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A hard look at FDA's review of GRAS notices

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ABSTRACT

Generally Recognized as Safe (GRAS) substances are exempt from premarket approval; however, the standard of "reasonable certainty of no harm" is the same. In 1997, the voluntary GRAS affirmation process was replaced with the voluntary U.S. Food and Drug Administration (FDA) GRAS notice process. Under the GRAS notice process, pivotal safety data are required to be in the public domain, and consensus of safety among experts is required. FDA issues responses of "FDA has no questions", "Notice does not provide a basis for a GRAS determination", or, "At Notifier's request, FDA ceased to evaluate the notice." Of 528 notices reviewed, there were 393 "no questions letters", 17 "insufficient basis letters", and 84 "cease to evaluate letters". Of those deemed to be insufficient, most failed to meet the general recognition criteria. Only four raised questions about potential safety, of which three received a no questions letter upon providing more data. Of the 84 withdrawn notices, 22 received a no questions letter upon resubmission. In spite of criticisms, the FDA GRAS notice process is clearly defined, efficient, and cost-effective, and there have been no known public health issues following its implementation.

1. Introduction

According to United States (U.S.) law, any substance that is intentionally added to food is a food additive and is subject to premarket approval by the U.S. Food and Drug Administration (FDA) unless the substance is considered Generally Recognized as Safe (GRAS). The GRAS provision has been in effect since the 1958 Food Additives Amendment to the Federal Food, Drug and Cosmetic (FD&C) Act. While the concept of GRAS is well entrenched, the GRAS Notification Program is a more recent endeavor. Although the GRAS Notification is based on a proposed rule (62 FR 18938) (U.S. FDA, 1997) that has yet to be finalized, it has been in practice since 1998 and as of September 29, 2014 a total of 528 notices had been filed. The FDA stopped accepting petitions for GRAS affirmation once the GRAS notification program was implemented (Gayner et al., 2006).

The GRAS Notification Program superseded the GRAS Affirmation Program (initiated in 1972; 21 CFR §170.35, 2015) which was slow and resource intensive (Rulis and Levitt, 2009). Substances published in 21 CFR Parts 184 and 186 as affirmed GRAS included ingredients are from the GRAS list review by the Select Committee on GRAS Substances (SCOGS) as well as industry petitions for GRAS affirmation review.

While the GRAS process has come under recent criticism (GAO, 2010), the safety standards applied are considered to be the same as for an ingredient subject to a food additive petition review (Rulis and Levitt, 2009). As noted in 21 CFR §170.30 (b), "*General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient.*" Similar to a food additive petition, the FDA GRAS Notice requires detailed information about the identity of the ingredient, chemistry and manufacturing details, conditions of intended use and dietary exposure assessment which would take into consideration both existing and the proposed new uses. A GRAS determination on the basis of scientific procedures requires toxicology and other data to support safety being available in the published literature and, if based on history of use, documentation supporting use in food before 1958 would be required. However, the general recognition component of GRAS is not a food additive petition requirement (Rulis and Levitt, 2009). Also, FDA GRAS notices, on the basis of scientific procedures, generally include a signed "Expert Opinion Statement" supporting general consensus among the scientific community. It is important to note that it is not the Expert Panel that makes the GRAS determination. The Notifier makes the GRAS determination but generally upon consultation with the GRAS panel.

With respect to toxicological studies, in practice, a GRAS Notice

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determination requires the data to be available in the public domain (*e.g.*, peer-reviewed journal article) (Rulis and Levitt, 2009), while the toxicology data supporting a food additive petition can be proprietary but the full studies must be submitted to the FDA for review.

The Expert Opinion Statement and the requirement for publication of pivotal studies for a GRAS determination thereby demonstrate common knowledge about safety of the ingredient under the intended conditions of use, thus meet the following regulatory requirements:

> "… any substance that is intentionally added to food is a food additive, that is subject to premarket review and approval by FDA, unless the substance is **generally recognized**, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use …" [Section 201(s) and 409 Federal, Food, Drug, and Cosmetic Act (21 USC §321 & 21 USC §328, 2014)].

> "Safe or safety means that there is a reasonable certainty **in the minds of competent scientists** that the substance is not harmful under the intended conditions of use …" (21 CFR §170.3 (i), 2015).

Hence, the distinguishing features of the GRAS process in comparison to that of a food additive petition are the common knowledge about safety of the ingredient (under intended use) and the general availability and acceptance by the scientific community (food safety experts).

