MEMORANDUM

Via Electronic Mail

TO: Interested Parties

FROM: Melvin S. Drozen and Natalie E. Rainer

(202) 434-4222
drozen@khlaw.com

DATE: August 29, 2016

RE: FDA Issues Final Rule on GRAS Notices

On August 17, 2016, the U.S. Food and Drug Administration (FDA) published a final rule that amends and clarifies the criteria for determining when a substance may be considered "generally recognized as safe" (GRAS) for an intended use in food and, thus, exempt from the premarket approval requirements applicable to "food additives" as defined under Section 201(s) of the Federal Food, Drug, and Cosmetic (FD&C) Act.[1] The final rule does not reflect any meaningful departure from FDA's position on the level of support required to make a GRAS determination (either when making a self-GRAS determination or submitting a GRAS Notice to FDA). However, the final rule details the new format requirements for GRAS Notices submitted to FDA, which will be required to include the following seven parts:

1. Signed statements and certification, under 21 C.F.R. § 170.225)
2. Identity, method of manufacture, specifications, and physical or technical effect, under 21 C.F.R. § 170.230
3. Dietary exposure, under 21 C.F.R. § 170.235
4. Self-limiting levels of use, under 21 C.F.R. § 170.240
5. Experience based on common use in food before 1958, under 21 C.F.R. § 170.245
6. Narrative, under 21 C.F.R. § 170.250
7. List of supporting data and information, under 21 C.F.R. § 170.255.

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[1] 81 Fed. Reg. 54960-55055 (Aug. 17, 2016), available at https://www.federalregister.gov/articles/2016/08/17/2016-19164/substances-generally-recognized-as-safe (hereinafter "Final Rule").

While not all parts will be relevant to each notice, each notice needs to include information on each part (*e.g.*, if self-limiting levels of use are not relevant to your notice, you will state so in Part 4). Analogous regulations address a seven-part GRAS Notice for substances to be used in animal feed in 21 C.F.R. §§ 570.225-570.255. In light of the final GRAS Notice regulations, FDA will no longer accept GRAS affirmation petitions and is closing the dockets for the 45 petitions that are currently pending review.

The final rule includes several changes as compared to the proposed rule. Some notable changes are as follows:

- **Specifying the seven required parts of a GRAS Notice, including determination of dietary exposure.** The proposed rule described a four part notice that did not explicitly require calculation of a dietary exposure, a discussion of use in food before 1958, or a list of supporting data (*i.e.*, these are addressed in Parts 3, 5, or 7, respectively, under the Final Rule).

- **Submitting trade secret and confidential information in the GRAS Notice.** The proposed rule assumed that GRAS Notices would not contain any information protected under FOIA. The final rule prohibits trade secret and confidential information in Part I of the GRAS Notice but permits the submission of trade secret and confidential information in other parts (*e.g.*, in describing the manufacturing process). However, if trade secret or confidential information is included, the notifier must establish how GRAS status can be supported if the information marked as a trade secret or confidential has any bearing on the safety determination.

- **Sets a review timeline of 180 days, with a possible 90-day extension.** The proposed rule included a 90-day review period.

- **Requires that a GRAS Notice discuss information that is or appears to be inconsistent with your conclusion of GRAS status or certify that you are not aware of such information.** The proposed rule did not include a certification provision if no inconsistent information was discussed in your notice.

- **Requires discussion of technical effect when such information has bearing on the safety evaluation.** While CVM has typically requested information on technical effect for animal food GRAS Notices, a discussion of technical effect was not typically included on the human food side but will now be required when such information has bearing on safety (*e.g.*, an antimicrobial suppresses one group of microorganisms, which could allow other microorganisms to proliferate).

- **Explicitly addresses supplementing a GRAS Notice with additional information and asking FDA to cease evaluation of the notice.** The proposed rule was silent on these issues. The preamble to the final rule also states that (unlike FDA's practice since 1998), when FDA issues a "cease to evaluate letter," such letters will be publicly available and include a discussion of the substantive reason(s) why FDA is ceasing its evaluation.

