 170.

As we noted in the GRAS final rule, we use the term "GRAS panel" to mean a panel of individuals convened for the purpose of evaluating whether the available scientific data, information, and methods establish that a substance is safe under the conditions of its intended use in food (81 FR 54960 at 54964). A GRAS panel is not required to demonstrate that a substance is GRAS under the conditions of its intended use, but is one mechanism that the regulated industry has used to demonstrate that the safety of a substance under the conditions of its intended use is generally recognized by qualified experts (81 FR 54960 at 54975).

Under the framework established by sections 201(s) and 409 of the FD&C Act and our regulations, it is the substance under its intended conditions of use, rather than the substance itself, that is eligible for the GRAS provision. A substance that is GRAS for a particular use may be marketed for that use without our review and approval. However, when the GRAS criteria are not met or when the use of the substance is not otherwise excepted from the statutory definition of a food additive, the use of the substance in food is subject to premarket approval by FDA as mandated by the FD&C Act. In such circumstances, and in the absence of an effective food additive regulation, FDA can take enforcement action to stop distribution of food containing the unapproved food additive on the grounds that such food is adulterated. (See the discussion in section I of this guidance.)

B. What You Need to Know About the GRAS Notification Procedure

In the GRAS final rule, we also established a GRAS notification procedure in part 170, subpart E (for a substance intended for use in human food) and in part 570, subpart E (for a substance intended for use in animal food). Using the GRAS notification procedure, any person may notify us of a view that a substance is not subject to the premarket approval requirements of section 409 of the FD&C Act based on that person's conclusion that the substance is GRAS under the conditions of its intended use.

A GRAS Notice has seven parts:

- Part 1: Signed statements and a certification (21 CFR 170.225 and 21 CFR 570.225);
- Part 2: The identity, method of manufacture, specifications, and physical or technical effect of the notified substance (21 CFR 170.230 and 21 CFR 570.230);
- Part 3: Dietary exposure (21 CFR 170.235 and 21 CFR 570.235)[5];

[5] Part 3 of a GRAS notice for a substance intended for use in animal food addresses both target animal and human exposures and is entitled "Target animal and human exposures."

- Part 4: Self-limiting levels of use, in circumstances where the amount of the notified substance that can be added to human food or animal food is limited because the food containing levels of the notified substance above a particular level would become unpalatable or technologically impractical (21 CFR 170.240 and 21 CFR 570.240);
- Part 5: Evidence of a substantial history of consumption of the substance for food use prior to January 1, 1958, if a GRAS conclusion is based on common use of the substance in food prior to 1958 (21 CFR 170.245 and 21 CFR 570.245)[6];
- Part 6: A narrative that provides the basis for your GRAS conclusion, including why the scientific data, information, methods, and principles described in the notice provide a basis for your conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use (21 CFR 170.250 and 21 CFR 570.250); and
- Part 7: A list of the data and information that you discuss in the narrative of your GRAS notice, specifying which of these data and information are generally available, and which of these data and information are not generally available (21 CFR 170.255 and 21 CFR 570.255).

We make a list of filed GRAS notices readily accessible to the public (21 CFR 170.275(b)(1) and 21 CFR 570.275(b)(1)). We respond to a filed GRAS notice by letter, and we also make the text of these letters readily accessible to the public (21 CFR 170.275(b)(2) and (3) and 21 CFR 570.275(b)(2) and (3)). The data and information in a GRAS notice are considered a mandatory, rather than voluntary, submission for purposes of their status under the Freedom of Information Act and our public information requirements in 21 CFR part 20, and are available for public disclosure in accordance with 21 CFR part 20 as of the date that we receive a GRAS notice. (See 21 CFR 170.275(a) and 21 CFR 570.275(a)).

See 21 CFR part 170, subpart E, and 21 CFR part 570, subpart E, for the complete regulatory requirements applicable to the GRAS notification procedure for a substance intended for use in human food or animal food, respectively.

III. Discussion and Recommendations

A. GRAS Criteria

Fundamental to all GRAS conclusions is the criterion that general recognition of safety requires common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food that there is reasonable certainty that the substance is not harmful under the conditions of its intended use (see 21 CFR 170.30(a) and 21 CFR 570.30(a)). In addition, the criteria for eligibility for classification as GRAS through scientific procedures require that general recognition of safety through scientific procedures be based upon the application of generally available and accepted scientific data, information, or

[6] For a substance intended for use in human food, "evidence of a substantial history of consumption" of the food substance is by "a significant number of consumers." For a substance intended for use in animal food, "evidence of a substantial history of consumption" of the food substance is by "a significant number of animals of the species to which the substance is intended to be fed … and … by humans consuming human foods derived from food-producing animals."

methods, which ordinarily are published, as well as the application of scientific principles (21 CFR 170.30(b) and 21 CFR 570.30(b)). Although general recognition of safety through scientific procedures may be corroborated by the application of unpublished scientific data, information, or methods (21 CFR 170.30(b) and 21 CFR 570.30(b)), to satisfy GRAS criteria qualified experts must be able to conclude that the substance is not harmful under the conditions of its intended use without access to "corroborative" information. For example, there could be no basis for a conclusion of GRAS status if trade secret information (or other non-public information) is necessary for qualified experts to reach a conclusion that the substance is safe under the conditions of its intended use. Importantly, all GRAS conclusions must be considered in context based on the knowledge and information available at a point in time, because scientific knowledge and information about a particular substance can evolve and sometimes change over time.

During the rulemaking leading to the GRAS final rule, we received several comments regarding the GRAS criteria in 21 CFR 170.30(a) through (c) and 21 CFR 570.30(a) through (c). The preamble of the GRAS final rule describes those comments and responds to them. We believe that these preamble discussions will be useful to any person who intends to market a food substance on the basis of a GRAS conclusion, and recommend that you refer to these preamble discussions in the GRAS final rule if you intend to do so. For your convenience, in the Appendix of this guidance we present some of the key discussions extracted from the preamble of the GRAS final rule regarding GRAS criteria. Importantly, you should consider these extracts in the context of the complete preamble discussion in the GRAS final rule. In addition, be advised that the GRAS final rule discusses issues raised by comments we received under the rulemaking process; considerations other than those discussed in the GRAS final rule may play a role in a specific evaluation of whether a use of a substance in food satisfies GRAS criteria.

B. GRAS Notification Procedure

We strongly encourage you to submit a GRAS notice to us if you intend to market a food substance on the basis of a GRAS conclusion even though neither the FD&C Act nor our regulations in 21 CFR require you to do so. Submitting a GRAS notice to us represents prudent practice for those who claim an exclusion from a statutory requirement.

