DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 20, 25, 170, 184, 186, and 570

[Docket No. FDA–1997–N–0020 (formerly 97N–0103)]

RIN 0910–AH15

Substances Generally Recognized as Safe

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is issuing a final rule that amends and clarifies the criteria in our regulations for when the use of a substance in food for humans or animals is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) because the substance is generally recognized as safe (GRAS) under the conditions of its intended use. We also are amending our regulations to replace the voluntary GRAS affirmation petition process with a voluntary notification procedure under which any person may notify us of a conclusion that a substance is GRAS under the conditions of its intended use. The clarified criteria for GRAS status should help stakeholders draw more informed conclusions about whether the intended conditions of use of a substance in food for humans or animals complies with the FD&C Act, and the notification procedure will enable stakeholders to be aware of whether we have questioned the basis of a conclusion of GRAS status.

DATES: This rule is effective October 17, 2016. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by October 17, 2016 (see section XXIX, the ''Paperwork Reduction Act of 1995'' section of this document).

ADDRESSES: To ensure that comments on the information collection are received, the Office of Management and Budget (OMB) recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–7285, or emailed to *oira_submission@omb.eop.gov*. All comments should be identified with the OMB control number 0910–0342 and titled ''Substances Generally Recognized as Safe.'' Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: *Regarding substances that would be used in human food:* Paulette M. Gaynor, Center for Food Safety and Applied Nutrition (HFS–255), Food and Drug Administration, 5001 Campus Drive, College Park, MD 20740, 240–402–1192. *Regarding substances that would be used in animal food:* Geoffrey K. Wong, Center for Veterinary Medicine (HFV–224), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, 240–402–5838.

SUPPLEMENTARY INFORMATION:

Table of Contents

Executive Summary

Purpose and Coverage of the Rule

Although we have premarket review authority over food additives, a food manufacturer can intentionally add a substance to human food or animal food without our premarket review or approval if the substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use (GRAS). Since the 1970s, we have had regulations clarifying the statutory provision for eligibility for classification as GRAS. We also have had regulations governing a procedure for any person to voluntarily submit to us a petition asking us to affirm the GRAS status of a substance under the conditions of its intended use, and for us to engage in an intensive rulemaking process in response to that petition. Experience has shown that our regulations need further clarification to help stakeholders understand when a substance is eligible for classification as GRAS in human food or animal food under the conditions of its intended use. Experience also has shown that streamlining our evaluation of conclusions of GRAS status will enable us to evaluate more, and higher priority, substances. We are issuing this final rule to amend and clarify the criteria in our regulations for when a substance is GRAS under the conditions of its intended use in human food or animal food, and to replace the voluntary administrative procedure for petitioning us to affirm the GRAS status of a use of a substance in human food or animal food with a voluntary administrative procedure for notifying us about a conclusion that a substance is GRAS under the conditions of its intended use in human food or animal food.

Summary of the Major Provisions of the Rule

The final rule clarifies the criteria for the use of a substance to be eligible for classification as GRAS and establishes a new administrative procedure for any person to notify us of the basis for a conclusion that a substance is GRAS under the conditions of its intended use. With respect to criteria for eligibility for classification as GRAS, in the final rule we clarify that:

- A substance cannot be classified as GRAS under the conditions of its intended use if the available data and information do not satisfy the safety standard for a food additive under the FD&C Act;
- 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'' can be based on either ''scientific procedures'' or on experience based on common use of a substance in food prior to January 1, 1958; and
- General recognition of safety through scientific procedures must be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

With respect to the procedure for submitting a GRAS notice, we provide:

- Definitions for certain terms, including amendment, GRAS notice, notified substance, notifier, qualified expert, supplement, we/our/us, and you/your;
- A clear statement of the opportunity for any person to submit a GRAS notice;
- Information on available formats (electronic and paper) and where to send a GRAS notice;
- What data and other information may be incorporated into a GRAS notice;
- General provisions applicable to a GRAS notice;
- Specific information you must provide in your GRAS notice, including:
  - Signed statements and a certification (Part 1);
  - The identity, method of manufacture, specifications, and physical or technical effect of the notified substance (Part 2);
  - Dietary exposure (Part 3);
  - Self-limiting levels of use, in circumstances where the amount of the notified substance that can be added to human food or animal food is limited because the food containing levels of the notified substance above a particular level would become unpalatable or technologically impractical (Part 4);
  - The history of consumption of the substance for food use by a significant number of consumers (or animals in the case of animal food) prior to January 1, 1958, if a conclusion of GRAS status is based on common use of the substance in food prior to 1958 (Part 5);
  - A narrative that provides the basis for your conclusion of GRAS status, including why the scientific data, information, methods, and principles

described in the notice provide a basis for your conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use (Part 6); and

○ A list of the data and information that you discuss in the narrative of your GRAS notice, specifying which of these data and information are generally available, and which of these data and information are not generally available (Part 7); and

- Process for you to submit an amendment to your GRAS notice; and
- Process for you to request that we cease to evaluate your GRAS notice.