FDA is accepting comments on the final rule until October 17, 2016, at which time the rule will become effective. We provide a brief synopsis on the background on the final rule below, followed by a summary of highlights from the final rule.

I. Background on the Final Rule

When Congress passed the Food Additives Amendment Act of 1958, it carved out an exemption from the definition of "food additive"[2] which exempted substances from the definition of term if "generally recognized, among experts qualified by scientific training and experience to evaluate [their] 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] While the same quality and quantity of scientific data required to support a food additive petition are needed to support a GRAS determination, GRAS substances are not subject to the premarket clearance requirement for food additives.[4] That said, the definition of GRAS includes the requirement that there is "general recognition" of safety, meaning that data supporting the safety conclusion (*e.g.*, toxicology data) be published (*e.g.*, in a peer-reviewed journal) or otherwise available to the relevant scientific community.

After the passage of the Food Additives Amendment, FDA has promulgated food additive regulations under 21 C.F.R. Part 182 ("Substances generally recognized as safe"). Between 1958 and 1970, FDA has issued informal opinion letters to those who requested them, regarding the Agency's opinion on the GRAS status of a substance. Because these letters were often only available to the requestor and were not binding on the agency, FDA discontinued

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[2] A "food additive" is defined in Section 201(s) of the FD&C Act as a substance that is reasonably expected to become a component of food under the intended conditions of use.

[3] *Id.*

[4] Food that contains an "unsafe" food additive (*i.e.*, one that is not being used in accordance with an applicable regulation, exemption, or notification) is deemed adulterated, *per se*, under Section 402(a)(2)(C) of the Act.

issuing informal GRAS opinion letters in 1970. Following a comprehensive review of GRAS substances, FDA conducted a rulemaking in 1972 to establish a voluntary GRAS affirmation petition process. Under the process, an individual could petition FDA to review the GRAS status of a substance. FDA would publish a notice of the filing in the Federal Register, request comments, conduct a comprehensive review and then publish a final rule in the Federal Register, if warranted. The resulting food additive regulations are found under 21 C.F.R. Part 184 ("Direct food substances generally recognized as safe").

Because the GRAS affirmation petition process was administratively burdensome (*i.e.*, review of petitions often took several years), a backlog of petitions developed. By the late 1980s, petitioners often began marketing a substance once FDA had accepted the petition for filing, and FDA typically did not take further action on the petition. Because of these issues with the GRAS affirmation petition process, FDA introduced in 1997 the GRAS Notification proposed rule that sought to clarify eligibility for classification as GRAS and replace the GRAS affirmation petition process with a GRAS notification procedure.[5] (We note that the term "notification" describes the procedure, whereas the term "notice" is used to describe the submission itself.[6]) Although the rule was never finalized, FDA's Center for Food Safety and Applied Nutrition (CFSAN) started accepting GRAS Notices for human food substances in 1998 as a substitute for GRAS Affirmation Petitions. Since 1998, FDA has evaluated more than 600 notices on an informal basis in what FDA describes as its "Interim Pilot Program" for GRAS Notices. FDA's Center for Veterinary Medicine (CVM) began an Interim Pilot Program for GRAS Notices in June 2010 and responded to approximately 20 notices since then.

In 2010 after a two-year study, the Government Accountability Office (GAO) issued a report criticizing various aspects of the GRAS Notice program.[7] GAO recommended that FDA: (1) finalize the 1997 proposed rule, (2) minimize the potential for conflict of interest on "GRAS Panels" consisting of experts convened to support a GRAS determination (either a self-determination or a GRAS Notice submitted to FDA), (3) issue guidance on how to support GRAS conclusions, and (4) obtain more information on nanomaterials used in food. In December 2010, in part as a response to the GAO report, FDA requested further comments on the 1997 proposed rule in an effort to take final action on the proposal.