If you decide that your GRAS conclusion will be an independent GRAS conclusion that is not submitted to us, we believe that the provisions of the GRAS notification procedure will nonetheless be a useful resource for you. Therefore, we recommend that you:

- Use the provisions of the GRAS notification procedure in our regulations as guidance. For example, the requirements in Part 3 of a GRAS notice make clear that a GRAS conclusion requires consideration of dietary exposure for a substance intended to be used in human food; when the substance would be used in animal food, the requirements in Part 3 of a GRAS notice make clear that a GRAS conclusion requires consideration of target animal and human food exposures. Likewise, the requirements in Part 6 of a GRAS notice demonstrate the importance of a complete and balanced evaluation of all applicable data and information, including data and information that are, or may appear to be, inconsistent with a GRAS conclusion.

- Retain the data and information that support your independent GRAS conclusion and organize these data and information according to the organization presented by Parts 1 through 7 of a GRAS notice. Doing so would facilitate our evaluation of that independent GRAS conclusion if circumstances warrant – e.g., if we have cause to question your independent GRAS conclusion.
- Make the basis for your independent GRAS conclusion publicly available (e.g., by placing a publicly accessible document analogous to the narrative of a GRAS notice, a report of any GRAS panel (if you convene a GRAS panel), or both a narrative and a report of a GRAS panel on your Web site), because we make information about GRAS notices readily accessible to the public.
- Refer to FDA's guidance entitled "Frequently Asked Questions About GRAS for Substances Intended for Use in Human or Animal Food" (Ref. 1), which generally applies to a conclusion of GRAS status for a substance intended for use in human food or animal food regardless of whether that conclusion of GRAS status is submitted to FDA as a GRAS notice.

C. Safety Assessment

We address scientific issues associated with demonstrating the safety of a food substance in a series of guidance documents on our Web sites. For a substance intended for use in human food, see Ref. 2 through Ref. 9. For a substance intended for use in animal food, see Ref. 9 through Ref. 14 and Ref. 30.[7] We recommend that you periodically check the Web sites for CFSAN (Ref. 31) and CVM (Ref. 32) where we provide guidance for industry for any new guidance or revisions to current guidance.

Currently, some of our scientific guidance documents are expressly directed to evaluation of the safety of food additives. For example, our guidance entitled "Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions" (Ref. 4) currently is structured to address the specific requirements of a food additive petition submitted to CFSAN for a substance intended for use in human food. Likewise, our guidance entitled "Recommendations for Preparation and Submission of Animal Food Additive Petitions" (Ref. 10) addresses the specific recommendations for a food additive petition submitted to CVM for a substance intended to be used in animal food. However, many of the recommendations in these guidances could be useful to any person who evaluates whether a substance is GRAS under the conditions of its intended use. As resources allow, we intend to re-visit these scientific guidance documents to determine whether and how to modify them to clarify that our guidance on evaluating the safety of a food substance applies regardless of whether the substance would be used in food as a food additive or as a GRAS substance. Regardless of any implication (in the title or text of these guidance documents) that the subject of the document applies to a food additive, we recommend that you consider that the scientific recommendations in these guidance documents may also apply to substances that would be used in food on the basis of a GRAS conclusion.

[7] As noted in section IV.E, other guidance documents directed to animal drug products provide information that is relevant to CVM's evaluation of the safety of substances used in animal food (Ref. 15 through Ref. 29), and we recommend that you also refer to these guidance documents.

D. GRAS Panels

We intend to issue for public comment draft guidance providing recommendations regarding the use of a GRAS panel, including the potential for conflict of interest, in the near future. If you convene a GRAS panel, we recommend that you consult any final guidance that we issue regarding the use of a GRAS panel.

E. Additional Information Regarding a Substance Intended for Use in Animal Food

Some animals are used to produce food for humans and, thus, both the GRAS criteria in 21 CFR 570.30(a) through (c) and the submission requirements for a GRAS notice for a substance intended for use in animal food address the safety of a food substance for both the target animal and for humans consuming human food derived from food-producing animals. See the full regulatory text of 21 CFR 570.30(a) through (c), and the full regulatory text of 21 CFR part 570, subpart E, for the specific requirements.

Section IV lists a series of guidance documents on specific issues related to the safety of a substance for both the target animals and humans consuming human food derived from food-producing animals (Ref. 9 through Ref. 29). Although some of these guidance documents (i.e., Ref. 15 through Ref. 29) discuss animal drug products, we refer you to these guidance documents because they provide information that is relevant to our evaluation of the safety of substances used in animal food. For example, we evaluate the human food safety of tissue residues present in edible tissues in a similar manner for new animal drugs intended for use in food-producing animals and for food substances used in foods for food-producing animals. We recommend that you consider that the scientific recommendations in these guidance documents may also apply to substances that would be used in animal food on the basis of a GRAS conclusion.

IV. References

Ref. 1. FDA, "Frequently Asked Questions About GRAS for Substances Intended for Use in Human or Animal Food," (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm061846.htm), 2016.

Ref. 2. FDA, "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," (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm300661.htm), 2014.

Ref. 3. FDA, "Guidance for Industry: Estimating Dietary Intake of Substances in Food," (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm074725.htm), 2006.

Ref. 4. FDA, "Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions," (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm124917.htm), 2009.

Ref. 5. FDA, "Guidance for Industry: Microbiological Considerations for Antimicrobial Food Additive Submissions," (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm230417.htm), 2008.

Ref. 6. FDA, "Guidance for Industry: Enzyme Preparations: Recommendations for Submission of Chemical and Technological Data for Food Additive Petitions and GRAS Notices," (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm217685.htm), 2010.

Ref. 7. FDA, "Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food," (2006), (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm054658.htm), 2006.

Ref. 8. FDA, "Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients. Redbook 2000," (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm), 2007.

Ref. 9. FDA, "Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology," (http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm), 2014.

Ref. 10. FDA, "Guidance for Industry: Recommendations for Preparation and Submission of Animal Food Additive Petitions (# 221)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM367746.pdf), 2015.

Ref. 11. FDA, "Guidance for Industry: Target Animal Safety and Effectiveness Protocol Development and Submission (#215)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM241787.pdf), 2011.

Ref. 12. FDA, "Guidance for Industry: Evaluation of the Utility of Food Additives in Diet Fed to Aquatic Animals (#53)," (http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm053413.htm), 1994.

Ref. 13. FDA, "Guidance for Industry: Validation of Analytical Procedures: Definition and Terminology (#63)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052377.pdf), 1999.

