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ON FDA AND FOOD INGREDIENT SAFETY: IS THE “GRAS” HENHOUSE AT RISK?

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For over 50 years, U.S. food manufacturers and consumers have benefited from a provision of law that enables manufacturers to market a food ingredient without prior government approval – provided that the use of the ingredient is “generally recognized as safe” (GRAS). The right of manufacturers to engage in independent GRAS determinations (or self-determinations) has served as a useful tool to enable innovations in food technology supported by comprehensive safety reviews to reach the market, without tying up limited government resources. The GRAS exception to premarket approval can befuddle legal practitioners in other jurisdictions; accustomed to less flexible oversight regimes, those practitioners sometimes misperceive the exception as a shortcut to market or an egregious case of the fox guarding the henhouse. A brief explanation of the workings of the Federal Food, Drug, and Cosmetic Act (FDC Act) is usually sufficient to convince them that the GRAS self-determination process is no short cut – and that a fox that likes eggs can usually be counted on not to kill the chickens that lay them.

Recently, the GRAS exception has come under attack from sources closer to home. Earlier this year, the U.S. Government Accountability Office (GAO) issued a report criticizing the U.S. Food and Drug Administration’s (FDA or the Agency) oversight of GRAS ingredients.¹ This report, transparently titled “[FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe \(GRAS\)](#)” (GAO Report), was prepared at the request of Senator Tom Harkin and Representative Rosa DeLauro, two long-time food safety watchdogs. Not surprisingly, the call for reform is backed by public interest groups,² and has been echoed in academia.³ In the context of the broader call for reform, this article examines the GAO Report and its potential impact on FDA’s administration of the GRAS exception.

History of the GRAS Exception. The current controversy can only be understood in historical context. In the first half of the 20th century, there was no premarket approval scheme for substances added to food. Concerns about the increasing use of chemicals in the manufacture of food prompted Congress to amend the FDC Act in 1958 to impose requirements for the safe use of “food additives,” broadly defined 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.” *See* 21 U.S.C. § 321(s). Generally, the use of a food additive must be approved by FDA prior to marketing unless that use is eligible for an exemption. A

¹U.S. Gov’t Accountability Office, GAO-10-246 (2010) *FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe (GRAS)* (hereinafter referred to as the GAO Report).

²As far back as 1997, the Center for Science Public Interest took the position that all manufacturers should be required to inform FDA of their GRAS self-determinations.

³James T. O’Reilly, *FDA’s Appetite for Desuetude: Food Safety Exceptions Swallow Statutory Norms*, 35 A.B.A. Sec. Admin. & Reg. L. News 8-9 first file (Winter 2010).

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company must file a food additive petition with FDA, *see generally*, 21 C.F.R. Part 171, which requires a company to submit data demonstrating with reasonable certainty that no harm will result from the intended use of the additive. *See id.* § 171.1. If FDA agrees that this standard has been met, FDA will issue a regulation that prescribes conditions of use for the additive. If the additive is used in a manner that deviates from the conditions of use prescribed in the regulation, then that use of the additive is not covered by the regulation and might be considered “unsafe.” Any food that contains an “unsafe” food additive is deemed adulterated and prohibited from interstate commerce. *See* 21 U.S.C. § 348(a)(2).

However, not all uses of substances in food fall under the premarket approval scheme for food additives. Congress exempted GRAS uses of substances from the definition of food additive and the corresponding requirement that companies obtain approval of a food additive petition.⁴ Congress did so in part as a means of minimizing investment of government and industry resources in premarket approval process when the safety of the use of a substance has been established and recognized by qualified experts. The GRAS exception permits a company to self-determine whether the intended use of a substance is both safe and generally recognized as such.

A complete account of the evolution of FDA’s approach to the GRAS exception in the latter half of the 20th century is beyond the scope of this article.⁵ Suffice it to say that, for a time, FDA narrowly interpreted the GRAS exception and voluntarily assumed the resource intensive role of affirming the GRAS status of food ingredients through notice and comment rulemaking at its own initiative or in response to GRAS affirmation petitions. Soon it became evident that this approach precluded the efficient administration of the GRAS exception and threatened to stifle innovation in the food supply – notably the introduction of bioengineered foods.