With respect to our administration of a GRAS notice, we specify:

- Information about how we will file a GRAS notice, respond to it, and send subsequent correspondence about it;
- Our commitment to respond within 180 days of filing of a GRAS notice, with a potential to extend our response timeframe by another 90 days;
- Our procedures in the event the intended conditions of use of the notified substance include use in a product subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture (USDA); and
- Provisions governing the public disclosure of a GRAS notice, including the actions we take to make some information regarding a GRAS notice readily accessible to the public.

As of the effective date of the final rule, we will close the docket for any pending GRAS affirmation petition. The petitioner may incorporate the applicable petition into a new GRAS notice.

Costs and Benefits

The final rule eliminates the petition process to affirm that a substance is GRAS under the conditions of its intended use and replaces that petition process with a GRAS notification procedure. We estimate that over 10 years with a 7 percent discount rate, the present value of the total costs of the final rule range from $0.9 million to $3.3 million; with a 3 percent discount rate, the present value of the total costs range from $0.9 million to $3.4 million. The annualized costs of the rule range from $0.1 million to $0.4 million with a 7 percent discount rate and range from $0.1 million to $0.5 million with a 3 percent discount rate. We do not quantify the benefits of the final rule, but assume that firms will only participate in the GRAS notification procedure when they expect to receive a non-negative private benefit. The GRAS notification procedure will allow us to complete our evaluation within the timelines specified in the final rule. The following table includes a summary of the benefits and costs of the final rule.

SUMMARY OF BENEFITS AND COSTS OF THE FINAL RULE

Total benefits	Present value of total costs with 7 percent discount rate ($ mil)	Present value of total costs with 3 percent discount rate ($ mil)	Total annualized costs over 10 years with 7 percent discount rate ($ mil)	Total annualized costs over 10 years with 3 percent discount rate ($ mil)
Not estimated	$0.9 to $3.3	$0.9 to $3.4	$0.1 to $0.4	$0.1 to $0.5.

TABLE OF ABBREVIATIONS AND ACRONYMS

Abbreviation/acronym	What it means
1958 amendment	1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act.
AAFCO	Association of American Feed Control Officials.
Affected petitioner	Any person who had submitted a pending petition.
BATF	Bureau of Alcohol, Tobacco, and Firearms.
CFSAN	Center for Food Safety and Applied Nutrition.
CVM	Center for Veterinary Medicine.
EPA	U.S. Environmental Protection Agency.
FDA	U.S. Food and Drug Administration.
FDAMA	1997 Food and Drug Administration Modernization Act.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FOIA	Freedom of Information Act.
FSIS	Food Safety and Inspection Service of the U.S. Department of Agriculture.
GAO	Government Accountability Office.
GRAS	Generally Recognized as Safe.
JECFA	Joint Expert Committee on Food Additives.
MOU	Memorandum of Understanding.
N/A	Not Applicable.
OMB	Office of Management and Budget.
Pdf	Portable document format.
Pending petition	A filed GRAS affirmation petition that is pending on the date that the petition process is replaced with a notification procedure.
PHO	Partially hydrogenated oil.
PRA	Paperwork Reduction Act.
TTB	Alcohol and Tobacco Tax and Trade Bureau.
USDA	U.S. Department of Agriculture.

I. Introduction

A. History of FDA's Approach to the GRAS Provision of the FD&C Act

In 1958, in response to public concern about the increased use of chemicals in foods and food processing and with the support of the food industry, Congress enacted the Food Additives Amendment (the 1958 amendment) to the FD&C Act. The basic thrust of the 1958 amendment was to require that, before a substance could be used in food, its sponsor demonstrate the safety of the substance to FDA, and that we establish a regulation prescribing the conditions under which the substance may be safely used. The 1958 amendment

defined the terms ''food additive'' (21 U.S.C. 321(s)) and ''unsafe food additive'' (21 U.S.C. 348(a)), established a premarket approval process for food additives (21 U.S.C. 348(b) through (g)), and amended the food adulteration provisions of the FD&C Act to deem adulterated any food that is, or bears or contains, any food additive that is unsafe within the meaning of 21 U.S.C. 348 (see 21 U.S.C. 342(a)(2)(C)).