Ref. 14. FDA, "Guidance for Industry: Validation of Analytical Procedures: Methodology, Final Guidance (#64)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052379.pdf), 2010.

Ref. 15. FDA, "Guidance for Industry: General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals (#3)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052180.pdf), 2016.

Ref. 16. FDA, "Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing VICH GL33 (#149)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052521.pdf), 2009.

Ref. 17. FDA, "Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing VICH GL23 (#116)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052656.pdf), 2015.

Ref. 18. FDA, "Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Carcinogenicity Testing VICH GL28 (#141)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052527.pdf), 2006.

Ref. 19. FDA, "Guidance for Industry: Safety Studies for Veterinary Drug Residues in Human Food: Reproduction Toxicity Testing VICH GL22 (#115)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052655.pdf), 2006.

Ref. 20. FDA, "Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (90-Day) Toxicity Testing VICH GL31 (#147)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052523.pdf), 2006.

Ref. 21. FDA, "Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing VICH GL32 (#148)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052522.pdf), 2006.

Ref. 22. FDA, "Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing VICH GL37 (#160)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052505.pdf), 2006.

Ref. 23. FDA, "Guidance for Industry: Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-producing Animals: Metabolism Study to Determine the Quantity and Identify the Nature of Residues (MRK) VICH GL46 (#205),"

(http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207939.pdf), 2011.

Ref. 24. FDA, "Guidance for Industry: Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Animals: Comparative Metabolism Studies in Laboratory Animals VICH GL47 (#206)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207940.pdf), 2011.

Ref. 25. FDA, "Guidance for Industry: Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Animals: Marker Residue Depletion Studies to Establish Product Withdrawal Periods VICH GL48 (#207)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207941.pdf), 2015.

Ref. 26. FDA, "Guidance for Industry: Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Animals: Validation of Analytical Methods used in Residue Depletion Studies VICH GL49 (#208)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207942.pdf), 2015.

Ref. 27. FDA, "Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern (#152)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf), 2003.

Ref. 28. FDA, "Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI VICH GL36(R) (#159)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM124674.pdf), 2013.

Ref. 29. FDA, "Guidance for Industry: Target Animal Safety for Veterinary Pharmaceutical Products VICH GL43 (#185)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052464.pdf), 2009.

Ref. 30. FDA, "Guidance for Industry: Use of Nanomaterials in Food for Animals (# 220)," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM401508.pdf), 2015.

Ref. 31. FDA, "Food Guidance Documents," (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/default.htm), 2017.

Ref. 32. FDA, "Guidance for Industry," (http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm), 2017.

Appendix

In the *Federal Register* of August 17, 2016 (81 FR 54960), we published a final rule that amended and clarified the criteria in our regulations for when the use of a substance in food for humans or animals is not subject to the premarket approval requirements of the FD&C Act because the substance is GRAS under the conditions of its intended use. That final rule also established a voluntary notification procedure under which any person may notify us of a conclusion that a substance is GRAS under the conditions of its intended use.

For your convenience, in this Appendix we present some of the key discussions extracted from the preamble of the GRAS final rule regarding GRAS criteria. Importantly, you should consider these extracts in the context of the complete preamble discussion in the GRAS final rule. In addition, be advised that the GRAS final rule discusses issues raised by comments we received under the rulemaking process; considerations other than those discussed in the GRAS final rule may play a role in a specific evaluation of whether a use of a substance in food satisfies GRAS criteria.

Several of the extracts cite references. Those references are available in the GRAS final rule published in the *Federal Register* and are distinct from the references listed in section IV of this guidance. You should refer to the GRAS final rule to identify these references.

Likewise, several of the extracts cite to specific sections or tables in the GRAS final rule or to additional responses to specific comments. You should refer to the GRAS final rule for the cited discussions.

Extracts from the GRAS final rule:

(Comment 8) One comment asserts that the criterion for the generally available data or information establishing safety to ordinarily be published is artificial. Other comments point out that information that is not published can nonetheless be considered "generally available." Some comments object to the proposed amendment to the criteria for eligibility for classification as GRAS through scientific procedures and assert that it would de-emphasize or eliminate the existing criterion for peer-reviewed studies.

(Response 8) Regardless of whether the data and information are published or unpublished, under the revised criteria a GRAS conclusion must be based on data and information that are generally available and accepted, and as such, are publicly available. As we stated in the proposed rule, the common knowledge element of the GRAS standard precludes a GRAS conclusion if the data and information (e.g., as evaluated by a "GRAS panel") are only available in files that are not publicly accessible, such as in confidential industry files (62 FR 18938 at 18943). We disagree that the criterion for the generally available data or information establishing safety to ordinarily be published is artificial. Publication in a peer-reviewed

scientific journal is the usual mechanism to establish that scientific information is generally available, provided that the journal is representative of scientific publications accessed by the expert scientific community (62 FR 18938 at 18943). Nonetheless, the revised criteria provide flexibility for supporting a conclusion of GRAS status through the application of scientific data, information, or methods that are generally available through a mechanism other than publication in a peer-reviewed scientific journal, such as publication in a textbook and other sources of technical literature. One example of another source of technical literature is the Joint Expert Committee on Food Additives (JECFA, a joint committee of the Food and Agriculture Organization/World Health Organization). We note, however, that the mere fact that data and information are published or otherwise publicly available does not satisfy the criteria for general recognition of safety. Regardless of the mechanism of making data and information generally available to qualified experts, it must be plausible that qualified experts would be accessing those data and information using that mechanism. For example, scientists who routinely access peer-reviewed journals in electronic form on the Internet may avoid Internet "publications" about a scientific topic when the "publication" is not associated with a reputable scientific institution.

We have not changed our position on the importance of peer review. The basis for GRAS status continues to be the application of generally available scientific data, information, and methods, which ordinarily are published (and, thus, are subject to peer review as part of the scientific publication process for most journals). We continue to believe that whether scientific data, information, and methods have been peer reviewed before publication in a scientific journal that is representative of scientific publications accessed by the expert scientific community is a factor that bears on the objectivity and scientific merit of study, and is a variable we consider in determining whether experts accept the report of a scientific investigation as a credible report and whether there is general knowledge of the scientific investigation.

