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FDA Issues a Final Rule on Substances Generally Recognized as Safe (GRAS) for Their Intended Use in Food

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Food, Beverage, and Dietary Supplements

This morning, August 17, 2016, FDA published in the *Federal Register* its final rule on substances generally recognized as safe (GRAS) for their intended use in food.[1] Coming nineteen years after the proposed rule, under which industry has effectively been operating for some time, the final rule mostly codifies the status quo. The final rule formalizes, through regulation, the voluntary notification program that has been running as an interim pilot for nearly two decades. It also modernizes the regulations in a few key respects, sweeping out obsolete provisions about a GRAS petition process that is no longer used and replacing them with a description of the voluntary GRAS notification procedure already familiar to the food industry.

Some of the biggest changes from the status quo may be terminology. "GRAS notifications" are now "GRAS notices"; "GRAS determinations" are now "GRAS conclusions" or "conclusions of GRAS status"; and the "exemption" of GRAS substances from the law on food additives is now an "exclusion."

The final rule—through its preamble and the new regulations—will help companies understand when a substance is GRAS under the conditions of its intended use in human or animal food.[2] The clarified GRAS criteria apply even when a company chooses not to submit a GRAS notice. These GRAS criteria include the following:

- General recognition of safety requires "common knowledge," throughout the expert scientific community knowledgeable about the safety of substances directly or indirectly added to food, that there is a reasonable certainty that the substance is not harmful under the conditions of its intended use;
- "Common knowledge" is based on "scientific procedures" or on experience based on common use of a substance in food prior to January 1, 1958; and

[1] 81 Fed. Reg. 54960 (Aug. 17, 2016).

[2] While the GRAS final rule applies to both human and animal food, this alert focuses on issues related to human food. Later this week, we will issue a separate Covington alert on key considerations in the GRAS final rule related to animal food.

- A substance is GRAS under the conditions of its intended use only if it satisfies the safety standard for food additives under the Federal Food, Drug, and Cosmetic Act.

For companies that seek to present their GRAS conclusions to the agency for its views, the final rule establishes requirements for how the GRAS conclusion should be structured and explained in a seven-part GRAS notice. FDA's detailed explanation of these seven parts, in the preamble and the regulations, will be helpful to anyone preparing a GRAS notice.

Importantly, the final rule does not do what some had feared and some had encouraged—make the GRAS notice process mandatory. Companies can make their own GRAS conclusion, and they need not go to the agency for its views before using an ingredient based on that conclusion. To comply with FDA's final rule, companies should ensure, however, that their GRAS conclusions satisfy the criteria for GRAS status that FDA explains in the final rule, even when they decline to present proactively their conclusions to the agency in a GRAS notice.

Background

Section 201(s) of the Federal Food, Drug, and Cosmetic Act (FDCA) describes the two most common types of ingredients in conventional food: food additives and GRAS substances. Food additives require FDA approval before they can be marketed. GRAS substances do not. Both types are tied to their intended use. The same ingredient can be a food additive for one intended use and a GRAS substance for another.[3]

Section 201(s), which excludes a GRAS substance from the definition of "food additive" and related premarket approval requirements, describes a GRAS substance as one that is

> "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."[4]

According to this definition, experts can generally recognize a substance as safe through either (1) scientific procedures or (2) experience based on common use before January 1, 1958. Some substances qualify under both prongs.

The date in the statute—January 1, 1958—reflects the year in which Congress enacted the Food Additives Amendment. Shortly after this enactment, FDA issued a nonexclusive list of GRAS substances, periodically amended, which companies can use without premarket approval. In the 1970s, FDA established procedures that allowed the agency to affirm substances as GRAS by regulation. The procedures also allowed individuals to voluntary submit to the agency a petition asking FDA to affirm the GRAS status of a substance under the conditions of its intended use; the procedures generally directed FDA to engage in an intensive rulemaking process in response to a petition.

[3] In the preamble to the final rule, FDA explains that a GRAS notice can be an appropriate mechanism for informing the agency of a GRAS use for substance approved as a food additive for another use.
[4] 21 U.S.C. § 321(s).

The GRAS affirmation petition process has not been used since FDA issued the proposed rule on the voluntary notification process in 1997. Since then, FDA has followed what it has called its "Interim Pilot" program on voluntary notifications. Under this program, which has become familiar to industry, a company submits a notice stating its conclusion that the substance involved is GRAS for its intended use. If FDA does not disagree, the agency sends a letter to the company stating that it has "no questions" regarding the company's GRAS conclusion.

Both the petition process and the notification process that replaced it have always been voluntary. A food company has always had the option, under the statutory language of the FDCA, to conclude that a substance is GRAS and sell it on this basis without receiving approval, affirmation, or a "no questions letter" from FDA. Under the final rule, companies can continue to do so.

