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Best Practices for Convening a GRAS Panel: Guidance for Industry

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Best Practices for Convening a GRAS Panel: Guidance for Industry[1]

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I. Introduction

This guidance document is intended to provide our recommendations on best practices for convening a "GRAS panel." By "GRAS," we mean "generally recognized as safe." See section II.A for a discussion of the GRAS provision of the Federal Food, Drug, and Cosmetic Act (FD&C Act). By "GRAS panel," we mean a panel of qualified experts who independently evaluate whether the available scientific data, information, and methods establish that a substance is safe under the conditions of its intended use in human food or animal food as part of an evaluation of whether adding that substance to food is lawful under the GRAS provision of the FD&C Act.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe FDA's 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.

In this document, we refer to a person who is responsible for a conclusion that a substance may be used in food on the basis of the GRAS provision of the FD&C Act as the "proponent" of

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

GRAS status for that substance under the conditions of its intended use. In many cases, the process whereby the proponent evaluates whether the available data and information support a conclusion that a substance is GRAS under the conditions of its intended use need not include a GRAS panel. However, in some cases, the proponent might decide that the opinion of a GRAS panel may be useful. Depending on the outcome of the GRAS panel's analysis, the proponent could either reach a conclusion regarding the safety of the substance under the conditions of its intended use, or be advised of one or more issues (such as gaps in the data and information, or alternative interpretations of the available data and information) that warrant investigation before a conclusion can be drawn about whether the substance is safe under the conditions of its intended use.

Importantly, the outcome of a panel's deliberations does not create or confer general recognition of the safety of the use of an ingredient. Rather, it could provide evidence supporting the proponent's contention that there is general acceptance based on generally available information among relevant scientific communities. When the outcome of the GRAS panel's analysis supports the proponent's conclusion that a substance is safe under the conditions of its intended use, in essence the proponent is relying on the members of the GRAS panel to act as a representative sample[2] of the larger scientific community knowledgeable about the safety of substances directly or indirectly added to food. In so doing, the proponent relies on the outcome of the GRAS panel's analysis to support the proponent's conclusion that the safety of the intended use is "generally recognized" by qualified experts. Whether a GRAS panel is a sufficiently representative sample with respect to the larger scientific community depends on a number of factors, such as the subject matter expertise of the members of the GRAS panel and whether the members of the GRAS panel are 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." 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 "GRAS panel" opinion (see Response 11, 81 FR 54960 at 54974, August 17, 2016).

A GRAS panel is just one mechanism that proponents have used to provide evidence of general acceptance in support of their GRAS conclusion. In most cases, a well-supported GRAS conclusion will not require an analysis by a GRAS panel (see Figure 1). We suggest that proponents considering whether a GRAS panel would be useful in supporting their GRAS conclusion consult with FDA before embarking on such an effort. In addition, we realize that it can be challenging to identify, screen, and select a comprehensive panel of qualified experts when specialized expertise applicable to the scientific considerations associated with the intended conditions of use of a food substance is needed, given the potentially finite number of

[2] In other words, the panel functions as a sample of the scientific community, and thus the views of the panel members can provide evidence of their respective disciplines' generally accepted views on a particular question. However, if there is reason to believe that the sample is unrepresentative in some way, the credibility of the panel's views as evidence of general acceptance could be significantly reduced.

experts who would be both qualified and available to serve on a GRAS panel. Thus, it may be worth considering whether the effort to convene a GRAS panel is warranted in any particular case before allocating resources to it.

This guidance document is intended for and directed to:

- Those proponents who intend to consider the opinion of a GRAS panel in reaching a conclusion that the intended use of a substance in human food or animal food is GRAS;

- Those persons who assemble a GRAS panel and provide the framework for its deliberations ("organizers"); and/or

- Those persons who are interested in our views and recommendations on best practices for convening a GRAS panel.

The recommendations in this guidance address best practices for convening a GRAS panel to:

- Identify GRAS panel members who have appropriate and balanced expertise;

- Take steps to reduce the risk that bias (or the appearance of bias) will affect the credibility of the GRAS panel's output (often called a "GRAS panel report"), including the assessment of potential GRAS panel members for conflict of interest and the appearance of conflict of interest; and

- Limit the data and information provided to a GRAS panel to public information (e.g., by not providing the GRAS panel with information such as trade secret information).

The recommendations in this guidance reiterate certain statutory and regulatory considerations that we have previously discussed regarding the use of a GRAS panel in addressing the GRAS provision of the FD&C Act related to food and food additives (81 FR 54960 at 54966, 54994, and 55000). However, this guidance document is not intended to address the statutory and regulatory criteria that govern eligibility for classification of a substance as GRAS under the conditions of its intended use or to describe the proponent's responsibilities for complying with those statutory and regulatory criteria. For the most recent discussions of those statutory and regulatory criteria, see the final rule entitled "Substances Generally Recognized as Safe" (81 FR 54960 (the GRAS final rule)) and our guidances entitled "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" (the regulatory framework guidance) (Ref. 1) and "Frequently Asked Questions About GRAS for Substances Intended for Use in Human or Animal Food: Guidance for Industry" (the GRAS FAQs) (Ref. 2).

Rather, this guidance includes recommendations for GRAS panels that are informed by federal law, regulations, and FDA guidance documents related to FDA advisory committee members. Our reference to these requirements and guidances is solely for the purpose of discussing

concepts that are relevant to conflict of interest issues for GRAS panels (the topic of this guidance), rather than to imply that FDA bears the same organizing role in relation to a GRAS panel as it does for an FDA advisory committee or to imply that the processes are wholly analogous. In addition, for more background and information, this guidance notes some available conflict of interest policies from other organizations. This guidance is intended to support the organizers of GRAS panels in their own development of procedures for convening GRAS panels.

II. Background

A. Statutory and Regulatory Framework for Substances Added to Food

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

[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.

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)).

B. GRAS Notification Procedure

In 2016, we issued a final rule establishing the GRAS notification procedure ("Generally Recognized as Safe (GRAS) Notice") 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 (81 FR 54960). That final rule completed the rulemaking that we initiated through a proposed rule (62 FR 18938, April 17, 1997) and a notice reopening the comment period for the proposed rule to update comments and to solicit comment on specific issues ("reopening notice") (75 FR 81536, December 28, 2010).

The GRAS final rule provides that any person may notify FDA 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 submission containing this view (a GRAS notice) must contain seven parts, including an explanation of how the generally available data and information relied on to establish safety provide a basis for the proponent's 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(b) and 570.250(b)).

C. Evidence for General Recognition

For a substance to be eligible for GRAS status under the conditions of its intended use, the publicly available data and information must satisfy the safety standard for a food additive in accordance with section 409(c)(5)(C) of the FD&C Act. Furthermore, there must be common knowledge throughout the expert 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 intended conditions of use (see 21 CFR 170.30(a) and 570.30(a)). This requirement of "general recognition" is itself composed of both "general availability" and "general acceptance" aspects.

1. General Availability

As discussed in GRAS rulemaking documents, publication in a peer-reviewed scientific journal is the usual mechanism to establish that scientific information is generally available (see Response 8, 81 FR 54960 at 54973; 62 FR 18938 at 18940).

2. General Acceptance

There are a variety of ways to provide evidence of general acceptance. The type of evidence necessary in a particular case will depend on the properties and intended use of an ingredient as well as the state of the science and the available public data.

A GRAS panel is just one mechanism that proponents have used to provide evidence of general acceptance, thus supporting the proponent's GRAS conclusion (see Response 13, 81 FR 54960 at 54975). However, use of a GRAS panel is not the only mechanism for doing so. While it is true that some GRAS notices evaluated by FDA have included statements from a GRAS panel, in our view, the presence and conclusions of the panel were not essential evidence supporting the proponent's GRAS conclusion for most of these notices.

Conversely, the use of a GRAS panel does not necessarily mean that the "general acceptance" aspect of the criteria for eligibility for GRAS status has been met (see Response 13, 81 FR 54960 at 54975).

Figure 1 illustrates the continuum of value that the output of a GRAS panel could contribute to a proponent's GRAS conclusion, ranging from likely unnecessary to potentially useful to likely insufficient. Table 1, further discussed below, provides examples when a GRAS panel may be either unnecessary – because there is likely already sufficient evidence of general acceptance -- or insufficient – because it is unlikely that a GRAS panel could provide credible evidence of general acceptance -- to satisfy the "generally accepted" aspect of the criteria for eligibility for GRAS status. In cases where the proponent is unsure of the potential value of a GRAS panel in helping to satisfy the "general acceptance" criteria, the proponent should consult with FDA.