CFSAN's 2010 experience document (Ref. 18) provides factual information on how CFSAN already has interpreted the criteria for eligibility for classification of GRAS status through scientific procedures for GRAS notices CFSAN received during the Interim Pilot program (see section III.A.1 of CFSAN's 2010 experience document), and we intend to continue this approach in the future. In most cases, a submitted GRAS notice described a mixture of information published in peer-reviewed journals, information (such as in textbooks) that was generally available in a form other than a peer-reviewed journal, and unpublished information. As shown in table 1 in CFSAN's 2016 experience document, CFSAN had no questions about GRAS status based on this mixture of information in approximately 81 percent of the GRAS notices CFSAN evaluated between 1998 and 2015 (Ref. 19). Importantly, CFSAN's evaluation of the basis for a conclusion that a use of a food substance is GRAS in addition to being safe was a case-by-case evaluation. As discussed in section III.A.4 of CFSAN's 2010 experience document, in some cases it was CFSAN's view that the available data and information were sufficient to demonstrate safety, but not GRAS status, and CFSAN established a food additive regulation for the use of the substance in response to a food additive petition for that use (Ref. 18).

(Comment 9) Some comments state that all available relevant data, including unpublished data, should be used in evaluating GRAS status. Some of these comments cited the placement of the word "ordinarily" in the criteria for classification as GRAS through scientific procedures as support for this interpretation. Several comments urge us to interpret, in a flexible manner, the proposed criteria for the scientific data, information, methods or principles that establish safety to be "generally available and accepted" and "ordinarily ... published."

(Response 9) We agree that all relevant data should be used in evaluating GRAS status, including unpublished data. However, regardless of whether data and information are published or unpublished, a GRAS conclusion based on scientific procedures must be based on data and information that are generally available and accepted, and as such, are publicly available (see Response 8). The GRAS criteria for scientific procedures, as established in 1976, state that the applicable data and information are "ordinarily" published and may be "corroborated" by unpublished data and information, and this rule retains these criteria. The common meaning of "corroborate" is to make more certain or confirm (Ref. 23). Although unpublished data and information can confirm a conclusion of GRAS status, to satisfy GRAS criteria qualified experts must be able to conclude that the substance is not harmful under the conditions of its intended use without access to "corroborative" information (see § 170.30(a)). Under this rule, a notifier is required to explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to non-public safety-related data and information considered in reaching a conclusion of GRAS status (see § 170.250(e)).

Whether data and information are corroborative of safety, rather than establish safety, depends on what those data and information are and how they relate to the safety assessment, not just whether they are published or otherwise publicly available. Whereas unpublished data and information that have a bearing on a safety conclusion, and therefore could help confirm a safety conclusion based on other data and information, in general, can only be considered as corroborative in the context of a GRAS conclusion, published data and information may be either the basis for a safety conclusion or corroborative of a safety conclusion, depending on the nature of the data and information. For example, a published 90-day toxicology study could be the basis for a safety conclusion, but a preliminary toxicology study conducted primarily for the purpose of selecting the doses to be used in that 90-day toxicology study is unlikely to be the basis for a safety conclusion, regardless of whether that preliminary toxicology study is published.

See also the discussion in Response 58 regarding the requirement for you to submit a signed statement certifying 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 (§ 170.225(c)(9)). See also the discussion in section XVII regarding the requirement for your narrative to identify, 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 (§ 170.250(c)).

(Comment 10) One comment asks us to explicitly acknowledge publication of information in the secondary scientific literature as a mechanism to satisfy the standard for general availability.

(Response 10) We decline this request. In general, the secondary scientific literature includes publications (such as review articles, textbooks, and compendia) which disseminate the views of scientists who are critically evaluating a primary body of data and information already published in peer-reviewed scientific journals that are representative of scientific publications accessed by the expert scientific community (i.e., the primary scientific literature). Whether a publication in the secondary scientific literature satisfies the criteria for GRAS status through scientific procedures is a case-by-case determination that depends on the circumstances. See section III.A.1 of CFSAN's 2010 experience document (Ref. 18) for examples of how CFSAN considered publications in the secondary scientific literature during the Interim Pilot program.

When the underlying data being reviewed in the secondary scientific literature are themselves generally available, a publication in the secondary scientific literature can provide evidence that the data and information discussed in the publication are generally accepted as well as generally available. If a publication in the secondary scientific literature discusses data and information that are available to the authors, but not previously published in the primary scientific literature, whether that publication could satisfy the "generally available" aspect of the criteria for eligibility for GRAS status through scientific procedures would depend on the nature and extent of the discussion in the publication. For example, a very general statement that a study was conducted and reported no adverse findings would not suffice to make the study "generally available"; instead, such a statement would merely be a generally available opinion about data and information, in that study, that are not generally available. Such a publication may satisfy the "generally accepted" aspect of the criteria for GRAS status through scientific procedures for that study, but would be insufficient, by itself, to satisfy the "generally available" aspect of those criteria. However, a comprehensive description in the secondary scientific literature of a previously unpublished study, including details similar to details that would be included in a publication in the primary scientific literature, may suffice to make the study published in the secondary scientific literature "generally available." In such circumstances, the publication in the secondary scientific literature may be able to satisfy both the "generally available" and "generally accepted" aspects of the criteria for eligibility for GRAS status through scientific procedures for certain data and information.

(Comment 11) One comment asks us to recognize that publication of an opinion of a specially convened "expert panel" would satisfy the standard for general availability because, in the comment's view, review by such a panel would be equivalent to, or exceed, peer review. (By "expert panel," we assume that the comment is referring to a "GRAS panel", i.e., a panel of individuals convened for the purpose of evaluating whether the available scientific data, information, and methods establish that a substance is safe under the conditions of its intended use in food. See the discussion in section III.A.1 of CFSAN's 2010 experience document (Ref. 18).)

(Response 11) We would consider publication of an opinion of a specially convened "GRAS panel" to be part of the secondary scientific literature as discussed in Response 10. As with any publication in the secondary scientific literature, when the underlying data being reviewed in a published "GRAS panel" opinion are themselves generally available, a published "GRAS panel" opinion could provide evidence that the data and information discussed in the publication are generally accepted, depending on factors such as the subject matter expertise of the members of the GRAS panel and whether the members of the GRAS panel would be considered representative of experts qualified by scientific training and experience to evaluate the safety of the substance under the conditions of its intended use. For example, a "GRAS panel" opinion published by scientists without expertise appropriate to address the applicable safety questions could not provide evidence that the conclusions in the publication are "generally accepted."

If a published "GRAS panel" opinion discusses data and information that are available to the members of the GRAS panel, but not generally available to qualified experts, whether that publication could satisfy the "generally available" aspect of the criteria for eligibility for GRAS status through scientific procedures would depend on the nature and extent of the discussion in the publication (see Response 10). Unless both criteria, i.e., "generally available" and "generally

accepted", are satisfied, there would be no basis for a conclusion of GRAS status based on a published "GRAS panel" opinion.