What it means to be GRAS

The final rule discusses what it means to be GRAS, including the data that must be considered in reaching a GRAS conclusion. A GRAS conclusion depends on "common knowledge," which must be based on either scientific procedures or experience of common use before 1958. The same safety standard that would be required to support a food additive regulation—"reasonable certainty of no harm"— must underpin a conclusion of GRAS status, though the evidence to meet that standard can be different. A GRAS conclusion must be based primarily upon publicly available data on both safety and exposure, whereas a food additive petition may be based upon non-public proprietary data.

A GRAS conclusion hinges on "common knowledge," gleaned either through scientific procedures or based on common use before 1958

Like the old GRAS regulations and the proposed rule, new section 170.30(a) establishes that a GRAS conclusion—general recognition of safety—requires "common knowledge" about an ingredient's safety:

> "General recognition of safety requires common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food that there is reasonable certainty that the substance is not harmful under the conditions of its intended use."[5]

Common knowledge can be based either on "scientific procedures" or on experience based on common use of a substance in food prior to January 1, 1958.

Scientific procedures

If common knowledge is established through scientific procedures, it must be based upon the application of generally available and accepted scientific data, information, or methods, which are ordinarily published, as well as the application of scientific principles. Under the final rule, scientific procedures includes scientific data (such as human, animal, analytical, or other scientific studies), information, methods, and principles, whether published or unpublished, appropriate to establish the safety of a substance.

[5] 21 C.F.R. § 170.30(a).

Under the final rule, recognition of safety based on scientific procedures requires the "same quantity and quality of scientific evidence as is required to obtain approval of a food additive."[6] FDA indicated that it intends to issue guidance to further clarify that food substances should be evaluated for safety in the same way regardless of whether they are food additives or GRAS substances for a given use.

Experience of common use before 1958

Common knowledge can also be based on pre-1958 use if there was substantial history of consumption of the substance for food use by a significant number of consumers. According to the preamble, a substance is not GRAS under the conditions of its intended use merely because it was commonly used in food prior to 1958 (in the United States or abroad). Instead, any person who relies on a conclusion of GRAS status through experience based on common use in food prior to 1958 should evaluate whether the conditions of use associated with the applicable substance, such as the foods in which the substance would be used and the levels of use of the substance, still support a GRAS conclusion, FDA specifically identified in the preamble recent circumstances in which the agency has concluded that a substance used in food before 1958 is not GRAS under its intended conditions of use, including the use of caffeine in alcoholic beverages and the use of partially hydrogenated oils in human food.

Safety must be to a "reasonable certainty"

Under section 170.3(i), "safe" and "safety" is defined as "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use" [7] In the preamble, FDA equates this standard to the standard for food additives:

> "Congress recognized that, under [the Food Additives Amendment], the safety of a food additive could not be established with absolute certainty, and thus provided for a science-based safety standard that requires sponsors of food additives to demonstrate to a reasonable certainty that no harm will result from the intended use of an additive. We have incorporated this safety standard into our regulations for food additives and GRAS substances."[8]

In the other words, GRAS substances are neither safer nor less safe than approved food additives.

General recognition requires consensus, not unanimity

In the preambles to the proposed and final rules, FDA affirmed that general recognition of safety requires consensus but not unanimity. FDA claims that this interpretation is consistent with court opinions. FDA declines, however, to define the extent of agreement needed to establish such a consensus: "Although courts have established that general recognition of safety requires a consensus of expert opinion regarding the safety of the use of the substance, we disagree that we must define the extent of agreement needed to establish such a consensus."[9]

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[6] 21 C.F.R. § 170.30(b).
[7] 21 C.F.R. § 170.3(i).
[8] 81 Fed. Reg. at 54963.
[9] *Id* at 54967-77 (internal citations omitted).

In the final rule, FDA opted not to use the proposed term "consensus." It decided instead to use the statutory language "generally recognized." Unfortunately, FDA leaves to further interpretation, including potentially by the courts, what it actually means to be "generally recognized." In practice, FDA's experts will likely evaluate GRAS notices and decide whether it agrees that something is safe, implying that experts generally would agree that it is safe. But the legal meaning of "general recognition" may continue to be debated in courts or other venues.

A GRAS conclusion must rely on public data on safety and exposure

A substance is GRAS under its intended conditions of use only if qualified experts can reach that conclusion. According to FDA, experts can reach the conclusion only if critical information is public. Whether a person submits a GRAS notice or not, the data and information that it relies upon for a GRAS conclusion must be public. Publication in peer-reviewed scientific journals is best, but FDA will also accept other types of public information, including publication in a textbook or technical literature such as the publications of the Joint Expert Committee on Food Additives (a joint committee of the Food and Agriculture Organization and World Health Organization).