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[5] 62 Fed. Reg. 18938 (April 17, 1997).

[6] Final Rule, Response 44, *supra* Footnote 1 at 54985.

[7] GAO, "FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be GRAS" (GAO-10-246), Feb 3, 2010, available at http://www.gao.gov/products/GAO-10-246.

In February 2014, the 1997 proposal had yet to be finalized, and the Center for Food Safety filed a lawsuit claiming that FDA had violated the Administrative Procedure Act in informally administering the GRAS Notice program without having completed notice-and-comment rulemaking. The Center for Food Safety petitioned the court to vacate the 1997 proposed rule. FDA entered into a Consent Decree issued by the U.S. District Court for the District of Columbia in which the Agency agreed to issue a final rule on the GRAS review program by August 31, 2016. Thus, the recently finalized rule represents FDA's compliance with the requirements of the Consent Decree.

II. Highlights of the Final Rule

As a preliminary matter, we note that the final rule essentially leaves intact the GRAS framework and interpretation that FDA has long held. In other words, the final rule does not create "new" information burdens for self-GRAS determinations or GRAS Notices (apart from changes that are largely administrative in nature). For this reason, FDA confirms that recipients of "no questions letters" received in response to GRAS Notices submitted since 1998 need not resubmit such notices or provide supplemental information.[8] FDA declined to take actions that would have represented a major shift in its review of GRAS substances, such as creating a database of GRAS substances populated with not only on GRAS Notices but GRAS self-determinations or requiring GRAS Notices (and ending the ability to make GRAS self-affirmations). In this regard, the level of support required for a GRAS self-determination and a successful GRAS Notice are consistent with the level of support that the Agency has required for some time.

Relatedly, FDA confirms that a GRAS self-determination and GRAS Notice submitted to FDA require the same level of support.[9] That is, both conclusions must establish the safety of the substance under the intended conditions of use as required under Section 409(c)(5) of the FD&C Act and 21 C.F.R. § 170.30 and establish that such safety is "generally recognized" under Section 201(s) of the FD&C Act and Section 170.30.

A. The Use of Both Published and Unpublished Data and Information to Support a GRAS Conclusion

The final rule includes a detailed discussion of the use of unpublished data to support a "GRAS conclusion," which describes conclusions in both GRAS self-determinations and

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[8] Final Rule, Response 36, *supra* Footnote 1 at 54983.

[9] Final Rule, Response 128, *supra* Footnote 1 at 55027.

Notices.[10] FDA states that a GRAS conclusion "must be based on data that are generally available and accepted, and as such, are publicly available."[11] FDA notes that both the "usual mechanism" to establish that scientific information is generally available to the expert scientific community, which is publication in a peer-reviewed journal. Published "technical literature," including textbooks and reports by the Joint Expert Committee on Food additives (JECFA, a joint committee of the Food and Agriculture Organization and World Health Organization), would be supportive of a GRAS conclusion. However, FDA clarifies that the "mere fact that data and information are published or otherwise publicly available does not satisfy the criteria for general recognition of safety."[12] For such publicly available information to be supportive of a GRAS conclusion, it "must be plausible that qualified experts would be accessing those data and information using that mechanism."[13] Accordingly, publishing scientific data on a company website would not meet the GRAS through scientific procedures requirements, as experts may avoid such publications and do not offer an opportunity for peer review.