Figure 1: Continuum of Value for GRAS Panels in Providing Evidence of General Acceptance

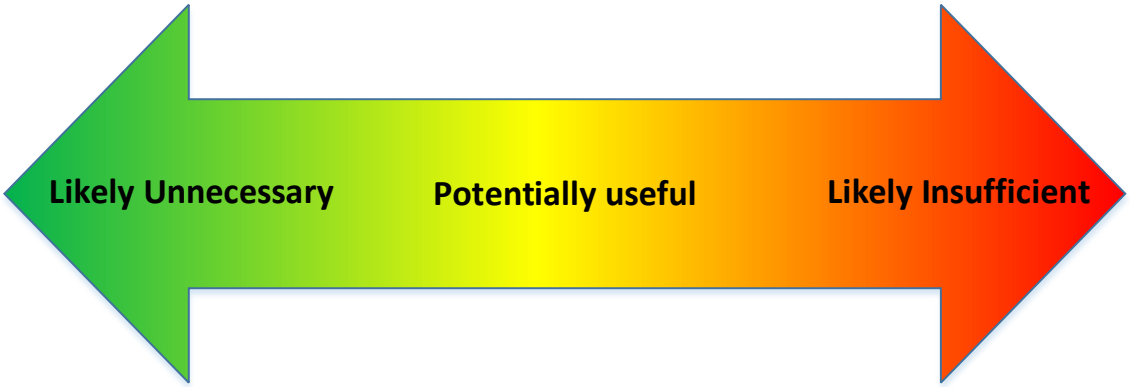

Table 1: Examples of Scenarios Where GRAS Panels Are Likely Unnecessary or Insufficient to Provide Evidence of General Acceptance

GRAS Panel Likely Unnecessary	GRAS Panel Likely Insufficient
Published results in the primary scientific literature raise no questions that experts would need to interpret and resolve (see "d. Basis for concluding expert consensus," 62	Ongoing scientific discussion or controversy about safety concerns raised by available data (see "d. Basis for concluding expert consensus," 62 FR 18938 at 18949)

GRAS Panel Likely Unnecessary	GRAS Panel Likely Insufficient
FR 18938 at 18949; see Response 13, 81 FR 54960 at 54975)	
Publication of data and information in the primary scientific literature has been supplemented by publication of data and information in the secondary literature, such as scientific review articles, textbooks, and compendia (see "C. Elements of the GRAS Standard," 62 FR 18938 at 18940 through 18941; see Responses 10, 11, and 13, 81 FR 54960 at 54974 through 54975)	Safe level of intake is in a narrow range (see "1. Establishing General Recognition of Safety," 62 FR 18938 at 18943)
Publication of data and information in the primary scientific literature has been supplemented by the opinion or recommendation of an authoritative body […] on a broad or specific issue that is related to a GRAS conclusion (see "C. Elements of the GRAS Standard," 62 FR 18940 through 18941; see Response 13, 81 FR 54960 at 54975)	Severe conflict among experts regarding the safety of the use of a substance (*United States v. An Article of Drug* * * 4,680 Pails,* 725 F.2d 976 at 990 (5th Cir. 1984)*; Premo Pharmaceutical Laboratories v. United States,* 629 F.2d 795 at 803 (2d Cir. 1980))

In most cases, a well-supported GRAS conclusion will not need an analysis by a GRAS panel as evidence of general acceptance (the left-hand side of Figure 1; the left-hand examples in Table 1). Depending on the specifics of the intended use of a substance, peer-reviewed primary safety studies, secondary reviews of primary literature, or the findings of an authoritative body could provide adequate evidence of general acceptance. Each of these three types of evidence is discussed below.

- Published peer-reviewed primary studies. In many cases, the type of evidence provided by published peer-reviewed primary studies consistent with generally accepted safety assessment strategies is sufficient to satisfy both the general availability as well as the general acceptance aspects of the GRAS criteria. We stated in the GRAS proposed rule that "there could be a basis to conclude that there is expert consensus[4] that the published results of a particular safety study (i.e., the primary scientific literature) establish the safety of a substance for its intended use if the study raises no safety questions that experts would need to interpret and resolve" (62 FR 18938 at 18943). We also noted this point in the GRAS final rule (see Response 13, 81 FR 54960 at 54975). However,

[4] In general, FDA describes this concept using "general acceptance" rather than "expert consensus," a term derived from case law, for reasons discussed in the GRAS Final Rule (81 FR 54960 at 55007). We use the term "expert consensus" where we are quoting directly from the proposed rule within the paragraph.

"…data published in the primary scientific literature may not provide a basis for expert consensus if those data raise unresolved safety questions" (62 FR 18938 at 18949).

- Secondary literature. In some cases, the type of evidence provided by secondary literature, such as reviews of published primary literature, may be sufficient and appropriate to satisfy the general acceptance aspect of the GRAS criteria. In the GRAS proposed rule, we noted that publication of data and information in the primary scientific literature can be supplemented by publication of data and information in the secondary scientific literature, such as scientific review articles, textbooks, and compendia (see "C. Elements of the GRAS Standard," 62 FR 18938 at 18940 through 18941). In the GRAS final rule, we further observed that there may be 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 (see Response 17, 81 FR 54960 at 54976). We also noted that technical literature from the Joint Expert Committee on Food Additives (JECFA, a joint committee of the Food and Agriculture Organization/World Health Organization) can provide evidence that generally available safety data and information are generally accepted (see section III.A.1 of Ref. 3).
- Findings of an authoritative body. The findings of an authoritative body are another type of evidence that could be used to support the general acceptance aspect of the GRAS criteria. As an example, this could include the opinion or recommendation of an authoritative body such as the National Academy of Sciences on a broad or specific issue that is related to a GRAS conclusion (see "C. Elements of the GRAS Standard," 62 FR 18938 at 18940 through 18941). The findings of an authoritative body may also be the most appropriate type of evidence to support general acceptance in those cases where the safe level of intake is a narrow range because the difference between the intended or recommended dietary intake (e.g., of a nutrient) and the intake at which the substance exhibits toxic properties is small. In such cases, the opinions or recommendations of the authoritative body may provide evidence of general acceptance, thus supporting a proponent's conclusion that that the safety of a substance under the conditions of its intended use is generally accepted by qualified experts (see Response 13, 81 FR 54960 at 54975).

By contrast, although unanimity among experts regarding the safety of a substance is not required, "an ongoing scientific discussion or controversy about safety concerns raised by available data would make it difficult to provide a basis for expert consensus about the safety of the substance for its intended use" (see "d. Basis for concluding expert consensus," 62 FR 18938 at 18949). While "mere conflict among experts is not enough to preclude a finding of general recognition [of safety]" (*United States v. Articles of Food and Drug (Coli-Trol 80)*, 518 F.2d 743 at 746 (5th Cir. 1975)), it does not exist if there is a genuine dispute among qualified experts that the use of the substance is safe (See, *e.g., Premo Pharmaceutical Laboratories v. United States*, 629 F.2d 795 at 803 through 804 (2d 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)). In such cases (the right-hand side of Figure 1; the right-hand column of Table 1), the type of evidence provided by a GRAS panel, no

matter how well constructed, may not be appropriate or sufficient to support the "general acceptance" aspect of the criteria for eligibility for GRAS status through scientific procedures.

Finally, there are occasionally circumstances in which a GRAS panel may provide the appropriate type of evidence to support the general acceptance aspect of the criteria for eligibility for GRAS status through scientific procedures (the middle of Figure 1). For example, as noted in the proposed rule, "the opinion of an expert panel is [...] useful when multiple studies bearing on the safety of a substance are published but there are no secondary sources that evaluate these studies and draw general conclusions based on this comprehensive body of knowledge" (62 FR 18938 at 18943). A GRAS panel may also be useful if "the published results of a particular safety study […] raises safety questions that require additional data to be resolved" (62 FR 18938 at 18943). In such cases where published primary or even secondary literature might not be sufficient, a well-constructed GRAS panel may provide the type of evidence necessary to conclude that the published safety data are generally accepted.

D. 2010 Report of the Government Accountability Office

From 2008 to 2010, the Government Accountability Office (GAO) conducted a study related to ingredients used in human food on the basis of the GRAS provision in section 201(s) of the FD&C Act. In 2010, GAO issued a report (Ref. 4; the GAO report) that included a number of recommendations for FDA. The GAO report recommended that FDA develop a strategy to minimize the potential for conflicts of interest, including issuing guidance for companies on conflict of interest, and we requested comment on issuing such a guidance in our reopening notice (75 FR 81536 at 81542). In the GRAS final rule, we stated our intent to issue such guidance (see Response 125, 81 FR 54960 at 55026). This guidance addresses conflict of interest as part of the best practices for convening a GRAS panel.