In recognition of a need for a more flexible approach to the GRAS exception, FDA issued a proposed rule in 1997 under which a company may voluntarily notify FDA of its GRAS self-determination. The Agency promptly stopped accepting GRAS affirmation petitions and began accepting GRAS notices under the criteria specified in the proposed rule. 62 Fed. Reg. 18,938 (Apr. 17, 1997). In response to a GRAS notice, FDA does not make its own determination regarding the GRAS status of a notified substance, but rather informs the company in a letter of one of three responses: (1) FDA has no questions about the company’s conclusion that the use of the substance is GRAS; (2) FDA concludes that insufficient information is available to determine that the use of the substance is GRAS; or (3) at the company’s request, FDA has ceased to evaluate the GRAS notice. *Id.* at 18,950-18,951; *see also* GAO Report at 6. Although FDA has yet to issue a final rule, the Agency’s voluntary GRAS notification program has been in continuous operation for 13 years, and the Agency recently implemented a voluntary GRAS notification program for animal feed ingredients.

Notably, under the law and under FDA’s proposed rule, it is the use of a substance (and not the substance itself) that is determined to be GRAS or subject to regulation as a food additive. Thus, the same substance might have some uses that are GRAS and other uses that are governed by a food additive regulation. Nonetheless, many observers (including GAO) use the short-hand term “GRAS substance” or “food additive” to refer to such a substance. Because GAO followed that convention in its report, we also follow it here.

The GAO Report Findings. The GAO Report heavily criticized FDA’s current approach to monitoring the safety of GRAS substances. For instance, GAO determined that FDA lacks information about certain GRAS determinations because of the voluntary nature of the GRAS notification program. *See* GAO Report at 12. Consequently, GAO believes that FDA is not well-informed about the food supply and consumers’ cumulative dietary exposure to certain substances. *See id.* at 13. According to GAO, FDA may face challenges in identifying a specific substance as a potential source of a food safety problem after the substance has entered the marketplace. *See id.* at 12.

⁴*See id.* §§ 321(s), 348. There are other uses of substances also exempt from the definition of food additive, which we do not address here.

⁵For a more complete accounting of that history, *see* Frederick H. Degnan, *The GRAS Concept: Ensuring Food Safety and Fostering Innovation, in FDA’s Creative Application of the Law*, 15-35 (2nd ed. Food and Drug Law Institute, 2006).

GAO also criticized FDA for its failure to reconsider the GRAS status of substances as new information or methods become available. *See id.* at 20. In particular, the report pointed to FDA's lack of a response to concerns raised in 10 of 11 citizen petitions submitted between 2004 and 2008 regarding the safety of certain substances whose use is asserted to be GRAS. *See id.* at 22. Further, GAO found that FDA generally does not know whether and to what extent companies track scientific information regarding substances that have been the subject of GRAS self-determinations. *See id.* at 25.

GAO's concern over FDA's lack of access to information extends to the integration of emerging technologies into the food supply. GAO concluded that FDA has no way of knowing the extent to which engineered nanomaterials have entered the food supply because a company can market such ingredients without informing FDA under the voluntary GRAS notification program. *See id.* at 29. GAO found that as of December 2009, no company had submitted to the GRAS notification program any substance described as including engineered nanomaterials. In contrast, these ingredients are required to undergo review by regulators in Canada and the European Union before they can be marketed. *See id.* at 32.

In addition to raising alarm over FDA's limited monitoring activities, GAO also raised questions about the reliability of GRAS self-determinations. Because of the limited number of available experts on food safety, GAO found that "these experts may have corporate or financial affiliations that could bias their decisions," *id.* at 15, in making GRAS determinations on behalf of companies.

GAO's Recommendations. GAO recommended, in part, that FDA develop strategies to:

- require any company that conducts a GRAS determination to provide FDA with basic information . . . about this determination, such as the substance's identity and intended uses, and to incorporate such information into relevant agency databases and its public Web site;
- minimize the potential for conflicts of interest in companies' GRAS determinations . . . ;
- monitor the appropriateness of companies' GRAS determinations through random audits or some other means, including issuing guidance on how to document GRAS determinations;
- help ensure the safety of engineered nanomaterials that companies market as GRAS substances without the agency's knowledge, including taking steps such as issuing guidance recommended by the agency's nanotechnology taskforce, developing an agency definition of engineered nanomaterials, and requiring companies to inform FDA if their GRAS determinations involve engineered nanomaterials.

See id. at 34-35. More broadly, the report recommends that, "[i]f FDA determines that it does not have the authority to implement one or more of these recommendations, the agency should seek the authority from Congress." *Id.* at 35.

