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Generally Recognized as Safe: Establishing a Suitable U.S. Regulatory Status for Food Ingredients

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GRAS Regulatory Pathway: GRAS Notification

The onus on making a determination that a conventional food ingredient is GRAS, and therefore not subject to FDA preapproval, is on the food manufacturer. That is because a substance that is generally recognized, "among experts qualified by scientific training and experience to evaluate its safety," to be safe under the conditions of its use is an exception to the FDA premarket approval requirement for "food additives" under the Federal Food, Drug, and Cosmetic Act. GRAS status may exist based on a level of scientific agreement about a substance's safety, or for a substance used in food before January 1, 1958, on scientific procedures or common use in food.

As noted in our first advisory, the starting point for evaluating whether a conventional food ingredient may be used in a food product is determining whether the use of a particular food ingredient already has an existing regulatory status. Without an existing clearance, manufacturers have a number of regulatory pathways that can be used to establish a suitable regulatory status for a particular food ingredient. In addition to filing a food additive petition (FAP), manufacturers could either (1) submit a GRAS notification to the FDA; or (2) pursue an independent conclusion that a substance is GRAS.

If an independent GRAS conclusion has been reached, the submission of a GRAS notification (also referred to as a "GRAS notice") to assert that a substance is not subject to premarket approval is not required to market the product. However, this route may be advantageous for various reasons, including to satisfy a customer requiring FDA review of a manufacturer's independent GRAS conclusion or because of the complexity of the ingredient at issue.

The main features of a GRAS notification are:

General Requirements: A GRAS notification must include a description of the identity and method of manufacture, specifications, physical or technical effect of the substance, estimation of dietary exposure, limitation on the conditions of use, and supporting data and information. Unlike an FAP, which generally relies on unpublished data or data from published studies sponsored by the entity submitting the FAP, a GRAS conclusion must be supported by information that is "generally available" or "generally accepted," i.e., the information must be published in a journal or have other similar availability. The submission may be strengthened by the inclusion of the conclusion of a panel of independent experts (a GRAS panel).

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Review Period: The FDA will conduct an initial evaluation upon receipt and will decide to either file the notification and inform the notifier of the filing date or send the notifier a letter explaining the agency's reasons for not filing the GRAS notification. Once filed, the FDA will respond to a GRAS notification within 180 days but may extend its response time by 90 days. In reality and despite these time limits, the FDA has historically taken more time—up to a year—to respond to a GRAS notification. Still, this review period is typically shorter than the time required for the FAP process.

Outcomes: Based on the FDA's evaluation of the submission, the FDA may: (1) issue a letter saying it has "no questions"; (2) issue a letter declaring that the notification does not provide a sufficient basis for a GRAS conclusion; or (3) issue a "cease-to-evaluate" letter in response to a request by the notifier. Unlike a successful FAP, which culminates in FDA approval of the petitioned substance, a favorable GRAS notification does not result in FDA "approval." Further, unlike a successful FAP, the FDA reserves the right to change its determination of a substance's GRAS status.

Information Disclosure: Both the submission and the FDA's review are publicly posted on the FDA's website, and unless exempt from disclosure under the Freedom of Information Act, the data and information provided to support the GRAS notification will be made publicly available. Importantly, like a successful FAP, which culminates in a rulemaking, GRAS notifications are not proprietary to the submitter; rather, other manufacturers can piggyback off an existing GRAS notification if using the same ingredient for the same intended use.

Independent Conclusion of GRAS Status

Instead of submitting a voluntary GRAS notification to the FDA, a manufacturer can also opt to compile information to make an independent conclusion that the intended use of a particular food substance is GRAS and market a product based on that conclusion.

General Requirements: An independent conclusion of GRAS status must fully satisfy the criteria for eligibility for classification as GRAS based on FDA requirements. The FDA recommends that companies engaged in independent GRAS conclusions follow its framework for formal GRAS submissions so that the FDA can easily undertake an independent review of the self-GRAS assessment should the FDA have questions or concerns about its regulatory status.

There are benefits and drawbacks to seeking an independent conclusion of GRAS status:

Benefits

- Review time: Unlike a GRAS notification, which can take over a year for the FDA to review, a manufacturer may immediately market the food ingredient once reaching an independent GRAS conclusion.
- Confidential or proprietary information: Unlike a GRAS notification, confidential or proprietary information remains under a manufacturer's control and others cannot use the food ingredient on the basis of the manufacturer's GRAS conclusion.

Drawbacks

- No benefit of agency review: Unlike a "no questions" letter in response to a GRAS notification where the FDA has indicated it has reviewed the notification and has no questions, an independent GRAS conclusion receives no such agency review, which some customers may require.
- Variability in reliability of independent GRAS conclusions: Without agency review, there is significant variability in the level of robustness of independent GRAS conclusions throughout the food industry. The strength (and reliability) of the legal basis for an independent GRAS conclusion depends on the data used to support it and the robustness of the scientific review—both of which should be considered either when determining whether a company can rely on its supplier's GRAS statement or when coming to its own independent conclusion of GRAS status.

- Lack of transparency in the food supply: Because the FDA neither reviews nor is informed about the expected use of a substance that undergoes an independent GRAS conclusion, some have expressed concerns that certain food substances may be introduced into food by multiple manufacturers in such a way that some consumers may ingest more of the substance than is healthy.

Conclusion

Concluding that a food ingredient is GRAS, either via submission of a GRAS notification to the FDA or through an independent conclusion of GRAS status, is one regulatory pathway industry can take to establish a suitable regulatory status of ingredients used in food. Our next advisory will focus on additional considerations and best practices for bringing dietary supplements to market.

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