III. Key Ideas Relevant to Our Recommendations

As noted in the Introduction, among other things, this guidance document recommends best practices to reduce the risk that bias (or the appearance of bias) will affect the credibility of the GRAS panel's output (often called a "GRAS panel report"), including the assessment of potential GRAS panel members for conflict of interest and the appearance of conflict of interest. In developing these recommendations, we considered federal law, regulations, and FDA guidances, as well as published literature and conflict of interest policies from several organizations (e.g., the National Academies of Sciences, Engineering, and Medicine (NASEM) and the National Academy of Medicine (NAM); (see sections III.B through III.D)) that have developed policies to address topics such as bias, balance of expertise, procedures for organizing a scientific panel and managing its deliberations, conflict of interest, and the appearance of conflict of interest, for use by their own organizations (or the scientific community at large) during the conduct of scientific research. In this section, we summarize key ideas from these sources that are relevant to our recommendations.

A. Bias

Bias is a particular tendency, trend, inclination, feeling, or opinion, especially one that is preconceived or unreasoned (Ref. 5) and can operate either for or against an outcome that the sponsor of an investigation might view as the "preferred" outcome (Ref. 6). Bias can be created both by cognitive patterns (Ref. 7 and Ref. 8)[5] and by factors such as the potential for financial gain and can operate at both an individual level and a group level. Individuals may be more vulnerable to bias when they have competing interests (Ref. 9 and Ref. 10).

The credibility of an opinion from a panel of scientific experts can be undermined if one or more members is, or is perceived to be, biased. Although bias typically operates at a subconscious level and is difficult for external observers to identify or even for individuals to self-assess (Ref. 11, Appendix D), the risk of bias can be reduced if the organizer of a scientific panel of experts identifies and addresses sources of potential bias during the assembly and deliberations of the panel.

In sections III.B through III.D, this document discusses the following sources of potential bias that are particularly relevant for when a panel of scientific experts is being convened:

- Balance of expertise[6];
- Procedures for organizing a scientific panel and managing its deliberations; and
- Conflict of interest and an "appearance issue" (i.e., an interest or relationship that may create the appearance that an individual lacks impartiality on an issue).

B. Balance of Expertise

The significant omission of any required discipline or subdiscipline might seriously compromise the quality of the panel's analysis and judgments, even if the panel is composed of highly qualified individuals. NASEM issued a policy (the NASEM policy) (Ref. 12) emphasizing that the knowledge, experience, and perspectives of potential members of a committee convened by

[5] Examples of cognitive patterns that can create bias (Ref. 7 and Ref. 8) include:
- Availability bias (i.e., the tendency to assume that the most available evidence is the most relevant);
- Confirmation bias (i.e., the tendency to look for or interpret subsequent data to support an initial hypothesis);
- Order of effects bias (i.e., the tendency to overweigh or recall more about information received at the beginning and end of an exchange);
- Outcome bias (i.e., the tendency to interpret data in ways that support a more benign or preferred outcome);
- Posterior probability bias (i.e., the tendency to assume that a history of certain outcomes or causes can be extrapolated to the present assessment);
- Search "satisficing" (i.e., the tendency to stop gathering information once sufficient information has been gathered to form a hypothesis); and
- Redundancy bias (i.e., the tendency to accord more weight to data that is greater in quantity or volume).

[6] Members of a GRAS panel should have the appropriate scientific expertise in order to evaluate safety. This discussion is focused on the need for the panel to have a balance of expertise.

NASEM must be thoughtfully and carefully assessed and balanced in terms of the subtleties and complexities of the particular scientific, technical, and other issues to be addressed, and the functions to be performed by the committee. The NASEM policy points out that failure to include an appropriate discipline can compromise the quality of a panel's analysis and judgments, and that, even within a particular discipline, there may be important differences and distinctions within the field that require careful consideration in the committee composition and appointment process.

C. Procedures for Organizing a Scientific Panel and Managing Its Deliberations

Several organizations' policies and publications address sources of potential bias that could occur as a result of procedures for organizing small groups such as scientific expert panels and managing their deliberations (Ref. 11 through Ref. 19). NAM has issued a report (the NAM report) (Ref. 11) that discusses sources of potential bias in development of clinical practice guidelines.[7] The NAM report states that the adoption of explicit, systematic methods for reviewing evidence and developing and documenting practice guidelines is an important strategy for reducing the opportunities for bias, whether the source might be intellectual and professional preconceptions, financial interests, or something else. Immediately below, we describe some examples from published literature of how the composition and organization of a scientific expert panel, and procedures for managing its deliberations, could introduce potential bias into the panel's deliberations.

- Seniority or perceived status among panel members could influence the extent to which members are willing to volunteer information or raise objections (Ref. 13). Such effects on the composition of the panel have the potential to introduce bias in the kinds of data and information considered by the group.
- The leader (whether formal or informal) of a panel could shape the group's norms around evaluation of information and decision-making, moving the panel's focus either towards sharing and discussion of information or toward consensus (Ref. 14). Such influence has the potential to lead to bias in the kinds of information considered and the weight attached to various kinds of data. A consensus-focused norm can also discourage members from voicing dissenting opinions (Ref. 13).
- An effect called "illusory transactive memory" can occur when a group that does not hear any discussion of significant issues associated with a topic assigned to a particular member of the group later believes that they heard an actual discussion to the effect that there were no significant issues even though the group actually did not hear any discussion at all (Ref. 15). (In other words, the lack of discussion of a topic can translate in the mind to an affirmation that there are no issues related to that topic.) If a panel member does not share significant information identified in his or her discipline-specific review, other members of the panel could later "recall" that no significant information was found. This in turn has the potential to bias group assessments about the overall weight of the evidence.

[7] When NAM issued its report, the name of the organization was the "Institute of Medicine."

- The way in which information is presented to a panel could create bias. Framing the charge to the panel to emphasize potential risks or potential benefits has the potential to create bias toward particular avenues of reasoning or a particular decision (Ref. 16 and Ref. 17). Furthermore, the order in which information is presented to the panel has the potential to lead to bias in the importance it is assigned by participants (Ref. 18 and Ref. 19).

D. Conflict of Interest and Appearance Issues

1. Federal Regulations and FDA Guidances

As noted in the Introduction, this guidance includes recommendations for GRAS panels that are informed by federal law, regulations, and FDA guidance documents related to FDA advisory committee members. With respect to FDA advisory committees, we use the term "conflict of interest" when we are referring to a conflict of interest within the meaning of 5 CFR part 2640 and the term "appearance issue" when we are referring to an interest or relationship within the meaning of 5 CFR 2635.502 ("section 502"). A GRAS panel is not a federal advisory committee under the Federal Advisory Committee Act (FACA) (5 U.S.C. App.), and a GRAS panel and its members are not affiliated with the federal government. Therefore, our reference to these requirements and guidance, which generally do not apply to GRAS panels or GRAS panel members, is solely for the purpose of discussing concepts that are relevant to conflict of interest and appearance issues for GRAS panels.

FDA's advisory committees provide independent expert advice to us on scientific, technical, and policy matters related to the development and evaluation of FDA-regulated products. Although advisory committees provide recommendations to us, we make the final decisions. FDA's advisory committee process has some similarities to the GRAS panel process that is the subject of this document. For example, both processes consider scientific and technical matters and both processes provide information to a second party (FDA or the proponent) who uses the information to reach a decision. In addition, the credibility of the conclusions of an advisory committee or GRAS panel can be undermined when one or more members of the committee or panel has a conflict of interest or an appearance issue and, thus, both the FDA advisory committee process and the GRAS panel process can benefit from established, clear, transparent criteria for identifying and managing conflicts of interest and appearance issues. However, FDA's relationship to a GRAS panel is not equivalent to an FDA advisory committee. Instead, the GRAS panel organizer (together with the proponent, if these roles are distinct) stands in an analogous relationship to the panel as we do to an FDA advisory committee. Thus, any decisions regarding, for example, the design or application of waivers are the responsibility of the GRAS panel organizer or proponent.

The regulations and guidances applicable to participation in an FDA advisory committee are intended to provide transparency, clarity, and consistency for the advisory committee process and enhance public trust in the advisory committee process. The statutory and regulatory requirements for determining whether an advisory committee member (a special government employee; SGE) has a potential conflict of interest and whether participation in an advisory

committee meeting is appropriate are found in 18 U.S.C. 208(b), 21 U.S.C. 379d-1, and 5 CFR part 2640. Where such a conflict exists, these statutory and regulatory requirements permit us to grant a waiver allowing SGE participation in an advisory committee meeting when statutory criteria are met; for example, when the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved (5 CFR 2640.302). A draft guidance that we issued for public comment (Ref. 20; FDA's draft appearances guidance) will, when finalized, describe our process for evaluating whether an advisory committee member has potentially disqualifying interests or relationships that fall into the category of "appearance issues" under section 502 rather than financial interests that may create a recusal obligation under federal conflict of interest laws.