FDA's Response. In its response to the report, FDA generally agreed with GAO's findings and recommendations, and concurred that the Agency's oversight of GRAS substances should be strengthened. *See id.* at 57. The Agency conceded that certain actions are beyond the scope of its current authority, such as requiring a company to notify FDA and submit evidence regarding the safety and intended use of GRAS substances. FDA agreed that having this authority would enhance its ability to oversee the safety of GRAS substances. However, FDA sidestepped GAO's broader recommendation that the Agency seek additional authority to implement the report's specific recommendations, which suggests that the Agency has little appetite for major changes in the status quo. *See id.* at 39.

FDA also generally agreed with GAO that an awareness of all GRAS self-determinations "would be informative." *See id.* at 62. However, FDA does not appear to be interested in half-measures whereby firms would submit basic information regarding their GRAS self-determinations to FDA. Rather, if FDA is to ensure that all GRAS determinations are "rigorous, robust, [or] consistent with the agency's criteria," *id.* at 36, the way to do so would be to make submission of GRAS notices mandatory for all self-determinations. Such a move likely would require a statutory amendment – a rather drastic measure in the absence of any evidence of a threat to public health.

FDA also agreed with GAO that an inherent conflict of interest exists because a company has an interest in the outcome of a GRAS determination. *See id.* at 63. However, FDA noted that a company must consider all publicly available information, including potentially negative information, when making a GRAS self-determination. To address GAO's concern over conflicts of interest, the Agency stated it will consider the conflict of interest issue when it finalizes the GRAS program regulation. Left unsaid by both GAO and FDA is the fact that any reputable company engaged in a GRAS self-determination has strong incentives to ensure that the credibility of the experts it relies on is beyond reproach. Not the least of these incentives is the need to minimize product liability exposure, which drives a company to retain experts who will undertake a critical evaluation of both the substance's intended use and the information and data pertinent to a determination of safety. As for the experts themselves, they recognize that their professional reputations are on the line when they sign their names to a GRAS expert opinion – a significant deterrent to the compromise of scientific principles.

FDA demurred with respect to GAO's recommendation to conduct random audits of GRAS self-determinations. FDA stated that it has a "very limited basis on which to audit" such determinations when a company does not submit a GRAS notice to FDA. *Id.* at 64. When a company submits a GRAS notice, the Agency stated it "does not hesitate to ask" a company to provide data or information to supplement a GRAS notice. *Id.* at 37. Although these responses suggest a potentially problematic gap in FDA's authority to access information, any company that makes a GRAS self-determination is unlikely to decline a request by FDA to provide evidence of the basis for its determination that use of a substance is GRAS. The FDC Act and relevant case law make clear that the burden of demonstrating GRAS status rests with a company. As discussed previously, a company that fails to meet that burden is vulnerable to being charged with marketing a food that is adulterated by virtue of containing an "unsafe" food additive.

Finally, FDA agreed that it needs to develop a strategy to ensure the safety of engineered nanomaterials that companies market as GRAS without prior notification to FDA. To that end, FDA stated its intention to issue guidance on how the GRAS concept applies to nanomaterials. Additionally, FDA is considering developing guidance on the regulatory status and safety of nanomaterials used in food and food packaging. Although industry would doubtless welcome such guidance, no reputable company would regard the absence of such guidance as presenting *carte blanche* to proceed to market with a substance containing engineered nanomaterials without first establishing its eligibility for the GRAS exception or complying with the Agency's premarket approval requirements. FDA's success with its regulatory approach to bioengineered foods, which closely parallels the voluntary GRAS notification program, suggests that there is little risk that industry will exploit the GRAS exception to rapidly commercialize novel ingredients that present unresolved safety issues.

Conclusions. Remarkably, the GAO Report does not identify a single food safety problem that has arisen as a result of FDA's current approach to the administration of the GRAS exception. Instead, the report points to gaps in FDA's access to information and to the specter of nanomaterials as apparent bases for the conclusion that more regulations, and possibly amendments to the FDC Act, are necessary to protect the public. At the same time, the GAO Report fails to acknowledge the current regime's important role in fostering innovation in the food supply. The GAO Report also fails to acknowledge the incentives that drive industry to maintain the integrity and viability of the GRAS exception.

On the whole, FDA's responses to GAO's recommendations suggest that the Agency believes that tighter oversight of GRAS substances is warranted. However, the Agency also evidently believes that its GRAS notification program is a success, and appears to recognize that attempting to play an active role in the conduct of all GRAS self-determinations would require resources that are better invested elsewhere. The considerable benefits of the current regime are implicitly acknowledged in FDA's response to GAO: "FDA believes that the GRAS concept has continuing utility as a practical tool for distinguishing between substances and new uses of substances that merit a full pre-market safety evaluation by FDA and those that do not." *Id.* at 57.