Congress recognized that, under this scheme, 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 (Ref. 1). We have incorporated this safety standard into our regulations for food additives and GRAS substances (§ 170.3(i)) (21 CFR 170.3(i)). (We note that although this rule addresses substances intended for use in animal food as well as substances intended for use in human food, in this introduction we describe the history of the our GRAS regulations from the perspective of human food only.) If we find an additive to be safe, based ordinarily on data submitted by the sponsor to us in a food additive petition, we promulgate a regulation specifying the conditions under which the additive may be safely used.

In enacting the 1958 amendment, Congress recognized that many substances intentionally added to food would not require a formal premarket review by FDA to assure their safety, either because their safety had been established by a long history of use in food or by virtue of the nature of the substance, its customary or projected conditions of use, and the information generally available to scientists about the substance. Congress thus adopted, in section 201(s) of the FD&C Act (21 U.S.C. 321(s)), a two-step definition of ''food additive.'' The first step broadly includes 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 food. The second step, however, excludes from the definition of ''food additive'' substances that are generally recognized, among experts qualified by scientific training and experience to evaluate their safety (''qualified experts''), 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 through experience based on common use in food) to be safe under the conditions of their intended use. Importantly, under section 201(s) of the FD&C Act, it is the use of a substance, rather than the substance itself, that is eligible for GRAS status. It is on the basis of the GRAS provision within the food additive definition that many substances (such as vinegar, vegetable oil, baking powder, and many spices, flavors, gums, and preservatives) are lawfully marketed today without a food additive regulation. Under the 1958 amendment, a substance that is GRAS for a particular use may be marketed for that use without our review and approval. However, when a use of a substance does not qualify for GRAS status or other exceptions provided under section 201(s) of the FD&C Act, that use of the substance is a food additive use subject to the premarket approval mandated by the FD&C Act. In such circumstances, we can take enforcement action to stop distribution of the food substance and foods containing it on the grounds that such foods are or contain an unlawful food additive.

Shortly after passage of the 1958 amendment, we clarified the regulatory status of a multitude of food substances that were used in food prior to 1958 and amended our regulations to include a list of food substances that, when used for the purposes indicated and in accordance with good manufacturing practice, are GRAS. This list was incorporated into our regulations as § 121.101(d) (21 CFR 121.101(d)) (now part 182 (21 CFR part 182)) (24 FR 9368; November 20, 1959). As part of that rulemaking, however, we acknowledged that it would be impracticable to list all substances that are GRAS for their intended use (§ 121.101(a); current § 182.1(a)).

Section 121.101(d) became commonly referred to as ''the GRAS list.'' We added other categories of substances (*e.g.,* spices, seasonings, and flavorings) to the GRAS list in subsequent rulemakings (25 FR 404, January 19, 1960; and 26 FR 3991, May 9, 1961).

Many substances that were considered GRAS by the food industry were not included in our GRAS list. Under the 1958 amendment, a substance that is GRAS under the conditions of its intended use may be marketed for that use without Agency review and approval. Nonetheless, as a practical matter, manufacturers who concluded on their own initiative that use of a substance qualified for GRAS status frequently decided to obtain our opinion on whether their conclusion was justified. Many manufacturers wrote to us and requested an ''opinion letter,'' in which Agency officials would render an informal opinion on the GRAS status of use of a substance. Although convenient and expedient, these opinion letters were often available only to the requestor. Moreover, these opinion letters were not binding on us even at the time they were issued and letters issued before April 9, 1970, were in fact revoked (21 CFR 170.6; 35 FR 5810; April 9, 1970).

In 1969 (34 FR 17063; October 21, 1969), we deleted various cyclamate salts, a family of nonnutritive sweeteners, from the GRAS list because they were implicated in the formation of bladder tumors in rats (Ref. 2). In response to the concerns raised by the new information on cyclamates, then-President Nixon directed us to reexamine the safety of GRAS substances (Ref. 3), and we announced that we were conducting a comprehensive study of substances presumed to be GRAS (35 FR 18623; December 8, 1970). The purpose of the study was to evaluate, by contemporary standards, the available safety information regarding substances presumed to be GRAS and to promulgate each item in a new (*i.e.,* affirmed) GRAS list, a food additive regulation, or an interim food additive regulation pending completion of additional studies.