Regulations concerning the prohibition of conflicts of interest under 18 U.S.C. 208(a) explain that an employee (including an advisory committee SGE) may not participate in any "particular matter" [8] (5 CFR 2640.103(a)(1)) that would have a "direct and predictable effect" [9] (5 CFR 2640.103(a)(3)) on their interests. As explained in FDA's draft appearances guidance (Ref. 20), 5 CFR 2635.502 ("section 502") addresses interests or relationships that may create the appearance that an individual lacks impartiality on an issue. Section 502 implements the ethical principle that a government employee should be impartial in performing official duties, meaning that the employee must not give preferential treatment to any private organization or individual or use public office for private gain. To the extent that an individual's performance of official duties might appear to benefit the individual or certain other individuals close to the individual, the individual should take appropriate steps to avoid even an appearance of violating these ethical principles. Section 502 places the initial burden of identifying potential appearance issues on the potential advisory committee member,[10] who reports interests related to the subject matter of the meeting on Form FDA 3410 (Ref. 21). Form FDA 3410 asks for information about current and past financial interests that directly relate to the particular matter. Form FDA 3410 also asks for information about any other interests or relationships that might give rise to an appearance issue. The member may make a threshold judgment as to whether the information would cause a reasonable person to question his or her participation, and so inform FDA.

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[8] The term "particular matter" includes only matters that involve deliberation, decision, or action that is focused upon the interests of specific persons, or a discrete and identifiable class of persons. It does not cover consideration or adoption of broad policy options directed to the interests of a large and diverse group of persons such as actions that will affect all companies or the economy in general (5 CFR 2640.103(a)(1)).

[9] A particular matter will have a "direct" effect on a financial interest if there is a close causal link between any decision or action to be taken in the matter and any expected effect of the matter on the financial interest. An effect may be direct even though it does not occur immediately. A particular matter will not have a direct effect on a financial interest, however, if the chain of causation is attenuated or is contingent upon the occurrence of events that are speculative or that are independent of, and unrelated to, the matter. A particular matter that has an effect on a financial interest only as a consequence of its effects on the general economy does not have a direct effect for the purposes of this guidance. See 5 CFR 2640.103(a)(3)(i).
A particular matter will have a "predictable" effect if there is a real, as opposed to a speculative, possibility that the matter will affect the financial interest. It is not necessary, however, that the magnitude of the gain or loss be known, and the dollar amount of the gain or loss is immaterial. See 5 CFR 2640.103(a)(3)(ii).

[10] Advisory committee members are considered to be special government employees during their service.

Section 502 identifies "covered relationships"[11] and specific circumstances that may cause a reasonable person to question a member's impartiality.[12]

FDA has issued a guidance (Ref. 22; FDA's waiver guidance) that describes the basis for public disclosure of certain financial interests by SGEs and regular government employees participating in an advisory committee meeting and provides a format for FDA waivers allowing participation in these meetings. FDA's waiver guidance also explains how and when these documents will be made publicly available by FDA.

While the FDA advisory committee process has some similarities to the GRAS panel process, there are some important differences. One difference is that the statutes and regulations applicable to FDA's advisory committee process expressly provide for circumstances in which FDA may grant a waiver that would allow an individual to participate in an advisory committee meeting, in either a voting or non-voting capacity, even though the individual has a conflict of interest (18 U.S.C. 208(b)(3), 5 CFR 2640.302, 21 CFR 14.80). FDA discloses such waivers as part of the record of the advisory committee process (Ref. 22). In contrast, if a proponent allows an individual to participate in a GRAS panel, in either a voting or non-voting capacity, even though the individual has a conflict of interest, there generally would not be a public process (such as a public meeting) whereby the proponent could disclose the conflict and the reasons for waiver; the lack of a public process to make a "waived" conflict of interest transparent presents a challenge to the proponent of the substance for waiving a conflict of interest or an appearance issue without undermining the credibility of the GRAS panel's opinion.

Another difference is that the primary function of the GRAS panel from FDA's perspective is to reflect the views of the broader scientific community, rather than to reach a scientific judgement on specific data and information. FDA's advisory committees often provide advice to FDA in cases where data are incomplete, contradictory, or preliminary, and we are seeking input on a decision or path forward in the face of these challenges. A GRAS conclusion, on the other hand, is meant to be based on publicly available safety data that are generally accepted by experts. The function of a GRAS panel is bound up with the extent to which it appears likely that most other scientists with similar training would reach a similar judgement. This is distinct from providing advice to FDA on an unresolved scientific issue to inform our decisions, as well as from the question of whether a scientific judgement is defensible or consistent with the available data.

[11] Examples of "covered relationships" include those with persons in the member's household and with persons in certain business relationships.

[12] Examples include where the particular matter coming before the advisory committee is likely to have a "direct and predictable effect" on the current financial interest of a member of the advisory committee member's household, and where a person (or entity) with whom the advisory committee member has a "covered relationship" is or represents a "party to the matter" coming before the advisory committee. Section 502 includes examples of "covered relationship" (e.g., a person or entity for which the member has, within the last year, served as an employee, officer, director, consultant, agent, attorney, trustee, contractor, or general partner) and "party to the matter" (in most cases, any sponsor of the product(s) coming before the advisory committee).

2. Policies and Literature Regarding Conflict of Interest and Appearance Issues

Several organizations' policies and literature address conflict of interest and appearance issues, and we have summarized them below.

a. The NASEM Policy

The NASEM policy explains that the FACA includes certain specific requirements regarding work performed by NASEM for the U.S. government, including certain requirements relating to committee composition and balance and conflict of interest. The NASEM policy emphasizes that conclusions by fully competent committees can be undermined by allegations of conflict of interest or lack of balance and objectivity.

The NASEM policy addresses both conflict of interest and appearance issues. The NASEM policy uses the term "conflict of interest" to mean any financial or other interest which conflicts with the service of the individual because it could: (1) significantly impair the individual's objectivity; or (2) create an unfair competitive advantage for any person or organization. Except for those situations in which the institution determines that a conflict of interest is unavoidable and promptly and publicly discloses the conflict of interest, no individual can be appointed to serve (or continue to serve) on a committee of the institution used in the development of reports if the individual has a conflict of interest that is relevant to the functions to be performed. The NASEM policy considers that appearance issues (which the NASEM policy discusses as questions of lack of objectivity and bias) ordinarily relate to views stated or positions taken that are largely intellectually motivated or that arise from the close identification or association of an individual with a particular point of view or the positions or perspectives of a particular group. Sources of potential bias in the context of appearance issues are not necessarily disqualifying for purposes of committee service. The existence of a possible bias would be a factor to be taken into account in the overall composition of the committee. However, the NASEM policy notes that some appearance issues may be so substantial that they preclude committee service (e.g., where one is totally committed to a particular point of view and unwilling, or reasonably perceived to be unwilling, to consider other perspectives or relevant evidence to the contrary).

b. The NAM Report

In 2007, NAM appointed the Committee on Conflict of Interest in Medical Research, Education, and Practice to examine conflicts of interest in medicine and to recommend steps to identify, limit, and manage conflicts of interest without negatively affecting constructive collaborations. The NAM report defines conflict of interest as "a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest" (Ref. 11). The committee stated that financial interests are the most readily identified and regulated and also noted that a financial interest does not have to be great for the influence to be undue, citing social science research on the effects of small gifts, particularly in the context of a sustained relationship. The committee acknowledged that other secondary interests may also influence professional decisions, including professional advancement, personal achievement, and favors to friends, family, and colleagues. The committee noted that conflicts are not binary, and proposed criteria for assessing both the likelihood of undue

influence as well as the seriousness of the harm that could result. The committee also proposed criteria for evaluating conflict of interest policies, including proportionality, transparency, accountability, and fairness. The committee discussed the role of disclosure in such policies, viewing it as a necessary but insufficient element and recommending that disclosures be sufficiently specific and comprehensive (with no minimum dollar threshold) to allow others to assess the severity of the conflict.

