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MEMORANDUM

From: Joseph Levitt
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Re: **FDA Issues Draft Guidance on Best Practices for Convening a GRAS Panel**

On November 16, 2017, the Food and Drug Administration (FDA or the agency) issued a federal register notice soliciting comments on its Draft Guidance for Industry, "Best Practices for Convening a GRAS Panel." [1]/,[2]/

The Draft Guidance is intended for persons responsible for a conclusion that a substance may be used in food on the basis of the generally recognized as safe (GRAS) provision of the Federal Food, Drug, and Cosmetic Act (FFDCA) when that person convenes a panel of experts (GRAS panel) to independently evaluate whether the available scientific data, information, and methods establish that the substance is safe under the conditions of its intended use in human or animal food. The Draft Guidance provides FDA's current thinking and detailed recommendations on best practices in the following areas:

- identifying GRAS panel members who have appropriate and balanced expertise;
- steps to reduce the risk that bias (or the appearance of bias) will affect the credibility of the GRAS panel's output (GRAS panel reports), including the assessment of potential GRAS panel members for conflicts of interest and the appearance of conflicts of interest; and
- limiting the data and information provided to a GRAS panel to public information (*e.g.*, by not providing the GRAS panel with confidential information).

The Draft Guidance document is intended for and directed to:

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

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[1]/ Best Practices for Convening a Generally Recognized as Safe Panel: Draft Guidance for Industry; Availability, 82 Fed. Reg. 53433 (Nov. 16, 2017) https://www.gpo.gov/fdsys/pkg/FR-2017-11-16/pdf/2017-24845.pdf.

[2]/ FDA Draft Guidance for Industry, Best Practices for Convening a GRAS Panel (Nov. 17, 2017) https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM584930.pdf [hereinafter "Draft Guidance"].

- companies or other persons who assemble a GRAS panel and provide the framework for its deliberations; and/or
- companies or other persons who are interested in FDA's views and recommendations on best practices for convening a GRAS panel. [3]/

Comments are due on the Draft Guidance by May 15, 2018. For comments related to the collection of information provisions in the Draft Guidance, comments are due by January 16, 2018.

1. Development of Recommendations and Major Topics Covered

Among other issues, the Draft Guidance recommends best practices to reduce the risk that bias (or the appearance of bias) will affect the credibility of the GRAS panel report, including the assessment of potential GRAS panel members for conflicts of interest. In developing the recommendations, FDA considered federal law, regulations, and other FDA guidance related to conflicts of interest, as well as published literature and policies from several organizations (*e.g.*, the National Academies of Sciences, Engineering, and Medicine (NASEM), and the National Academy of Medicine (NAM)) that have developed policies to address topics such as bias, balance of expertise, procedures for organizing a scientific panel and managing its deliberations, conflicts of interest, for use by their own organizations (or the scientific community at large) during the conduct of scientific research. FDA summarizes key strategies from these sources that are relevant to the agency's recommendations.

FDA's is particularly concerned with sources of potential bias that are relevant for a panel of scientific experts being convened, including: balance of expertise, procedures for organizing a scientific panel, management of deliberations, and conflicts of interest and appearance issues.

a. Balance/Breadth of Expertise

For the purposes of balance/breadth of expertise, FDA states that the significant omission of any required discipline or sub-discipline may seriously compromise the quality of the committee's analysis and judgments, even if the committee is composed of highly qualified individuals. Additionally, failure to include an appropriate discipline can compromise the quality of a panel's analysis and judgments. Even within a particular discipline, there may be important differences and distinctions within the field that require more careful consideration in the committee composition and appointment process. Therefore, FDA recommends that companies provide sufficient breadth of expertise so there is appropriate balance of views within the expert panel.

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

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 other factors.

[3]/ The Draft 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 responsibilities for complying with those statutory and regulatory criteria.

c. *Conflict of Interest and Appearance Issues*

The principal tool in FDA's conflict of interest guidance is a flowchart that sets out the questions and considerations to address in determining eligibility for participation in an FDA advisory committee in a step-wise manner. [4]/ The first two steps assess whether the subject matter of the meeting is a "particular matter," [5]/ and whether the particular matter will have a "direct and predictable effect" [6]/ on the financial interests of any organization or individual. Because a GRAS panel is assembled to advise the proponent about a specific substance that the proponent intends to market for an intended use in human or animal food, the subject matter that a GRAS panel would address is a "particular matter" that will have a direct and predictable effect on financial interests of those involved. Steps 3 through 10 in the flowchart are also relevant to the assembly of a GRAS panel, and the recommendations in the Draft Guidance address issues analogous to those steps.