With respect to unpublished data, if relying on "scientific procedures" as the basis of your GRAS conclusion, the definition of "scientific procedures" under Section 170.3(h) requires consideration of unpublished data, and in the preamble to the final rule, FDA states that "all relevant data should be used in evaluating GRAS status, including unpublished data,"[14] which can corroborate or counter a GRAS conclusion. FDA clarifies that unpublished data can confirm a conclusion of GRAS status and should not be ignored; however, to achieve GRAS status, qualified experts must be able to determine safety without corroborative unpublished information. In other words, unpublished information cannot be the basis of a GRAS conclusion. An example of data and information that is unpublished but supportive of a GRAS

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[10] As discussed in Part I, GRAS conclusions may be based on either *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. The final rule defines "scientific procedures" under Section 170.3(h) to "include the application of scientific data (including, as appropriate, data from human, animal, analytical, or other scientific studies), information, and methods, *whether published or unpublished*, as well as the application of scientific principles, appropriate to establish the safety of a substance under the conditions of intended use" (emphasis added).

[11] Final Rule, Response 8, *supra* Footnote 1 at 54973.

[12] *Id.*

[13] *Id.*

[14] Final Rule, Response 9, *supra* Footnote 1 at 54973.

conclusion is a preliminary toxicology study conducted for the purpose of selecting doses for a subsequent 90-day study. Whereas the 90-day study should be published, the fact that the dose-finding study is not public is not problematic because it would not be the basis of a GRAS conclusion.

On the other hand, the new GRAS regulations explicitly require the notifier to ensure that all data, including unfavorable unpublished data, are discussed. Under new regulation 21 C.F.R. § 170.250 ("Part 6 of a GRAS Notice: Narrative"), paragraph (c) requires GRAS Notices submitted to the Agency to either discuss data and information that are or may be inconsistent with a GRAS conclusion by the petitioner or state that you have reviewed the available data and are not aware of any data or information that would be inconsistent with the GRAS conclusion. Thus, the new regulations require notifiers to discuss inconsistent or unfavorable data and information, regardless of whether it is publicly available. Also, under paragraph (e) of that regulation, notifiers are required to explain how there could be a GRAS conclusion if non-public safety data and information exist if qualified experts do not have access to such data and information. A failure to include relevant information not discussed in the GRAS Notice could result in FDA issuing an "insufficient basis letter" in response to the filing.

FDA also discusses the issue of whether a published GRAS panel opinion (*i.e.*, the opinion of experts convened by the entity conducting a GRAS evaluation) would satisfy the requirement of "general availability" based on the view that a GRAS panel is equivalent to or exceeds peer review. FDA categorizes a GRAS panel opinion as an example of "secondary scientific literature," which would be supportive of a GRAS conclusion if both the underlying data considered by the panel are generally available and the experts have the expertise appropriate to evaluate the underlying data. If the experts did not have appropriate expertise to evaluate the data and/or if the underlying data were not publicly available information, FDA confirms that a published GRAS panel opinion would not be supportive of a GRAS conclusion.[15] Further, information that is not generally available to qualified experts (*i.e.*, unpublished data and information) cannot serve as the basis for a GRAS conclusion merely because a GRAS panel has reviewed it. FDA states explicitly that GRAS panels are not equivalent to determinations by authoritative bodies and peer reviewed published articles.[16,17]

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[15] Final Rule, Response 11, *supra* Footnote 1 at 54974.

[16] Final Rule, Response 13, *supra* Footnote 1 at 54975. In response to GAO's recommendation that FDA address conflicts of interest on GRAS Panels, FDA states that it will issue guidance on this topic in the future. *See* Final Rule, Response 125, *supra* Footnote 1 at 55026.

B. Requirement to Include Dietary Exposure Information

While the 1997 proposed rule did include a requirement that GRAS Notices discuss dietary exposure to the GRAS-notified substance, the final rule does include such a requirement. Under 21 C.F.R. § 170.235, Part 3 of the GRAS Notice requires the notifier to provide an estimate of dietary exposure from the proposed uses discussed in the Notice (and a description of the assumptions used to develop that estimate), as well as estimate dietary exposure to reaction products, contaminants, and byproducts to which a consumer may be exposed by consuming the GRAS-notified substance. This information is essential to the GRAS evaluation because the analysis is whether a specific intended use of a substance may be considered GRAS. In other words, GRAS is not an implicit characteristic of a food; rather, it is an evaluation whether a particular use of (and resulting exposure to) a given substance may be GRAS.