In addition to general principles and recommendations, the NAM report discusses conflicts of interest in a number of different areas, including the development of clinical practice guidelines. The NAM report recommends that groups developing such guidelines:

- Appoint a chair without a conflict of interest;
- Limit members with conflicting interests to a distinct minority of the panel; and
- Publicly disclose relevant conflicts of interest.

c. Other Published Reports

A report (Ref. 23) by a joint task force of the American College of Cardiology Foundation and the American Heart Association discusses codes of conduct in human subjects' research, including both financial and non-financial conflicts of interest. The report notes that many non-financial incentives exist and are well recognized within the academic community.

A systematic review (Ref. 24) of conflict of interest in the development of clinical practice guidelines defines such conflicts in accordance with the 2009 NAM report (primary versus secondary interests); states that such conflicts are an important potential source of bias in guideline development; and notes that the secondary interest in such conflicts may be financial or non-financial. The authors observe that intellectual interests are increasingly recognized and may be powerful motivators for researchers, systematic reviewers, and guideline authors.

A report (Ref. 25) by members of the American College of Chest Physicians involved in development of clinical practice guidelines recommends placing equal emphasis on both financial and intellectual conflicts of interest. The report defines intellectual conflicts as academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual's judgment about a specific recommendation. Such activities include receipt of a grant or participation in research or commentary directly related to that recommendation.

The National Comprehensive Cancer Network (Ref. 26) considers conflicts of interest, or the appearance of such conflicts, as a source of potential bias in the development of treatment guidelines that could compromise or diminish the integrity of such guidelines. Conflicts encompass financial interests as well as organizational affiliations, activities, or other interests that could impair objectivity or create an unfair competitive advantage. Recommendations and practices include the following, with additional restrictions on the interests and activities of chairs and vice-chairs:

- Public disclosure of all conflicts by guideline development panel members;
- Exclusion of potential members with financial conflicts above a threshold;
- Recusal of members from specific matters as warranted; and
- Removal of members if no longer able to serve effectively due to the number of recusals.

IV. Definitions

For purposes of this document, we define the following terms below.

Ad hoc GRAS panel – A GRAS panel that is convened on a temporary basis.

Appearance issue – An interest or relationship that may create the appearance that an individual lacks impartiality on an issue (see 5 CFR 2635.502 for guidance on the process used by federal agencies for analyzing and resolving appearance issues). Whereas conflicts of interest include financial interests that can be directly and predictably affected by the work of the GRAS panel, appearance issues include a broader and more complex set of interests and relationships that could cause a reasonable person to question impartiality.

Conclusion of GRAS status/GRAS conclusion – A conclusion that a substance is GRAS under the conditions of its intended use.

GRAS – Generally recognized as safe.

GRAS panel – A panel[13] of qualified experts who independently evaluate whether the available scientific data, information, and methods establish that a substance is safe under the conditions of its intended use in human food or animal food as part of an evaluation of whether adding that substance to food is lawful under the GRAS provision of the FD&C Act. The panel may be convened for evaluation of a single ingredient (ad hoc panel) or for longer periods of time to evaluate multiple substances (standing panel).

Notifier – The person (e.g., an individual, partnership, corporation, association, or other legal entity) who is responsible for a GRAS notice submitted to FDA, even if another person (such as an attorney, agent, or qualified expert) prepares or submits the notice or provides an opinion about the basis for a conclusion of GRAS status.

Organizer – The party (such as a proponent, an employee of the proponent, or an attorney or agent who acts on behalf of a proponent) who assembles a GRAS panel.

Proponent – The party who takes responsibility for a conclusion of GRAS status.

[13] A panel is "[a] group of persons selected for some service (such as investigation or arbitration)." Merriam-Webster.com. Accessed on October 31, 2019.

Qualified expert – An individual who is qualified by scientific training and experience to evaluate the safety of substances under the conditions of their intended use in food.

Standing GRAS panel – A GRAS panel that is convened on a permanent (or extended) basis.

Written GRAS panel policy – A written policy to govern procedures for assembling and managing a GRAS panel, including an assessment of the potential for bias created by a conflict of interest or an appearance issue in an individual under consideration for selection as a member of a GRAS panel and including strategies for managing conflicts and appearance issues.

V. Recommendations

A. Introduction

Convening a GRAS panel and relying on the GRAS panel as a representative sample of the larger scientific community knowledgeable about the safety of substances directly or indirectly added to food is one mechanism that proponents have used to support their conclusion that the safety of a substance under the conditions of its intended use in human food or animal food is generally recognized. However, the use of a GRAS panel is not the only mechanism for doing so, and the use of a GRAS panel does not necessarily mean that the GRAS criteria have been met. As discussed in section II.A, we have established criteria for eligibility for classification as GRAS in 21 CFR 170.30 and 21 CFR 570.30 for substances intended for use in human food and animal food, respectively. A GRAS panel is not a required element of these criteria.

In the remainder of the recommendations section of this guidance, we discuss detailed recommendations related to selecting GRAS panel members, the operation of a GRAS panel, submitting a GRAS notice to FDA, and other recommendations as summarized immediately below. As noted previously, a GRAS panel is just one mechanism that proponents have used to demonstrate that the safety of a substance under the conditions of its intended use is generally accepted by qualified experts. It may be worth considering whether the effort to convene a GRAS panel is warranted in any particular case before allocating resources to it.

1. Recommendations Related to Selecting GRAS Panel Members

To convene a GRAS panel that can effectively evaluate the available scientific data, information, and methods and act as a representative sample with respect to the larger scientific community of qualified experts, and to reduce the risk that bias (or the appearance of bias) will affect the credibility of the GRAS panel report, as discussed in more detail in sections V.B through V.D, we recommend that the organizer (whether it be a proponent who has identified a need for a GRAS panel or a third party in the business of convening such panels) establish and implement a written GRAS panel policy[14] that includes general principles and procedures for:

[14] A proponent who intends to convene the panel themselves and does not expect to convene further panels in the foreseeable future could also consider documenting the ways in which they identified and managed sources of potential bias described in this guidance as part of their documentation of the overall GRAS conclusion.

- Assessing and balancing the knowledge, experience, and perspectives of potential GRAS panel members in terms of the subtleties and complexities of the particular scientific and technical issues applicable to a food substance and its intended use in human food or animal food;

- Considering and taking steps to address procedural issues associated with the organization and deliberations of the GRAS panel;

- Considering and taking steps to assess potential GRAS panel members for conflicts of interest and appearance issues;

- Documenting how the organizer applied the written GRAS panel policy to the selection and vetting of each member of the GRAS panel; and

- Taking steps to provide transparency and clarity regarding the selection and vetting of each member of the GRAS panel.

2. Recommendations Related to the Operation of the GRAS Panel and to the Submission of a Notice to FDA

As discussed in section II.B, we have established a GRAS notification procedure (in 21 CFR part 170, subpart E and part 570, subpart E for substances intended for use in human food and animal food, respectively) through which any interested person may notify us of a conclusion that a substance is GRAS under the conditions of its intended use in food. Our experience with GRAS notices in which the person who submitted the GRAS notice ("notifier") reported the findings of a GRAS panel, as well as comments we received during the rulemaking to establish the GRAS notification procedure,[15] have informed the recommendations in sections V.E through V.H for:

- The information that the proponent of a GRAS conclusion would provide to the GRAS panel;

- Documenting the deliberations and output of a GRAS panel;

- Considerations when a GRAS notice is submitted to FDA; and

- Considerations when a GRAS notice is not submitted to FDA.

3. Other Recommendations

- In section V.I, we provide our recommendations regarding honoraria provided to a GRAS panel.

[15] See, e.g., the discussion in section I.E of the GRAS final rule and Comment/Response 8, 11 through 13, 58, 69, and 78 in the GRAS final rule (81 FR 54960).

We received fewer than a dozen GRAS notices where the statutory basis for the notifier's conclusion of GRAS status was through experience based on common use in food (Ref. 27). Therefore, in this guidance, we focus on best practices applicable to a GRAS panel that is convened when the statutory basis for the proponent's conclusion of GRAS status is through scientific procedures.

B. Appropriate and Balanced Expertise in a GRAS Panel

1. General Considerations When Convening a GRAS Panel

We recommend that the organizer, the proponent's attorney or agent, or employees of the proponent, organizer, or the proponent's attorney or agent not be members of a GRAS panel, because such individuals generally would have a conflict of interest due to a direct and predictable financial interest in the outcome of the panel's deliberations (see the examples of conflict of interest in Table 3). However, if such an individual has specialized experience that could be helpful to a GRAS panel, the proponent or organizer could consider whether that individual could act as a scientific advisor to the GRAS panel by providing factual information to the GRAS panel without participating in any of the GRAS panel's deliberations. Alternatively, the proponent or organizer could consider having that individual participate in deliberations of the GRAS panel without providing an opinion that would be included in any report generated by the GRAS panel; such participation would be analogous to "non-voting members" who are granted a waiver per 5 CFR part 2640 when necessary to afford essential expertise to an FDA advisory committee. The potential value of such an individual's participation, even in an advisory or non-voting capacity, should be carefully weighed against the introduction of another significant source of potential bias, which could reduce the credibility of the GRAS panel as a representative sample with respect to the views of the broader expert community.