In the notice announcing the comprehensive review of presumed GRAS substances, we proposed criteria that could be used to establish whether these substances should be listed as GRAS, become the subject of a food additive regulation, or be listed in an interim food additive regulation pending completion of additional studies (35 FR 18623). These criteria were incorporated into our regulations as § 121.3 (precursor of current § 170.30) (36 FR 12093; June 25, 1971).

We made a second announcement that we were conducting a study of presumed GRAS substances (36 FR 20546; October 23, 1971) and subsequently instituted a rulemaking to establish procedures that we could use, on our own initiative, to affirm the GRAS status of substances that were the subject of that review and were found to satisfy the criteria established in § 121.3 (proposed rule, 37 FR 6207, March 25, 1972; final rule, 37 FR 25705, December 2, 1972). These procedures were subsequently codified at § 170.35(a) and (b). Because the GRAS review did not cover all GRAS substances (*e.g.,* it did not cover many substances that were marketed based on a manufacturer's independent conclusion of GRAS status), that rulemaking included a mechanism (the GRAS affirmation petition process; § 170.35(c)) whereby

an individual could petition us to review the GRAS status of substances not being considered as part of our GRAS review. We codified our affirmations of GRAS status in current parts 184 and 186 (21 CFR parts 184 and 186).

In 1974, we proposed to clarify the criteria for GRAS status, the differences between GRAS status and food additive status, and the procedures being used to conduct the current review of food substances (39 FR 34194; September 23, 1974). The final regulations based on this proposal amended § 121.3 (now § 170.30) to distinguish a conclusion of GRAS status through scientific procedures (§ 170.30(b)) from a conclusion of GRAS status through experience based on common use in food (§ 170.30(c)) (41 FR 53600; December 7, 1976). Those final regulations also established definitions for ''common use in food'' (now § 170.3(f)) and ''scientific procedures'' (now § 170.3(h)). We subsequently added criteria (§ 170.30(c)(2)) for the determination of GRAS status through experience based on common use in food when that use occurred exclusively or primarily outside of the United States (53 FR 16544; May 10, 1988).

To the extent that a person elected to submit a GRAS affirmation petition, the GRAS affirmation process could facilitate awareness, by us as well as the domestic and international food industry, of independent conclusions of GRAS status. However, the GRAS affirmation petition process involved the resource-intensive rulemaking process. In the **Federal Register** of April 17, 1997 (62 FR 18938; the proposed rule), we proposed to: (1) Clarify the criteria for eligibility for classification as GRAS; and (2) replace the GRAS affirmation petition process with a notification procedure whereby any person may notify us of a conclusion that a particular use of a substance is GRAS. We explained that we would evaluate whether the notice provides a sufficient basis for a GRAS conclusion and whether information in the notice or otherwise available to us raises issues that lead us to question whether use of the substance is GRAS. We would respond to the notifier in writing and could advise the notifier that we had identified a problem with the notice. Although information in a notice would be publicly available consistent with the Freedom of Information Act (FOIA), we would make readily accessible to the public a basic description the notified substance, the conditions of its intended use, and the statutory basis for GRAS status (*i.e.,* through scientific procedures or through experience based on common use in food), as well as our response to the notice. In 2010, we reopened the comment period for the proposed rule to update comments and to solicit comment on specific issues (75 FR 81536, December 28, 2010; the 2010 notice). (See section II.D for additional information about this reopening of the comment period).

In the proposed rule, we invited interested persons to notify us about their conclusions of GRAS status as described in the proposed rule (62 FR 18938 at 18954; the ''Interim Pilot program''). Our Center for Food Safety and Applied Nutrition (CFSAN) filed its first GRAS notice in 1998 and has filed 614 GRAS notices as of December 31, 2015. Our Center for Veterinary Medicine (CVM) established its Interim Pilot program more recently (75 FR 31800, June 4, 2010) and filed its first GRAS notice in December 2010. As of December 31, 2015, CVM has filed 18 GRAS notices.