FDA further specifies that consideration of dietary exposure must discuss the potential cumulative dietary exposure of considering the proposed use and existing uses, also taking account of "any chemically or pharmacologically related substances in the diet under Section 170.250(a)(1) (*i.e.*, to be included in the narrative section of the notice under Part 6). FDA acknowledges that the final rule does not require a notifier to determine an "acceptable daily intake" as part of the narrative.

C. Treatment of Trade Secret and Confidential Information

The final rule includes a detailed discussion of the handling of trade secret and confidential information that the notifier includes in a GRAS Notice but views as exempt from disclosure under FOIA, as well as the public availability of correspondence that FDA has with the notifier. Specifically, Part 1 of the GRAS Notice, which is required to discuss general aspects of the filing (*e.g.*, the identity of the substance, its intended conditions of use, the basis for the GRAS conclusion, and certification as to the comprehensiveness of the submission), is not permitted to include any information that is marked as trade secret or confidential. However, the other parts of the GRAS Notice may include confidential information. In general, FDA "believe[s] that it will be rare for a GRAS notice to include trade secret information."[18] For example, under Part 2, notifiers are required to provide "sufficient detail to evaluate" safety of the notified substance. If information considered to be trade secret can be omitted and the remaining manufacturing process information would still be sufficiently detailed to evaluate the

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[17] Once again, as indicated above, the level of information necessary for a GRAS self-determination is equivalent to that required in a GRAS Notice.

[18] Final Rule, Response 69, *supra* Footnote 1 at 55000.

safety of the notified substance, the notifier should omit the trade secret information. If, however, the trade secret information is submitted, the notifier must explain "how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to the trade secret information that the notifier considered in concluding that the substance is safe under the conditions of its intended use."[19] This requirement applies to any non-public information that could have a bearing on the safety determination, including trade secret information provided to a GRAS panel.

D. Freedom of Information Act (FOIA) Requests

The final rule includes a discussion of what information submitted in support of and in response to GRAS Notices will be public on its website and in response to FOIA requests. With respect to GRAS Notices, such filings are publicly available under FOIA when the Agency receives the filing even if the notice is subsequently not accepted for filing (or if FDA responds to the submission as general correspondence, rather than as a GRAS Notice, which FDA describes as a rare outcome).[20] However, FDA declined requests to publish a notice in the Federal Register when a GRAS Notice is filed; thus, the public would not likely be aware of the submission of a GRAS Notice until it has been accepted for filing and listed on FDA's website inventory, which FDA states it is updating on a monthly basis. Thus, from a practical standpoint, it is unlikely that the public would make a request for a copy of a GRAS Notice that had not been accepted for filing unless the existence of the filing was otherwise public information. FDA also confirms that a GRAS Notice cannot be withdrawn from the public record once submitted.

FDA also discusses the public availability of its response letters on its website. FDA may issue three different types of letters in response to a GRAS Notice: (1) a "no questions letter" (FDA has no questions in response to the filing concluding that a proposed use is safe); (2) an "insufficient basis letter" (FDA has evaluated the filing and other available information and concluded that there is not a sufficient basis for the GRAS conclusion); or (3) a "cease to evaluate letter" (in response to the notifier request, FDA is ceasing to evaluate the GRAS Notice). Both "no questions letters" and "insufficient basis letters" have been publicly available under the Interim Pilot Program from 1998 until the present on FDA's website and will continue to be publicly available.[21]

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[19] Final rule, Responses 69, *supra* Footnote 1 at 55000, and *see* Response 78, *supra* Footnote 1 at 55007-08.

[20] Final Rule, Response 113, *supra* Footnote 1 at 55021-22.

[21] Final Rule, Response 80, *supra* Footnote 1 at 55009.