In addition to safety data, exposure data must also be publicly available. The rule clarifies that exposure data is relevant for all GRAS conclusions, whether based on scientific procedures or pre-1958 use. Such data must now be included in all GRAS notices.

Non-public information can be "corroborative"

While the GRAS conclusion must hinge on public data, non-public data can be corroborative. Such data can support a GRAS conclusion, but they must not be necessary to it.

Non-public information includes unpublished data, information, and methods. It includes trade secrets and confidential commercial information. If a person choses to submit a GRAS notice, it can put trade secrets and confidential commercial information only in certain sections of the notice, reflecting the lower weight such information can bear in a GRAS conclusion.

An opinion of a GRAS panel can be evidence of general recognition

A GRAS panel, a panel of individuals who evaluate whether the data establish that a substance is GRAS for its intended use, is not necessary to a GRAS conclusion. FDA considers a GRAS panel one among many ways to demonstrate consensus. In the preamble, it says: "[C]onvening a GRAS panel has historically been a way to provide evidence that generally available data and information are generally accepted by the expert scientific community, but convening a GRAS panel is not the only way to provide such evidence."[10]

According to the preamble, FDA will consider an opinion of a GRAS panel "to be part of the secondary scientific literature" and thus something that "could provide evidence that the data and information discussed in the publication are generally accepted."[11] The weight of a GRAS panel's opinion would depend on factors such as the subject matter expertise of its members.

[10] *Id*. at 55026-27.
[11] *Id.* at 54974.

One issue that often comes up with a GRAS panel is potential conflicts of interest. FDA announced that it will issue guidance on conflicts of interest—first a draft guidance, then a final one after a comment period, though it has not announced a time frame for the release of these documents.

What a GRAS notice should contain

The final rule will be particularly helpful to persons preparing a GRAS notice. Of course, the final rule does not require a person to submit a GRAS notice, and it is still informative to those who decide not to submit a GRAS notice. As FDA explains in the preamble to the final rule, "we believe that the provisions of the GRAS notification procedure will be a useful resource to any person who intends to use a substance in food based on a conclusion of GRAS status, regardless of whether the conclusion of GRAS status is submitted to us in a GRAS notice."[12]

While the proposed rule did not specify individual parts for a GRAS notice, the final rule imposes requirements for any GRAS notice that is submitted to FDA. Specifically, each GRAS notice must contain the following seven parts:

1. **Signed Statements and Certification**. This part should include information about trade secrets, intended conditions of use, and the basis for the conclusion of GRAS status.

2. **Identity, Method of Manufacture, Specifications, and Physical or Technical Effect**. This part should include information necessary to characterize the substance well and to understand the method of manufacture.

3. **Dietary Exposure**. This part should include information about the amount of the relevant substance that consumers are likely to eat or drink as part of a total diet, regardless of whether the conclusion of GRAS status is through scientific procedures or through experience based on common use in food.

4. **Self-Limiting Levels of Use**. This part should describe circumstances where the amount of the notified substance that can be added to food is limited because the food containing levels of the notified substance above a particular level would become unpalatable or technologically impractical

5. **Common Use in Food Before 1958**. For common use in food to be the basis for the GRAS conclusion, the pre-1958 consumption must be by a significant number of consumers.

6. **Narrative**. This part should describe the basis for the conclusion of GRAS status.

7. **Supporting Data and Information**. This part should specify which of these data and information are generally available and which are not.

FDA commits to responding to GRAS notices in a reasonable time, typically 180 days. The regulations allow FDA to extend this timeframe by 90 days as needed. If FDA opts for an

[12] *Id.* at 55027.

extension, it will inform a notifier within 180 days of filing. Under the final rule, a notifier can amend a GRAS notice before FDA responds to it, and/or supplement it after the agency responds.

"No questions" will continue, at least for now

In the preamble to the final rule, FDA suggests that it will generally continue to respond to GRAS notices in one of three ways:

1. With a "no questions letter" when it does not have a concern about the safety of a substance;

2. With an "insufficient basis letter" when a GRAS notice does not provide a basis for a conclusion that the notified substance is safe under the conditions of its intended use (including when critical information is not public);

3. With a "cease to evaluate letter" when the notifier requests that FDA stop evaluating the GRAS notice.

Conclusion

The final rule formalizes the voluntary GRAS notification procedure under which industry has operated for years, imposing certain requirements for such notifications that were not in place previously. It also provides the agency's current view on what constitutes general recognition of safety and what should go into a GRAS conclusion. The final rule, including its preamble, will provide a useful guide for all companies who seek to use GRAS substances in their food products, regardless of whether they decide to submit their conclusions as notices to the agency.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food, Beverage, and Dietary Supplements practice:

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