(Comment 12) One comment states that all available relevant data, including unpublished data, should be used in evaluating GRAS status, as long as any unpublished data are generated by appropriate and valid scientific methods as judged and reviewed by an external qualified GRAS panel and are accessible to FDA for review.

(Response 12) We agree that all available relevant data should be used in evaluating whether a use of a substance in food is GRAS through scientific procedures. By "all relevant data," we mean data that support a conclusion of GRAS status as well as data that are inconsistent with a conclusion of GRAS status, not just whether the data are published. (See §§ 170.225(c)(9) and 170.250(c) and the discussion in Response 58, Response 69, and Response 78.) We also agree that it is appropriate for unpublished data to be generated by valid scientific methods and to be accessible to FDA for review (e.g., when such data are cited in a submission to FDA). In addition, we have acknowledged the practice of convening an external "GRAS panel" to evaluate whether the available scientific data, information, and methods demonstrate that a substance is safe under the conditions of its intended use in food (see section III.A.1 of CFSAN's 2010 experience document) (Ref. 18). However, we disagree that information that is not generally available to qualified experts could be used as evidence for a GRAS conclusion merely because a GRAS panel has reviewed it. Such information would need to be considered, but generally would only be corroborative of safety. (See Response 9 and Response 11.)

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(Comment 16) One comment asks us to require that both toxicology and exposure data be published because a safety assessment for the use of a substance in food requires consideration of both.

(Response 16) We agree that a safety assessment for the use of a substance in food requires consideration of both safety information (such as toxicology studies) and dietary exposure (i.e., the amount of the substance that consumers are likely to eat or drink). Toxicology data are ordinarily published.

A premarket exposure assessment typically would be calculated by applying generally available and accepted methods to two types of data and information: (1) Generally available and accepted data about food consumption; and (2) specific food categories, and levels of use in those food categories, projected by the sponsor of a food additive petition or by the proponent of GRAS status (Ref. 24 and Ref. 25). Using generally available and accepted data about food consumption, a qualified expert who has access to the specific food categories and associated levels of use intended by the proponent of GRAS status can calculate an estimated dietary exposure. When the proponent of GRAS status submits a GRAS notice, the proponent must: (1) Provide data and information about dietary exposure (see § 170.235); and (2) include a narrative that addresses the safety of the notified substance, considering all dietary sources (see § 170.250). Those calculations and discussions included in the GRAS notice are subject to the public disclosure provisions of this rule (see § 170.275) and, thus, would be available to the expert scientific community. However, when the proponent of GRAS status does not submit a GRAS notice, the expert scientific community that does not have access to the specific food categories and associated levels of use would not be able to calculate an estimated dietary exposure. When the available data and information suggest that the specific food categories and associated levels of use must be carefully chosen to keep consumption of the substance in a safe range (e.g., when fortifying food with certain vitamins), the expert scientific community that

does not have access to the specific food categories and associated levels of use would not be able to reach a conclusion about whether the substance is safe under the conditions of its intended use, and GRAS criteria would not be satisfied.

After market entry of the substance, it may be appropriate to re-assess dietary exposure. For example, dietary exposure may need to be reassessed when a key assumption in the methodology is changed; as dietary consumption patterns change; when there is an unresolved question about consumer intake; when there is a small margin of exposure; or when other new information becomes available. As with a premarket exposure assessment, a postmarket exposure assessment typically would be calculated by applying generally available and accepted methods to two types of data and information: (1) Generally available and accepted data about food consumption; and (2) specific food categories, and levels of use in those food categories. In some cases, postmarket exposure assessments have been published so that the expert scientific community has access to them. For example, exposure assessments have been published for some sweeteners using relative sweetness as the basis of the estimate (Ref. 26). As another example, estimates of dietary exposure to caffeine have been published to address consumer intake and patterns of use (Ref. 27 through Ref. 29). However, as with a premarket exposure assessment, when a postmarket exposure assessment is not publicly available, the expert scientific community that does not have access to the specific food categories and associated levels of use would not be able to reach a conclusion about whether the substance is safe under the conditions of its intended use when the available data and information suggest that the specific food categories and associated levels of use must be carefully chosen to keep consumption of the substance in a safe range.

(Comment 17) One comment asks us to recognize that published literature does not need to address a specific substance, but could involve publications on a class of substances or a related substance to support a conclusion that the use of a substance is GRAS through scientific procedures.

(Response 17) We agree that published information for a specific substance is not always necessary to support a conclusion that the use of a substance is GRAS through scientific procedures. For example, there may be situations where the safety of the use of the substance in food can be demonstrated by relevant published information on a closely, structurally related compound. In such cases, the analysis leading to the conclusion of GRAS status should explain how the information on the closely, structurally related compound is relevant to the safety assessment of the substance being evaluated. In other cases, there may a body of information published in the primary or secondary literature about a class of substances, which reflect generally available and accepted data and information that can be called to bear on the safety assessment of a specific substance. For example, generally available metabolism information about commonly consumed components of food, such as carbohydrates, lipids, and proteins, could support a conclusion that a specific substance is GRAS under the conditions of its intended use.

To help ensure that the data are, in fact, relevant to the safety assessment of the substance being evaluated, we strongly encourage any person who intends to rely on data and information regarding a class of substances, or a specific substance related to the substance that would be added to food, to submit any conclusion of GRAS status to FDA via the GRAS notification procedure.

(Comment 18) One comment states that the use of an approved food additive can, through the passage of time, become GRAS as the substance becomes widely used and as information about the substance becomes publicly available.

(Response 18) We disagree that widespread use of an approved food additive as time passes has any bearing on the eligibility of this use for classification as GRAS. Eligibility for classification as GRAS through scientific procedures would depend on the status of the information--as generally available and generally accepted--rather than on the amount of time that a food additive has been used in food. However, in general, much of the data submitted for our review of a food additive contains unpublished data and trade secret or confidential information that is neither published nor otherwise generally available. Although the safety data are available for public disclosure under 21 CFR 171.1(h)(1), they typically are based on unpublished studies sponsored by the petitioner.

See also the discussion in Response 19 regarding the impact of the passage of time and the discussion in Response 79 that the qualified experts who evaluate the basis for a conclusion that the notified substance is safe under the conditions of its intended use must not exclusively be "FDA's experts."