2. Appropriate Expertise in a GRAS Panel

We recommend that the organizer consider individuals with expertise that reflects the physical, chemical, and biological properties of the food substance and the scientific questions that arise in relation to the conditions of its intended use. At a minimum, we recommend that a GRAS panel include members with expertise suitable to establish the identity and properties of the ingredient (e.g., chemistry, biochemistry, protein chemistry, or microbiology) as well as expertise in toxicology and exposure assessment, because our experience with GRAS notices demonstrates that these scientific disciplines broadly apply to most safety evaluations. For substances intended for use in animal food, a GRAS panel should include members with expertise suitable to establish the identity and properties of the ingredient (e.g., chemistry, biochemistry, protein chemistry, or microbiology), expertise in toxicology and exposure assessment, as well as expertise suitable to evaluate the safety of the substance under the conditions of its intended use for the target animal(s) and, when added to food for food-producing animals, for humans consuming human food(s) derived from these animals. While one individual may have expertise in multiple areas, it may be difficult for a single individual to represent the broader views of multiple scientific disciplines credibly. See Table 2 for examples of additional recommended

expertise on a GRAS panel based on the food substance and/or the conditions of its intended use. Note that in cases where specialized expertise is appropriate, it is generally supplemental and complementary to the core disciplines identified above. Not every GRAS panel member need be versed in food ingredient safety assessment, as long as they are in dialogue with other members who are.

Table 2.—Examples of Recommended Expertise on a GRAS Panel Based on the Food Substance or the Conditions of its Intended Use

Food Substance or Conditions of its Intended Use	Recommended Expertise
Enzyme produced from a microorganism	Microbiology; enzymology
Botanically-derived substance	Plant chemistry
Substance that could have allergenic properties	Allergy
Use in infant formula	Pediatric nutrition
Substance that has a specific physiologic effect	Expertise to address the long-term significance of the physiological effect in the general population or in relevant subpopulations
Complex ingredient, or ingredient defined partly by its method of manufacture	Chemistry; food manufacturing; food processing
Microbial ingredient	Microbiology; immunology
Substance intended to supply a nutrient	Nutrition
Substance intended for a technical effect (e.g., emulsifier, binder)	Chemistry; food manufacturing; food processing

In some cases, the substance is already used in food but, for example, there has been a significant change in the manufacturing process; there would be an increased level of the substance compared to the levels already in use; or the intended use of the substance would be different from existing uses. As noted elsewhere in this document, in many cases, the process whereby the proponent evaluates whether the available data and information support a conclusion that a substance is GRAS under the conditions of its intended use need not include a GRAS panel. However, if a proponent decides to convene a GRAS panel in such circumstances, the emphasis in selecting members of a GRAS panel should be on the expertise necessary to assess the change. For example, if there has been a significant change in the manufacturing process, a chemist, biochemist, or food technologist should evaluate the potential for toxic contaminants or impurities associated with the new process, and a toxicologist or other scientist with expertise applicable to the nature of those contaminants or impurities should evaluate the safety of the substance produced using the new manufacturing process. For increased use levels, the key expertise would be toxicology or a related scientific discipline to evaluate whether the available data and information support the safety of an increased exposure to the substance. If the intended use of the substance would be significantly different from existing uses, an individual with expertise in exposure assessment should evaluate the new estimated dietary exposure and one or more individuals with expertise in the potential toxicological or physiological effects of the substance under the new conditions of use should evaluate whether the available data and information support the safety of the substance under the new conditions of use. In the case of a substance intended for use in animal food, for example, if the intended use of the substance would be for different animal species, an individual with expertise in assessing safety for the target animal, and potentially for human food(s) derived from the target animal, should evaluate

animal and human exposures and possible toxicological and physiological effects of the substance under the new conditions of use.

To optimize the applicable experience of the GRAS panel members, we recommend that an organizer who convenes a GRAS panel convene an ad hoc GRAS panel rather than a standing GRAS panel. However, a standing GRAS panel could be appropriate when considering a class of substances closely related by conditions of use, function, or other properties, where the experience and expertise of the panel members align with the scientific questions applicable to that class of substances, or if a standing GRAS panel is supplemented with members with additional expertise to address the physical, chemical, and biological properties of a specific food substance and the complexity of the scientific questions that arise in relation to the conditions of its intended use. One issue with standing GRAS panels is the potential for development of a particular group perspective over time,[16] which may reduce the ability to credibly represent the views of the broader scientific community. The organizer of such a panel may wish to consider strategies for occasionally calibrating or cross-checking the panel's perspective to ensure it remains representative.

3. Number of Members of a GRAS Panel

We recommend that the organizer determine the total number of GRAS panel members, as well as the number of GRAS panel members with the same expertise, based on the substance, the complexity of the scientific issues associated with the conditions of its intended use, and the available data and information about the substance. As noted above, when the evidence for safety comprises published peer-reviewed scientific literature consistent with generally accepted safety assessment strategies, a GRAS panel of any size may be unnecessary. However, when the available data and information relevant to the intended conditions of use of the substance involve complex scientific issues that experts would need to interpret and resolve, we recommend that the organizer consider having multiple representatives with expertise applicable to those scientific issues so that there can be genuine discussion and critical analysis on those complex scientific issues.

From FDA's perspective, the goal of a GRAS panel, unlike a federal advisory committee, is to provide some evidence of the generally accepted view in one or more scientific disciplines regarding the underlying publicly available safety data. Diverse scientific views can be extremely valuable in testing the robustness of a potential scientific acceptance, and we encourage panel organizers to consider taking advantage of diverse scientific viewpoints to enhance the credibility of the panel as a representative sample of the broader community. However, the GRAS panel's function is to adequately represent a scientific community of qualified scientific experts rather than society as a whole, and we do not anticipate or recommend that GRAS panel members participate as representatives of a specific societal sector.

Importantly, although general recognition of safety does not require unanimous agreement, general recognition of safety does not exist if there is a genuine dispute among qualified experts

[16] This can also be an issue if ad hoc GRAS panels are repeatedly populated from a small pool of individuals.

that the use of a substance is safe (See, e.g., *United States v. Articles of Drug Consisting of Following: 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)) or a severe conflict among experts regarding the safety of the use of a substance (*United States v. An Article of Drug 4,680 Pails*, 725 F.2d 976, 990 (1st Cir. 1984); *Premo Pharmaceutical Laboratories v. United States*, 629 F.2d 795, 803 (2d Cir. 1980)). Thus, when generally available data and information document a genuine dispute, or severe conflict, in the larger scientific community, a GRAS panel report could not provide evidence that the available data and information are "generally accepted" even if multiple members of a GRAS panel have expertise in a particular scientific discipline. Instead, the GRAS panel report would more appropriately be a resource for the proponent to use in identifying data gaps and information about ongoing scientific debate and dispute.

C. Assessment and Management of Procedural Issues Associated with the Organization and Deliberations of a GRAS Panel

We recommend that a written GRAS panel policy address the potential for bias that could occur through procedures associated with the organization and deliberations of a GRAS panel by:

- Establishing clear roles and responsibilities for each member of the GRAS panel;
- Establishing clear decision-making procedures that the GRAS panel will follow;
- Specifying whether the charge to the GRAS panel will inform the members of the GRAS panel about the potential for bias (e.g., due to cognitive patterns); and
- Considering factors such as seniority or perceived status among panel members and the leadership skills of an individual who would be the formal leader of the GRAS panel (or likely to become the informal leader if the organizer does not appoint a formal leader).

We also recommend that the proponent take appropriate steps to avoid influencing the deliberations of the GRAS panel – e.g., by formulating the charge to the panel in neutral, unbiased language; limiting communication with the GRAS panel to the minimum necessary to manage the affairs of the GRAS panel efficiently and effectively; and then awaiting the outcome.

D. Assessment and Management of Conflict of Interest and Appearance Issues of Potential GRAS Panel Members

1. Overview

We recommend that a written GRAS panel policy address the potential for conflict of interest and appearance issues during the selection and vetting of GRAS panel members. We also recommend that a written GRAS panel policy be publicly available and provide for transparency by allowing outside parties to assess the process used to assess and manage conflicts of interest

and appearance issues in members of the GRAS panel. We discuss in more detail our recommendations for a written GRAS panel policy to address the following factors:

- The process for identifying conflicts of interest and appearance issues;
- Criteria for evaluating identified conflicts of interest and appearance issues, including criteria for automatic or routine exclusion from panel membership, and strategies for managing conflicts of interest and appearance issues; and
- Documentation of conflicts of interest, appearance issues, and rationales for waivers.