2. Basis for GRAS determination and FDA pre-GRAS notification meeting

As already noted, the basis for GRAS status may be either "scientific procedures" or "common use in foods" and the GRAS notice must specify the basis for GRAS. While the notice for a GRAS determination based upon scientific procedures must include information demonstrating agreement among competent scientists and pivotal scientific data in the public domain, GRAS based on history of use must include documentation supporting a substantial history of consumption within and a significant number of consumers.

Regardless of the basis for GRAS, it is recommended that the Notifier request a pre-GRAS notification meeting to review the basis for the GRAS determination including presenting a summary of the available data (chemistry/intake/safety) prior to filling the notice. The objective of such a meeting is two-fold: it provides the agency with an understanding of the chemistry and safety data set as well as the general recognition condition; and it allows the Notifier an opportunity to hear any comments from the FDA regarding potential data gaps, which could then be addressed prior to filing. After a notice is filed, upon completion of the evaluation, the FDA will issue a letter with their decision as either "FDA has no questions" (*i.e.*, the "Good Day" letter) or "Notice does not provide a basis for a GRAS determination". However, if the notice is withdrawn prior to FDA concluding their evaluation, it is noted that "At the Notifier's request, FDA ceased to evaluate the notice". The letters are accessible through the online FDA GRAS Notice Inventory. In contrast, under the GRAS affirmation process, it was necessary to publish findings in the Federal Register.

Following a pre-notification meeting, the Notifier would have a better understanding of the likelihood of obtaining an FDA "Good Day" letter.

3. Methods

Among the critics of the FDA GRAS notification program there is a misconception of an FDA notification review as being a "rubber stamp". Legally, the GRAS safety standard and assessment is equivalent to that of a food additive. The FDA expectations for GRAS are in line with Section 201(s) and 409 of the *Federal, Food, Drug, and Cosmetic Act* (FD&C Act – 21 USC §321 & 21 USC §328, 2014) and the Agency conducts a comprehensive review over a duration of, on average, six months (Gayner et al., 2006). Longer review times apply based on complexity or if additional data are requested. If the FDA has questions about the notice, the Notifier will be asked to submit supplemental information within a designated time frame.

Following a request for additional information, if the data are not received in a timely manner, FDA will contact the Notifier and request they withdraw the notice and resubmit at a later date. If a company withdraws the notice, they can still theoretically market the substance on the basis of their own GRAS determination for specified food uses based on the consensus of independent qualified experts that they had convened; however, if FDA has concerns about the safety of any food or ingredient they have the authority to remove the product from the market.

While FDA staff can be qualified as "generalist" GRAS experts having knowledge of chemistry, dietary exposure and toxicology, they will consult outside experts with specific credentials (*e.g.*, microbiology, pediatrics, allergenicity), as needed (Rulis and Levitt, 2009). It is not feasible for the FDA to have an expert in every scientific field on staff.

It is important to note that the GRAS Notification Program, like the GRAS Affirmation Program that it replaced is voluntary; however, the legal requirements of the FD&C Act would still apply whether or not a notification is made. There are business advantages of filing a GRAS notice since the FDA letter of "No Questions" provides an assurance of safety. This status is considered to be beneficial when trying to sell an ingredient to the food industry.

In order to comment on the FDA's handling of the GRAS notice program, we reviewed the publicly available documentation for every notice received by the FDA as of September 2014. We itemized each notice on the basis of the GRAS determination (*i.e.*, scientific procedures or history of use) and on the responses received. If a "no questions" response was not received, we noted the reasons given for either a conclusion of "no basis for GRAS" or a request for the notice to be withdrawn. Any ingredients for which a notice was resubmitted were identified and the FDA response received on the later submission was noted. Additional information was obtained from a memorandum dated November 4, 2010 from the Office of Regulations, Policy and Social Sciences published to Docket No. FDA-1997-N-0020 (Kahl, 2010).

4. Summary of GRAS notice decisions

The FDA received 528 GRAS notices as of the end of September 2014. The FDA letters posted to the GRAS Notice Inventory page were reviewed for all 528 notices. It should be noted that the number of notices does not correspond to the number of ingredients, since withdrawn notices are given a new number upon resubmission. Likewise, several notices for which the FDA indicated a finding of no basis for GRAS were also given a new number upon resubmission. Furthermore, since the Notifier makes the GRAS determination relevant to their substance and production process and their proposed uses and use levels, there may be multiple notices for the "same" ingredient; for example, steviol glycosides.

Therefore, based solely on the GRAS inventory number, at the end of September 2014, 393 notices had a "no questions letter", 17 notices had an "insufficient basis letter", 84 have a "cease to