B. Report by the Government Accountability Office and How We Are Addressing Its Recommendations

From 2008 to 2010, the Government Accountability Office (GAO) conducted a study related to ingredients used in human food on the basis of the GRAS provision in section 201(s) of the FD&C Act. In 2010, GAO issued a report (Ref. 4; the GAO report) that included a number of recommendations for FDA. For example, the GAO report recommended that we finalize the proposed rule to establish a notification program for GRAS substances, strive to minimize the potential for conflict of interest on ''GRAS panels,'' issue guidance on how to document GRAS conclusions, and obtain more information about the use of engineered nanomaterials. (As we note in section VI.B, this document uses the term ''GRAS panel'' to mean a panel of individuals convened for the purpose of evaluating whether the available scientific data, information, and methods establish that a substance is safe under the conditions of its intended use in food.) Consistent with the recommendations in the GAO report, this document finalizes the GRAS notification procedure as requested by GAO. It also announces our intent to issue guidance in the near future to: (1) Provide recommendations regarding the use of a ''GRAS panel,'' including the potential for conflict of interest; and (2) remind the food industry that the same standards apply to a conclusion of GRAS status regardless of whether the conclusion is submitted to us as a GRAS notice or is not submitted to us. (See Response 125, Response 128, and Response 129).

In 2012, we made available a draft guidance entitled ''Draft Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients That Are Color Additives'' (Ref. 5) (77 FR 24722, April 25, 2012). We finalized this guidance in 2014 (Ref. 6) (79 FR 36533, June 27, 2014). The guidance includes recommendations for assessing the effect of a significant manufacturing process change (including the use of nanotechnology) on the safety and regulatory status of substances used in human food, including those that are GRAS. In this guidance, we stated that, at present, for nanotechnology applications in food substances, there are questions related to the technical evidence of safety as well as the general recognition of that safety, that are likely to be sufficient to warrant formal premarket review and approval by FDA, rather than to satisfy criteria for GRAS status. In addition, in 2011, we made available a draft guidance entitled ''Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology'' (Ref. 7) (76 FR 34715, June 14, 2011). We finalized this guidance in 2014 (Ref. 8) (June 27, 2014, 79 FR 36534), which describes our thinking on determining whether FDA-regulated products involve the application of nanotechnology.

C. Issues Regarding the Legal and Regulatory Framework for Substances Added to Food

The GAO report discussed issues fundamental to the legal and regulatory framework for our oversight of the safety of substances added to food, such as the voluntary nature of the GRAS affirmation petition process and the proposed GRAS notification procedure. In light of these issues, the GAO report recommended that we ask any company evaluating whether a substance is GRAS under the conditions of its intended use to provide us with basic information about any conclusion of GRAS status (Ref. 4). Some comments to this rulemaking raise similar issues. For example, some comments address the voluntary nature of the GRAS notification procedure or assert that we have implied legal authority to require that companies notify us of a conclusion of GRAS status (see Comment 1 and Comment 28). Some comments ask us to require companies to maintain active

and accurate listings for all GRAS substances, not just those that are the subject of a GRAS regulation or a GRAS notice, in a public database (see Comment 3). Some comments ask us to require certain postmarket submissions of exposure and safety data related to all GRAS substances, to require submissions for conclusions of GRAS status that predate the final rule, and to require any notifier who ''withdraws'' a GRAS notice or receives an ''insufficient basis letter'' to notify us about any use of that substance (see Comment 30). One comment asks us to exclude uses of ''novel'' substances from consideration for eligibility for classification as GRAS (see Comment 19).

Some comments discuss an industry practice of convening a ''GRAS panel'' of ''qualified experts'' to provide an opinion on whether a company's evaluation of the available data and information support a conclusion that a substance is safe under the conditions of its intended use, and express concern that such a ''GRAS panel'' may base its opinion partly on confidential data and information that are provided to the GRAS panel, but not provided to us in a submitted GRAS notice (see Comment 10 through Comment 14, Comment 69, and Comment 78).

Some comments express concern that the GRAS notification procedure would be viewed as a ''fast-track'' option that would tempt a company that should submit a food additive petition to submit a GRAS notice instead (see Comment 32). A published critique of the GRAS notification procedure (Ref. 9) likewise expresses concern that industry is simply using the GRAS notification procedure as an alternative to the food additive petition process, contrasting the number of food additive petitions filed in recent years with the number of GRAS notices filed in recent years. This report also expresses concern that there are an indeterminate—but not insignificant—number of industry conclusions of GRAS status that are not the subject of a GRAS notice to FDA.