(Comment 19) One comment asks us to exclude uses of "novel" substances from consideration for eligibility for classification as GRAS. The comment asserts that novel or newly discovered uses of substances that are the subject of a conclusion of GRAS status are in conflict with the original intent of the 1958 amendment and the plain meaning of "generally recognized," because there is no history of safe use for these substances. The comment also states that similar "general recognition" provisions for new drugs are not interpreted to allow industry-made safety determinations for new or novel drugs.

(Response 19) We do not have a regulatory definition for a "novel" substance. As a general matter, section 201(s) of the FD&C Act provides two alternatives for general recognition of safety--through scientific procedures, or through experience based on common use in food. Section 201(s) does not limit eligibility, or otherwise exclude, the use of a substance from classification as GRAS through scientific procedures if there is no history of use. Likewise, section 201(s) does not limit eligibility, or otherwise exclude, the use of a substance from classification as GRAS through scientific procedures based on other criteria, such as whether a substance or its use in food is "novel" or "newly discovered." Unlike the definition of a "new drug" in section 201(p) of the FD&C Act, section 201(s) does not require that a food ingredient be used "to a material extent or for a material time under such conditions" before it can become GRAS. Rather, the criteria for eligibility for classification as GRAS depend on whether generally available and accepted data and information establish that the substance is safe under the conditions of its intended use.

However, a conclusion of GRAS status must be based on common knowledge throughout the scientific community knowledgeable about the safety of substances added to food that there is reasonable certainty that the substance is not harmful under the conditions of its intended use (§ 170.30(a)), and a substance cannot be considered GRAS when its characteristics are known to only a few experts (Final rule establishing GRAS criteria, 41 FR 53600, December 7, 1976). In addition, the passage of time is relevant in an evaluation of whether a substance is GRAS under the conditions of its intended use. In our 1974 proposed rule on general recognition of safety and prior sanctions for food ingredients, we acknowledged that there would be at least some gap between the gathering of the scientific knowledge necessary to provide the toxicological underpinning for general recognition of safety and the dissemination to and assimilation by the

scientific community of this material that is necessary for general recognition of safety to exist." (39 FR 34194 at 34194, September 23, 1974). More recently, the discussions in sections III.A.4 and IV.K of CFSAN's 2010 experience document (Ref. 18) show our approach to the time gap between the publication of safety data and the use of the published safety data to support a conclusion of GRAS status during the Interim Pilot program. See also Response 67 regarding nanotechnology applications in food substances.

(Comment 20) One comment asserts that we must define the extent of agreement needed to establish a consensus among qualified experts, and that we must exclude from eligibility for classification as GRAS any substance whose safety has been called into question by expert authorities or authoritative entities within the scientific community.

(Response 20) The proponent of a GRAS conclusion for a food substance must demonstrate that the conditions of use of the substance satisfy the definition of "safe" in our regulations (i.e., that there is reasonable certainty that the substance is not harmful under the conditions of its intended use (see § 170.3(i)). The proponent of GRAS status also must demonstrate that there is common knowledge about this safety throughout the knowledgeable scientific community (§ 170.30(a)). Although courts have established that general recognition of safety requires a consensus of expert opinion regarding the safety of the use of the substance, (see, e.g., *United States* v. *Western Serum Co., Inc*., 666 F.2d 335, 338 (9th Cir. 1982) (citing *Weinberger* v. *Hynson, Westcott & Dunning*, 412 U.S. 609, 629-32 (1973)), we disagree that we must define the extent of agreement needed to establish such a consensus. Courts have established that general recognition of safety does not require unanimous agreement. See, e.g., *United States* v. *Articles of Drug * * * 5,906 Boxes*, 745 F.2d 105, 119 n. 22 (1st Cir. 1984); *United States* v. *Articles of Food and Drug (Coli-Trol 80)*, 518 F.2d 743, 746 (5th Cir. 1975) ("What is required is not unanimous recognition but general recognition"). Importantly, general recognition of safety does not exist if there is a genuine dispute among qualified experts that the use of a substance is safe. See, e.g., *Premo Pharmaceutical Laboratories* v. *United States*, 629 F.2d 795, 803-4 (2nd Cir. 1980) ("genuine dispute among qualified experts" precludes finding of general recognition, and no general recognition existed as a matter of law where there was a "sharp difference" of expert opinion); *United States* v. *Article of Food * * * Coco Rico*, 752 F.2d 11, 15 n 6 (1st Cir. 1985) (substance was not GRAS as a matter of law based on existence of "genuine dispute among qualified experts" regarding safety of use). For discussions of additional judicial decisions bearing on the criteria for eligibility for classification as GRAS, see the notice of declaratory order providing our final determination regarding partially hydrogenated oils (80 FR 34650).

A conclusion of GRAS status must be based on the totality of the publicly available and corroborative evidence about the safety of the substance under the conditions of its intended use, including both favorable and potentially unfavorable information. Thus, reports of expert authorities or authoritative entities within the scientific community may indicate that there is no general recognition of safety when the reports call into question the safety of a substance for use in food. However, we disagree that the outcome of an evaluation of such information can be predetermined as suggested by the comments. Regardless of whether particular scientific data and information lead experts to conclude that a substance is safe under the conditions of its intended use, or raise questions about the safety of the substance under the conditions of its intended use, the evaluation of whether a use of a substance in food is safe, and whether safety is generally recognized, is a case-by-case evaluation. For example, data and information that lead expert authorities or authoritative entities within the scientific community to raise a concern

about the safety of the substance under the conditions of its intended use in food would have reduced significance if the concern was related to a contaminant in the substance and scientifically valid data and information supplied by the proponent of GRAS status provide evidence that an improved method of manufacture eliminates that contaminant.

See also Response 77, in which we explain that we proposed to provide the judicial interpretation of section 201(s) of the FD&C Act in the requirement for the comprehensive discussion of the notifier's basis for a conclusion of GRAS status to provide more context to notifiers than merely repeating the statutory language. However, as discussed in Response 77, we have decided to use the statutory language (i.e., "generally recognized") rather than the proposed term "consensus" in the submission requirements for a GRAS notice to mirror the GRAS criteria in § 170.30, which continue to use the statutory language rather than the consensus standard applied by the courts in applying the statutory language to specific situations.

...

(Comment 34) One comment suggests that the GRAS notification procedure would shift the burden of proof to FDA to demonstrate that a use of a substance is not safe or not GRAS after the substance is already on the market.

(Response 34) We disagree. Under the FD&C Act, the burden of supporting a conclusion that a substance is GRAS under the conditions of its intended use is on the proponent of this conclusion. *United States* v. *An Article of Food*, 752 F.2d 11, 15 (1st Cir. P.R. 1985). This burden of proof remains after the substance is on the market regardless of whether the proponent asks FDA to evaluate that GRAS conclusion, and our rule does not change this. By establishing a process for the submission of GRAS notices for FDA to review, our rule encourages firms to seek our evaluation of their conclusions, before they introduce the substance into the market.