By contrast, FDA has not made public the underlying basis for FDA ceasing to evaluate a GRAS notice. Rather, under the Interim Pilot Program, FDA had issued "cease to evaluate" letters that simply cite the notifier's request that FDA cease its review but do not discuss the underlying basis for that outcome. FDA received comments citing the shift in FDA's issuance of "cease to evaluate letters" in recent years. Specifically, between 1998 and 2009, CFSAN responded to 16% of GRAS notices with a "cease to evaluate letter," and between 1998 and 2002, CFSAN issued equal numbers of "cease to evaluate" and "insufficient basis" letters (*i.e.*, 16 of each type of letter were issued). However, from 2003 to 2009, CFSAN issued 31 "cease to evaluate letters" and only one "insufficient basis letter."[22] FDA acknowledged that this is problematic and has committed to include in "cease to evaluate letters" a description of the basis for ceasing the evaluation, and if the notifier does not provide an explanation for the basis in its request for FDA to cease review, FDA intends to explain the reasons for ceasing the evaluation from the Agency's point of view.[23]

Lastly, FDA discusses whether FDA will make publicly available letters in which FDA informs the notifier that the notice is not being accepted for filing. Under Section 170.265(a)(3), FDA is required to send a letter to the notifier explaining the reasons for not filing the notice. FDA specifies that these letters will not be publicly available on FDA's website (*i.e.*, because there would not be a related entry for the GRAS Notice to which such a letter could be associated) but states that the decision to release the letter in response to a FOIA request would be made on a case-by-case basis under the parameters for FDA's response to such requests under 21 C.F.R. Part 20.[24]

E. Unique Aspects of GRAS Notices for Animal Feed[25]

As mentioned above, the regulations under 21 C.F.R. § 570.225-570.255, addressing CVM's GRAS Notice program for substances in animal feed, are analogous to CFSAN's regulations in terms of general content, administrative details, and FDA's review timeline. However, GRAS Notices for animal feed will require some additional types of information, such as: (1) the subpopulation of target animal (*e.g.*, weaning piglets, laying hens, mature cattle); (2) potentially more technical or nutritive effect data than is required for CFSAN GRAS Notices (*i.e.*, because animals can receive one food as the sole source of nutrition, CVM states that it has

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22 Final Rule, Response 81, *supra* Footnote 1 at 55010.

23 *Id.*

24 Final Rule, Response 85, *supra* Footnote 1 at 55012-13.

25 *See* Final Rule, Section XXV, *supra* Footnote 1 at 55031-41.

a burden to ensure that the substance has the effect it intends to have to protect against adverse outcomes in animals); and (3) information on residues in edible tissues for food-producing animals, as well as a safety evaluation of such residues in humans, if applicable. Again, the requirement of these types of information does not represent a change from CVM's current practice under its Interim Pilot Program, but CVM's expectations are now formalized under the final rules.

We note that CVM included in the preamble a lengthy discussion of why it will continue to require physical and technical effect data in its GRAS Notices when such information has a bearing on safety (despite comments requesting that CVM cease this practice).[26] It is clear from CVM's discussion that it broadly interprets when technical effect data can have a bearing on safety, specifying that both substances added for nutritive effect or other effect (*e.g.*, anti-caking agents, binders, emulsifiers, enzymes, mixing aids, preservatives, processing aids, stabilizers, and substances added for aroma or flavor) can have an impact on safety for the target animal. CVM provides numerous examples of how technical effect data have an impact on safety, but as an illustration, CVM states that flavors can act as an attractant (*e.g.*, in aquaculture in raising fish fry). If not effective in serving that purpose, the safety issue is that the fish fry may starve to death. Accordingly, CVM would expect animal feeding studies to support the function of the substance as a flavor when added to animal food.

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Please let us know if you have any questions regarding the final rules or GRAS evaluations in general.

[26] Final Rule, *supra* Footnote 1, at 55032-35.