2. Identifying Conflict of Interest and Appearance Issues

We recommend that a written GRAS panel policy include a process for identifying competing interests, including conflicts of interest and appearance issues. For the purposes of this document, conflicts of interest include financial interests that can be directly and predictably affected by the work of the GRAS panel, whereas appearance issues include a broader and more complex set of interests and relationships that could cause a reasonable person to question impartiality. See Table 3 for examples of sources of conflict of interest. See Table 4 for examples of appearance issues.[17] In our view, both sources of potential bias (conflict of interest and appearance issues) have similar significance with respect to a GRAS panel's core function of providing evidence of community views, as described in III.D.1. From FDA's perspective, the primary function of the GRAS panel is to reflect the views of the broader scientific community, rather than to reach a scientific judgement on specific data and information. A GRAS conclusion is meant to be based on publicly available safety data which are generally accepted by experts. Therefore, the function of a GRAS panel is bound up with the extent to which it appears likely that most other scientists with similar training would reach a similar judgement. This is distinct from the question of whether a scientific judgement is defensible or consistent with the available data. See section II.C.2.

Table 3.—Examples of Conflict of Interest

Source of Conflict of Interest
Ownership of any equity of an affected entity (excluding equity held through a publicly traded diversified (i.e., non-food sector specific) mutual fund)
Compensation for services, such as management or consulting services to an affected entity (excluding honoraria for service on the GRAS panel; see section V.I for recommendations regarding honoraria)
A role as director, officer, trustee, general partner, or employee of an affected entity (including trade and professional associations)

[17] Examples in both tables are drawn from 18 U.S.C. 208, 5 CFR parts 2635 and 2640, and FDA's guidance on advisory committees (Ref. 20 and Ref. 22), as well as from our review of the NAM report (Ref. 11), the NASEM policy (Ref. 12), the codes of conduct for the American College of Cardiology Foundation and the American Heart Association (Ref. 23), and a sample draft guidance submitted to the public docket for FDA's rulemaking to establish the GRAS notification procedure (Ref. 28). As noted in section III.D, our recommendations are informed by federal law, regulations, and FDA guidance documents related to advisory committee members and our reference to these requirements and guidance is solely for the purpose of discussing concepts that are relevant to conflict of interest issues for GRAS panels.

Source of Conflict of Interest
Funding for research purposes from an affected entity, regardless of whether there is post-grant oversight
A debt relationship of any kind with an affected entity, whether as lender, borrower, holder of debentures, or the like
Any of the above examples with respect to a spouse, minor child, general partner, or prospective employer

Table 4.—Examples of Appearance Issues

Direct and predictable effect on the current financial interest of a household member, including adult children and parents, as well non-relatives in residence
Having or seeking a business, contractual, or other financial relationship with an affected entity
Having a household member, or relative with a close personal relationship who is an affected entity
Serving in the last year as an employee, officer, director, consultant, agent, attorney, trustee, contractor, or general partner for an affected entity
Having a spouse, parent, or dependent child who currently serves or is seeking to serve as an employee, officer, director, consultant, contractor, agent, attorney, trustee, or general partner of an affected entity
Being an active participant in an organization that is an affected entity
Consistently and strongly advocating specific views or positions on a scientific issue relevant to safety assessment
Having one's own work as a key element of the relevant evidence for safety of the substance under the conditions of its intended use

3. Criteria for Evaluating Identified Conflicts of Interest and Appearance Issues and Strategies for Managing Identified Conflicts of Interest and Appearance Issues

We recommend that a written GRAS panel policy establish pre-existing criteria for evaluating the significance of conflicts of interest and appearance issues. Conflicts of interest are ordinarily financial. Some policy frameworks, including FDA guidance (Ref. 22) discussed above, as well as other policies from certain organizations (Ref. 26), ordinarily exclude members with significant financial conflicts of interest from a committee or panel. These frameworks assess the significance of a conflict in terms of the dollar value, although other factors such as the duration of the interest or value relative to overall assets could also be considered. Appearance issues, on the other hand, are often more complex and less clear-cut and may not be amenable to quantification in the same way. Factors that could potentially be considered in assessing the significance of an appearance issue include:

- The nature of a relationship of interest, including history and current status of the relationship;
- The effect that a particular conclusion would have upon the financial interests of a person involved in a relationship of interest;
- The extent to which a person has committed to or is associated with a particular point of view on a matter relevant to the decision; and
- The degree to which research conducted by the person bears on the specific questions before the GRAS panel.

We recommend that a written GRAS panel policy include strategies for managing conflicts and appearance issues. These strategies could include:

- Establishing pre-existing criteria for excluding an individual from service on a GRAS panel based on a conflict of interest or appearance issue of sufficient significance, such as those listed in Table 3 and Table 4;[18]

- Establishing pre-existing criteria for waiving an exclusion triggered by a conflict of interest or appearance issue;

- Including "balancing" viewpoints on a particular issue where one or more members is strongly associated with a particular viewpoint;

- Disclosing conflicts of interest and appearance issues to all panel members to allow them to weigh this information in their assessment of the perspectives and contributions of various panel members; and

- Including some panel members who have a conflict of interest or an appearance issue as non-voting members who can still contribute to deliberations, albeit in an advisory capacity only.

Waivers and monetary thresholds for acceptable conflicts are two commonly used strategies in assembling expert panels. We are not recommending specific criteria for administering waivers or defining specific monetary thresholds, in part because, unlike a federal advisory committee, GRAS panels are not organized by and do not report to FDA. These decisions are the GRAS panel organizer's responsibility, and we recommend that each organizer clearly document their rationale for whatever waiver or threshold criteria they establish.

We realize that it can be challenging to identify, screen, and select a comprehensive panel of qualified experts in light of the need for specialized expertise applicable to the scientific considerations associated with the intended conditions of use of a food substance and the finite number of experts who are both qualified and available to serve on a GRAS panel. There may be circumstances in which the need for the individual's services outweighs the potential for a conflict of interest or appearance issue in order to provide the GRAS panel essential expertise.[19] For this and other reasons it may be useful to prepare strategies of the types discussed above. However, it is also important to remember that a GRAS panel is just one mechanism that can be used to provide evidence of general acceptance, and in many cases a panel may not be necessary. In the limited number of cases where there are alternative interpretations of the available data and the proponent seeks the type of evidence of general acceptance that a GRAS panel could provide, successful management of sources of potential bias associated with the panel becomes a

[18] As discussed in section V.I., FDA recognizes that GRAS panel members are generally compensated for their time; we are not suggesting that such compensation represents an unacceptable conflict of interest, provided that the compensation is independent of the outcome.

[19] See, e.g., the discussion in FDA's draft appearances guidance (Ref. 21) regarding the criteria for granting a section 502 authorization enabling participation of a Special Government Employee in an FDA advisory committee.

pressing concern. In such cases, it may be necessary to find ways to address the challenges acknowledged above.

4. Documentation of Conflicts of Interest, Appearance Issues, and Rationales for Waivers

We recommend that a written GRAS panel policy describe how to document that the process used for identifying and managing conflicts of interest and appearance issues was implemented in the case of a particular GRAS panel. We also recommend that the policy address documentation of all conflicts of interest and appearance issues identified in the process of forming a GRAS panel and how these issues were managed, whether through waivers or some other method. This may include a discussion of the rationale for each waiver, along with the views of the organizer or proponent on the net effect of each conflict or appearance issue on the ability of the panel to serve as a credible representative sample of the larger scientific community. As noted elsewhere in this guidance, from FDA's perspective, a key criterion for evaluating a GRAS panel's conclusion is whether qualified scientists with similar training and experience would likely reach the same conclusion. This documentation may help in the interpretation of the significance and strength of a GRAS panel conclusion where the type of evidence of general acceptance that a panel could provide is necessary to support the common knowledge element of a GRAS conclusion.

5. Format of a Written GRAS Panel Policy

The format of a written GRAS panel policy should promote clarity and transparency. For example, the policy could be structured as a series of individual questions followed by a chart that organizes the flow of the individual questions.

E. Information Provided to a GRAS Panel

As noted in section V.A, in this guidance, we focus on best practices applicable to a GRAS panel that is convened when the statutory basis for the proponent's conclusion of GRAS status is through scientific procedures. When a conclusion of GRAS status is through scientific procedures, general recognition of safety is 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 (21 CFR 170.30(b) and 570.30(b)).