...

(Comment 58) Several comments support a requirement for a GRAS notice to include a certification statement similar to the certification statement that had been required in a GRAS affirmation petition. One comment agrees that the notifier should submit a statement that the notice is a representative and balanced submission, but does not agree that the notifier needs to certify the statement.

(Response 58) The final rule requires a certification statement as described in the 2010 notice, with one modification (see § 170.225(c)(9)). We added that the statement certify that the GRAS notices is "complete" in addition to "representative" and "balanced," to emphasize your responsibility to identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with a conclusion of GRAS status, regardless of whether those data and information are generally available (see the requirements of the narrative in Part 6 of a GRAS notice (§ 170.250, in particular § 170.250(c)). The certification is appropriate and necessary to underscore your legal responsibility for the conclusion of GRAS status. As discussed in the 2010 notice, the specific text of the certification statement that you must include in a GRAS notice is consistent with the specific text of the certification statement in the GRAS affirmation petition process that the notification procedure is replacing. The use of certification statements has become routine in other submissions to FDA for food programs (see, e.g., the certification statement in Part V of Form FDA 3480 (for a food contact notification submission) (Ref. 39); and the certification statement in Section 13 of Form FDA 3537 (for registration of a food facility) (Ref. 40)).

By "complete," we also mean that your GRAS notice identifies, and places in context, unpublished data and information that you believe corroborate GRAS status. For example, if you

conduct six toxicology studies, but only publish three of the studies, it may be that you consider the remaining three studies to be corroborative of safety. As an example, it may be that you were dissatisfied with the study design of one study, repeated that study with an improved study design, and published the study with the improved study design. If you consider that the findings of the unpublished studies corroborate safety, even if they do not establish it, a "complete, representative, and balanced" submission would briefly describe the unpublished studies. In addition, we expect that you would describe, and place in context, unpublished data and information if you consider that the findings of the unpublished data and information warrant sharing with any "GRAS panel" that you convene. See also the discussion in Response 69 and Response 78.

...

(Comment 69) Several comments address Issue 9a, i.e., whether the final rule should continue to stipulate that the method of manufacture exclude any trade secrets, as proposed. Some of these comments support stipulating that the method of manufacture exclude any trade secrets. The stated reasons varied. For example, some comments state that in the past experience of notifiers, it is generally possible to include sufficient information on the manufacturing process without disclosing trade secrets. One comment states that transparency, by both FDA and industry, and the use of publicly available information is critical to the continued success of the GRAS notification procedure. One comment states that the common knowledge element of the GRAS standard inherently limits the submission of confidential information and/or trade secrets by the notifier to substantiate a conclusion of GRAS status.

Other comments point to the proposed requirement that a GRAS notice include "detailed information about the … method of manufacture (excluding any trade secrets …)" and question whether a method of manufacture that excludes trade secrets can be sufficiently detailed to meet the requirements of a GRAS notice. One comment recommends that we clarify the rule by requiring that the notice include appropriate information on the method of manufacture, sufficient to conduct an adequate safety review, so that confidential information would not be submitted when a very general and non-confidential description suffices.

Several comments acknowledge that there may be situations where trade secret information is necessary to complete the description of the method of manufacture and recommend that the final rule provide flexibility for a notifier to provide trade secret information when appropriate (e.g., to help us evaluate the GRAS notice), and for FDA to protect trade secrets or other confidential information in a GRAS notice from public disclosure, just as we would in the case of submissions such as food additive petitions. To promote clarity and transparency, some of these comments recommend revising the rule to require that a notifier who includes trade secret information explain why the information is trade secret and why the trade secret information has a corroborative role in the safety assessment. Some comments emphasize that a notifier who submits trade secret information must mark the information as non-public. Other comments assert that information identified as trade secret or confidential information should only be allowed if the information is not critical to a conclusion of GRAS status.

One comment suggests that a notifier could provide trade secret information to a GRAS panel for review on a confidential basis because deliberations of the panel would not necessarily be subject to public disclosure. One comment notes that supporting information can be valuable to a GRAS panel and allowing submission of confidential information in a GRAS notice could inform FDA of the full range of information taken into consideration by a GRAS panel.

Some comments cite our regulations for new drugs, premarket notification for medical devices, and premarket approval of medical devices as evidence that our regulations implementing FOIA specifically regard methods of manufacture as confidential and urge us to adopt a similar approach for GRAS notices.

See also Comment 57.

(Response 69) See Table 11, and the regulatory text in §§ 170.230(b), 170.225(c)(8), 170.250(d), and 170.250(e), for a series of changes we made to the rule to address these comments about the method of manufacture included in a GRAS notice, including comments about trade secret information associated with the method of manufacture. Although the changes in Parts 1 and 6 of a GRAS notice broadly apply to any non-public information, in this response we focus on how these provisions apply to trade secret information that you may include in the description of the method of manufacture. Collectively, these changes: (1) Emphasize that the description of the method of manufacture must be in sufficient detail to evaluate the safety of the notified substance as manufactured, without stipulating that the method of manufacture exclude any trade secrets (§ 170.230(b)); (2) require the notifier to include a signed statement with his view as to whether the method of manufacture includes trade secret information (§ 170.225(c)(8)); (3) require the notifier to identify any trade secret information in the method of manufacture (§ 170.250(d)); and (4) require the notifier to explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to trade secret information that the notifier considered in concluding that the substance is safe under the conditions of its intended use (§ 170.250(e)). See also Response 57, Response 78, and section XVII.

Table 1.--Requirements That Apply When a Notifier Includes Trade Secret or Other Non-Public Information in a GRAS Notice

Final Designation in the Regulatory Text (§)	Proposed Designation in the Regulatory Text (§)	Description	Revision
170.230(b)	170.36(c)(2)	In Part 2 of your GRAS notice, you must include a description of the method of manufacture in sufficient detail to evaluate the safety of the notified substance as manufactured	• We replaced "detailed" with "sufficient detail to evaluate the safety of the notified substance as manufactured" • We no longer stipulate that the description of the method of manufacture must exclude trade secret information
170.225(c)(8)	N/A	In Part 1 of your GRAS notice, you must state your view as to whether any of the data and information in Parts 2 through 7 of your GRAS notice are exempt from disclosure under the FOIA (e.g., as trade secret or as commercial or financial information that is privileged or confidential).	Requires a notifier who includes information that the notifier views as non-public information to make FDA aware of that view. See Response 57.
170.250(d)	N/A	In Part 6 of your GRAS notice (the narrative), if you view any of the data and information in your notice as exempt from disclosure under the FOIA, you must identify the specific data and information	Requires a notifier who includes information that the notifier views as non-public information to identify the non-public information. See section XVII.