Additionally, the agency summarizes several organizations' policies and literature addressing conflicts of interest and appearance issues, including the NASEM policy, the NAM report, the Flavor and Extract Manufacturers Association (FEMA) expert panel procedures, and other published reports by the American College of Cardiology Foundation and the American Heart Association, the American College of Chest Physicians, and the National Comprehensive Cancer Network to provide guidelines on avoiding conflicts of interest for GRAS panel members.

2. Recommendations

FDA discusses detailed recommendations related to selecting GRAS Panel members, the operation of a GRAS panel, and submitting a GRAS notice to FDA.

a. Recommendations for Selecting GRAS Panel Members

To convene a GRAS panel that can effectively evaluate the available scientific data, information, and methods, and to reduce the risk that bias (or the appearance of bias) will affect the credibility of the GRAS panel report, FDA recommends that the organizer establish and implement a written GRAS panel policy to address the four areas discussed below:

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[4]/ FDA Guidance, Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees, Appendix 1 (Aug. 2008) https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf.

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

[6]/ A particular matter will have a "direct" effect on a financial interest if there is a close causal link between any decision or action taken, and any expected effect 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 if the chain of causation is attenuated or is contingent upon events that are speculative, 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 the Draft Guidance. 5 CFR § 2640.103(a)(3)(i). A particular matter will have a "predictable" effect if there is a real possibility that the matter will affect the financial interest. It is not necessary that the magnitude of gain or loss be known, and the dollar amount is immaterial. 5 CFR § 2640.103(a)(3)(ii).

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

Organizers should 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, FDA recommends that a GRAS panel include members with expertise in chemistry (or biochemistry), toxicology, and exposure assessment, because these three scientific disciplines broadly apply to most safety evaluations.

The organizer should determine the total number of GRAS panel members 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.

- address procedural issues associated with the organization and deliberations of the GRAS panel;

FDA recommends that a written GRAS panel policy addressing the potential for bias that could occur by: establishing clear roles and responsibilities for each member; establishing clear decision-making procedures; specifying whether to inform the members of the GRAS panel about the potential for bias; 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; and 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 efficiently and effectively, and then awaiting the outcome without interference).

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

FDA recommends that a written GRAS panel policy include a process for identifying competing interests, including conflicts of interest and appearance issues. This includes financial interests of GRAS panel members 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.

To address these concerns, FDA recommends that a written GRAS panel policy establish pre-existing criteria for evaluating the significance of conflicts of interest and appearance issues, including financial or other types of appearance issues. 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 publicly 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. A written GRAS panel policy should also include strategies for managing conflicts and appearance issues.

Note that the draft guidance focuses on the considerations to be taken into account in assessing and managing conflicts or potential conflicts of interest, but leaves it up to the company to determine how best to implement them in any given case.

- document how the organizer applied the written GRAS panel policy to the selection and vetting of each member of the GRAS panel, including steps taken to provide transparency and clarity regarding the selection and vetting of each GRAS panel member;

FDA recommends 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 appropriately. The agency also recommends that the policy require documentation of all conflicts of interest and appearance issues identified in the process of forming a GRAS panel, and how these issues were managed. This would include a discussion of the rationale, along with the organizer's views on the net effect of each issue on the ability of the panel to serve as a credible proxy for the larger scientific community.

b. Recommendations for Operating the GRAS Panel and Submission of a Notice to FDA

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, and may be corroborated by the application of unpublished scientific data, information, or methods.

Although general recognition of safety through scientific procedures may be corroborated by the application of unpublished information, to satisfy GRAS criteria, qualified experts must be able to conclude that the substance is not harmful under the conditions of its intended use *without* access to "corroborative" information. Because of this, FDA recommends that the organizer minimize the amount of non-public information provided to a GRAS panel. One exception relates to data and information that could raise a question about the safety of the substance under the conditions of its intended use. FDA recommends that the data and information that the organizer provides to a GRAS panel include a description of all data and information that could raise a safety question, regardless of whether those data and information are publicly available.

The organizer should also clearly document the deliberations and conclusions of a GRAS panel. The agency recommends clear and explicit documentation of: the available data and information that was reviewed; how the GRAS panel handled its deliberations; and the basis for the final conclusion. Moreover, each member of the GRAS panel should 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 the written GRAS panel report.

Lastly, FDA states that the GRAS criteria apply regardless of whether a conclusion of GRAS status is submitted to the agency or privately held as an independent conclusion of GRAS status that remains with the organizer. FDA advises any company that intends to market a food substance on the basis of an independent conclusion of GRAS status to carefully consider the recommendations and apply them to its own assembly and management of a GRAS panel.

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We will continue to monitor these and other developments related to GRAS Notice requirements and guidance. Please contact us if you would like assistance with drafting comments to the docket or have any questions.