Although general recognition of safety through scientific procedures may be corroborated by the application of unpublished scientific data, information, or methods, to satisfy GRAS criteria qualified experts need to be able to conclude that the substance is not harmful under the conditions of its intended use without access to "corroborative" information (81 FR 54960 at 54973). 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 notified substance is safe under the conditions of its intended use (81 FR 54960 at 55000). Therefore, we recommend that the organizer minimize the amount of non-

public information provided to a GRAS panel because access to unpublished or restricted information can make it more difficult to credibly identify what outcome the GRAS panel would have reached without that information. In cases where a proponent has identified a need for a GRAS panel, the proponent should carefully consider the value that the GRAS panel's exposure to confidential information would bring relative to the potential for reducing confidence that the GRAS panel's conclusion reflects general acceptance of public data.

An exception relates to data and information that could raise a question about the safety of the substance under the conditions of its intended use. We recommend that the data and information that the organizer provides to a GRAS panel include a description of all data and information that could raise such a safety question, regardless of whether those data and information are publicly available. Doing so is appropriate to make the data and information provided to the GRAS panel complete, representative, and balanced and would be consistent with the requirements we have established for a GRAS notice (see 21 CFR 170.250(c) and 570.250(c)).

In some cases, the proponent chooses to make the opinion of a GRAS panel public – e.g., by publishing the GRAS panel opinion in the peer reviewed scientific literature. Whether a published GRAS panel opinion that discusses data and information that are not generally available could support an independent GRAS conclusion would depend on factors such as whether the published opinion includes details similar to details that would be included in a publication in the primary scientific literature; 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 (81 FR 54960 at 54966).

F. Documenting the Deliberations and Conclusions of a GRAS Panel

The organizer should consider how to document the deliberations and conclusions of a GRAS panel. We recommend clear and explicit documentation of: (1) the available data and information that the GRAS panel reviewed; (2) how the GRAS panel handled its deliberations; and (3) the basis for the conclusion of the GRAS panel.

As noted in section I of this document, when the members of a GRAS panel agree that the generally available data and information demonstrate that a substance is safe under the conditions of its intended use, the members of the GRAS panel are serving as a representative sample of the larger scientific community knowledgeable about the safety of substances directly or indirectly added to food. Therefore, the deliberations and GRAS panel report should address this threshold question of whether the panel members agree that the generally available data and information demonstrate that substance would be safe under the conditions of its intended use rather than the subsequent question of whether the substance would be GRAS under the conditions of its intended use. It is the proponent's responsibility to subsequently draw a conclusion on whether the intended conditions of use of the substance satisfy the criteria for eligibility for classification as GRAS.

We recommend that each member of the GRAS panel identify the particular data or information that form the basis for his or her opinion on whether the intended use of the substance is safe, both during deliberations and in any written GRAS panel report. We also recommend that GRAS panel members avoid filling a gap in the available data and information through theoretical considerations and prior relevant experience – e.g., making overly broad inferences (in the absence of data) about safety of the substance in question based on the properties of other substances that are related in some way, or based on professional familiarity with a particular class of substances. From a procedural perspective, this approach is a significant source of potential bias. Members of the GRAS panel should limit the role of theoretical considerations and prior relevant experience to determining which of the available data and information are relevant to the safety of the substance under the conditions of its intended use. However, this recommendation is not meant to discourage the use of well-established, rigorous methods of extrapolation, such as read-across practices and quantitative structure-activity relationships (see Ref. 29, Ref. 30).

As discussed in section I of this document, the proponent may be relying on the deliberations and report of a GRAS panel to serve as a representative sample of the larger scientific community knowledgeable about the safety of substances directly or indirectly added to food. Therefore, we recommend that the organizer establish and implement a mechanism to demonstrate that the deliberations of a GRAS panel and any GRAS panel report broadly reflect the views of the scientific community knowledgeable about the safety of substances directly or indirectly added to food in addition to the individual views of each panel member. For example, each panel member could identify the basis for concluding that his or her view is representative of the views held by most scientists in the respective discipline.

G. Considerations When a GRAS Notice is Submitted to FDA

Any person who submits a GRAS notice to FDA must include a signed statement certifying that to the best of the notifier's knowledge, the GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to the notifier and pertinent to the evaluation of the safety and GRAS status of the intended use of the substance (21 CFR 170.225(c)(9) and 570.225(c)(9)). The certification statement is intended, in part, to emphasize the notifier's 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 (81 FR 54960 at 54994). Thus, as already noted in section V.E, we recommend that the data and information that organizer provides to a GRAS panel include a description of all 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 publicly available.

The certification statement also is intended, in part, to communicate our expectation that a notifier would describe, and place in context, unpublished data and information if the notifier considers that the findings of the unpublished data and information warrant sharing with a GRAS panel (81 FR 54960 at 54994). Although we recommend that the organizer minimize the amount of non-public information provided to a GRAS panel (see the discussion in section V.E), a

notifier who does provide non-public information to a GRAS panel should describe, and place in context, those unpublished data and information in any GRAS notice that mentions the findings of a GRAS panel. This includes, for example, studies that the notifier considers corroborative of safety (81 FR 54960 at 55994) as well as any trade secret information regarding the method of manufacture (81 FR 54960 at 55000).

Any person who submits a GRAS notice must include a narrative that explains how the generally available data and information that the notifier relies on to establish safety provide a basis for the notifier's 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 570.250). For non-public, safety-related data and information considered in reaching a conclusion of GRAS status, the notifier must explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to such data and information. If non-public information is provided to a GRAS panel, the notifier would be required to explain how there could be a basis for a conclusion of GRAS status if qualified experts (other than those on the GRAS panel) do not have access to such data and information (21 CFR 170.250(e) and 570.250(e)). As noted above, exposure to non-public data and information can sometimes make it much harder to credibly assert that the panel's conclusion is representative of the expert scientific community based on public data.

In our view, most GRAS conclusions do not need a GRAS panel (81 FR 54960 at 55026). However, in some cases, we might recommend consulting with us on whether a GRAS panel could be useful in generating evidence of general acceptance (see Figure 1). Where a panel's deliberations constitute primary evidence supporting the general acceptance aspect of the GRAS criteria for the intended use, FDA would be unable to evaluate this evidence and the significance of the GRAS conclusion unless the composition, deliberations, and the outcome of the GRAS panel are provided by the notifier.

H. Considerations When a GRAS Notice is Not Submitted to FDA

The GRAS criteria (21 CFR 170.30(a) to (c) and 21 CFR 570.30(a) to (c)) apply regardless of whether a conclusion of GRAS status is submitted to us as a GRAS notice or whether it is an independent conclusion of GRAS status that remains with the proponent. We advise any company that intends to market a food substance on the basis of an independent conclusion of GRAS status to carefully consider the recommendations in this guidance and to apply them to its own assembly and management of a GRAS panel. However, as previously noted, the outcome of a GRAS panel's deliberations does not create or confer general recognition status on the use of an ingredient. Rather, it can provide evidence supporting the proponent's contention that there is general acceptance based on generally available information among relevant scientific communities. Ultimately, all decisions regarding the safe and lawful use of a substance in food, including decisions about GRAS status, are subject to FDA review (see, for example 21 CFR 170.38). If a question arises, a well-constructed GRAS panel for which all sources of potential bias are addressed and managed may be useful to support the proponent's conclusion. When a use of a substance does not qualify for GRAS status or other exceptions provided under section 201(s) of the FD&C Act, that use of the substance is a food additive use subject to the premarket

approval mandated by the FD&C Act. Under Section 409 of the FD&C Act, a food additive not approved for its intended use is deemed unsafe. Any food that is, or bears or contains, a food additive that is unsafe is adulterated under section 402(A)(2) of the FD&C Act.

I. Honoraria Provided to Members of a GRAS Panel

We recommend that the written GRAS panel policy address the honoraria provided to a GRAS panel. We recognize that members of a GRAS panel are generally compensated, and in our opinion, such compensation is not itself an unacceptable conflict. However, an honorarium provided to members of a GRAS panel should not be contingent on the outcome of deliberations by a GRAS panel. We consider that such conditional compensation creates an unacceptable conflict of interest that undermines the credibility of a GRAS panel report.

VI. Paperwork Reduction Act of 1995

This guidance contains information collections that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521).

The time required to complete this information collection is estimated to average 20 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. There is also a one-time estimated recordkeeping burden of 40 hours per response. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Center for Food Safety and Applied Nutrition (HFS-255), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740.

An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0911 (To find the current expiration date, search for this OMB control no. available at https://www.reginfo.gov).

VII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500 and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

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