Final Designation in the Regulatory Text (§)	Proposed Designation in the Regulatory Text (§)	Description	Revision
170.250(e)		In Part 6 of your GRAS notice (the narrative), you must explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to non-public, safety-related data and information.	Requires a notifier to place non-public information in the context of a conclusion of GRAS status. See section XVII.
170.275(c)	170.36(f)(1)	We will disclose all remaining data and information that are not exempt from public disclosure in accordance with part 20.	Uses active voice to emphasize that we will apply the protections from public disclosure under the FOIA to non-public information included in a GRAS notice

This rule establishes requirements for the information that a notifier submits to FDA in a GRAS notice. GRAS criteria require that any conclusion of GRAS status be based on common knowledge (see § 170.30(a)) and, thus, there could be no basis for a conclusion of GRAS status if trade secret information (or other non-public information) is necessary for qualified experts to reach a conclusion that the notified substance is safe under the conditions of its intended use. In the particular case of a conclusion of GRAS status through scientific procedures, GRAS criteria require that the conclusion of GRAS status be based on data, information, and methods that are generally available (see § 170.30(b)). Non-public information may be used to corroborate safety but cannot be used to establish safety; as discussed in Response 9, qualified experts must be able to conclude that the substance is not harmful under the conditions of its intended use without access to "corroborative" information (see § 170.30(a)).

We believe that it will be rare for a GRAS notice to include trade secret information. Likewise, we expect it will be rare that trade secret information would warrant sharing with members of a GRAS panel, because a notifier must write a non-confidential description of the method of manufacture to include in the GRAS notice and could share this non-confidential description, rather than trade secret information, with the GRAS panel. If the GRAS panel had questions about that description of the method of manufacture, we expect that the notifier would revise the description to address those questions rather than provide the GRAS panel with trade secret information to address those questions. If, however, a notifier does provide the GRAS panel with trade secret information, we agree that the notifier should inform us of the full range of information taken into consideration by the GRAS panel, consistent with the signed statement that the GRAS notice is a complete, representative, and balanced submission (see Response 58 and § 170.225(c)(9)). The notifier could do so either by including in his GRAS notice a non-confidential description of the trade secret information that was shared, or by providing the trade secret information shared with a GRAS panel. Importantly, the notifier would be required to explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to non-public, safety related data and information (see Response 78 and § 170.250(e)). If the public description of the method of manufacture that a notifier includes in a GRAS notice cannot provide sufficient detail to evaluate the safety of the notified substance as manufactured, there could be no basis to support a conclusion of GRAS status. However, if that public description meets the requirements of the rule to provide sufficient detail to evaluate the safety of the notified substance as manufactured (see § 170.230(b)), it may be possible to explain

that trade secret information that a GRAS panel evaluated is corroborative of safety rather than necessary to demonstrate safety.

Under § 20.61, trade secrets and commercial or financial information which is privileged or confidential are exempt from public disclosure. Under §§ 20.100(c)(7) and 171.1(h)(2)(i), manufacturing methods or processes, including quality control procedures, are exempt from public disclosure unless they have been previously disclosed to the public (as defined in § 20.81) or they relate to a product or ingredient that has been abandoned. If a notifier believes that all information about the method of manufacture should be non-public, it is unlikely that the notifier has a basis to conclude that the notified substance is GRAS under the conditions of its intended use. The use of the substance would be a food additive use and, if the notifier submits a food additive petition for that use, our regulations governing a food additive petition would protect the information from public disclosure, as do our regulations for new drugs, premarket notification for medical devices, and premarket approval of medical devices.

(Comment 78) One comment notes that industry has various options for handling confidential information. For example, confidential agreements are commonly used instruments to help maintain the confidentiality of proprietary trade secret information, and therefore qualified experts on GRAS panels can have access to such information if it is necessary for a conclusion of GRAS status. The comment asks us to require that notifiers indicate whether qualified experts (such as on the notifier's GRAS panel) had access to trade secrets when they concluded that the substance is safe under the conditions of its intended use.

(Response 78) The rule establishes no requirements specific to a GRAS panel. However, we agree that it is appropriate for a notifier to indicate whether qualified experts (such as on the notifier's GRAS panel) who reviewed the data and information supporting safety had access to safety-related trade secrets in reaching a conclusion that the notified substance is safe under the conditions of its intended use. Therefore, we are requiring that a notifier explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to non-public safety-related data and information (see § 170.250(e)). This requirement applies to all non-public safety-related data and information, not just trade secret information, and is not limited to non-public safety-related data and information that are included in the notice. As requested by the comment, this requirement would apply if the notifier provided non-public safety-related information to outside experts (such as on a GRAS panel). As already discussed, if a GRAS panel considers non-public safety-related information that a notifier does not include in a GRAS notice, we also expect the notifier to inform us that the GRAS panel had access to such information, consistent with the notifier's signed statement that the GRAS notice is a complete, representative, and balanced submission (see § 170.225(c)(9)) (see Response 58 and Response 69).

See also Table 11 and Table 15. The rule also requires that a notifier state his view as to whether any of the data and information in Parts 2 through 7 of a GRAS notice are exempt from disclosure under the FOIA (see § 170.225(c)(8)) and identify what specific data and information in the notice are generally available, and what specific data and information in the notice are not generally available (see § 170.250(a)(2) and (d)). Collectively, the requirements in §§ 170.225(c)(8) and (9) and 170.250(a)(2), (d), and (e) address the underlying issue in the comment's request, i.e., that there must be a basis for a conclusion of GRAS status if some safety-related data and information that a notifier assesses in his deliberations are non-public (e.g., trade secret information or otherwise are confidential information), regardless of whether the notifier shares such information with a GRAS panel. If a GRAS notice does not provide a

basis for a conclusion that the notified substance is safe under the conditions of its intended use without access to such information, we would respond to the notice with an "insufficient basis letter." If we respond with a "no questions letter," and later determine that the GRAS notice was not "complete" (e.g., because it did not describe unpublished reports of investigations that are, or may appear to be, inconsistent with the conclusion of GRAS status), we may send the notifier a subsequent letter regarding the omission; such a letter would be readily accessible to the public (§§ 170.265(c) and 170.275(b)(2)).