In this document, we respond to such comments in the context of our proposed revisions to the criteria for eligibility for classification as GRAS and our proposal to replace one voluntary administrative procedure, *i.e.,* the GRAS affirmation petition process, with a different voluntary administrative procedure, *i.e.,* the GRAS notification procedure. (See Response 1, Response 3, Response 10 through Response 14, Response 19, Response 28, Response 30, Response 32, Response 69, and Response 78). As we discuss in Response 28, the broader issues raised by these comments about the legal and regulatory framework for our oversight of the safety of substances added to food are outside the scope of this rulemaking. Thus, this final rule does not address the possibility that we might enhance our oversight through additional rulemaking or other actions based on our current legal authority. Nonetheless, we will continue to consider the broader issues raised by these comments and take further action as appropriate under our existing authority through future rulemaking. Importantly, however, this final rule *does* establish uniform criteria for describing the basis for a conclusion that a substance is GRAS under the conditions of its intended use, and those uniform criteria apply to all conclusions of GRAS status, not just conclusions of GRAS status that are submitted to us as a GRAS notice. As discussed in Response 129, we are issuing a guidance directed to any person who evaluates whether the available data and information regarding the safety of a substance under the conditions of its intended use satisfy GRAS criteria. The purpose of the guidance is to: (1) Remind such persons of their responsibilities under the FD&C Act regarding a conclusion of GRAS status, regardless of whether the conclusion of GRAS status is submitted to us as a GRAS notice; and (2) refer such persons to key resources, such as those discussed in Response 128, for evaluating the safety of the substance under the conditions of its intended use and for evaluating whether the available data and information regarding safety satisfy the criteria for eligibility for classification as GRAS in § 170.30.

D. Recent FDA Actions Related to GRAS Criteria

In the following paragraphs, we describe two examples of steps we have taken to address concerns about the safety of certain substances marketed under the GRAS provision. The first example is partially hydrogenated oils (PHOs), which are the primary dietary source of industrially produced *trans* fatty acids, or *trans* fat. The second example is certain uses of caffeine.

Although we had not listed the most commonly used PHOs in either part 182 or part 184, they had been used in food for many years based on conclusions of GRAS status by industry. In a notice published in the **Federal Register** of November 8, 2013 (78 FR 67169), we described new scientific evidence and the findings of expert scientific panels regarding *trans* fat and requested comments and scientific data and information on our tentative determination that PHOs are not GRAS for any use in food based on current scientific evidence establishing the health risks associated with the consumption of *trans* fat. In the **Federal Register** of June 17, 2015 (80 FR 34650), we issued a declaratory order announcing our final determination that there is no longer a consensus among qualified experts that PHOs are GRAS for any use in human food.

The GRAS list in part 182 includes the use of caffeine in cola-type beverages at a maximum level of 0.02 percent (§ 182.1180). In 2010, we issued four warning letters regarding the use of caffeine under markedly different conditions of use than the use listed in § 182.1180, *i.e.,* the use of caffeine as an added ingredient in alcoholic beverages (Ref. 10 through Ref. 13). In our letters, we stated that, based on the publicly available literature, a number of qualified experts have concerns about the safety of caffeinated alcoholic beverages. We described these concerns, citing published literature. We further stated that FDA is not aware of data or other information to establish the safety of caffeine as used in these products. We therefore informed the companies who were marketing these caffeinated alcoholic beverages that caffeine, as used in the companies' products, is an unsafe food additive, and therefore the products are adulterated under section 402(a)(2)(C) of the FD&C Act (21 U.S.C. 342(a)(2)(C)). (The Alcohol and Tobacco Tax and Trade Bureau (TTB) also notified the four companies that if we deem their caffeinated alcohol beverage products adulterated under the FD&C Act, TTB would consider them to be mislabeled under the Federal Alcohol Administration Act, making it a violation for industry members to sell or ship the products in interstate or foreign commerce (Ref. 14).) The companies subsequently ceased distribution of these products.

In recent years, other food and beverage products containing caffeine as an added substance have been introduced into the marketplace, including so-called ''energy drinks'' that are frequently marketed for their stimulant properties. When there are new uses of an added food substance without FDA's premarket engagement, presumably because a manufacturer has concluded that such a use is GRAS, we must react to the new uses after they emerge. In such cases, it can be challenging for FDA to accurately assess consumption patterns and intake levels and to determine whether those new uses are safe and lawful in light of all of the available safety data. FDA has engaged with the National Academies of Science (Ref. 15), trade associations, and other industry representatives, some of

whom are conducting a systematic review on the health effects associated with the consumption of caffeine (Ref. 16 and Ref. 17).

E. Moving Forward Under This Final Rule

We believe that our filing of more than 600 GRAS notices for substances used in human food is evidence that the substitution of a GRAS notification procedure for the GRAS affirmation petition process has benefits for consumers, FDA, the regulated industry, and other stakeholders. We have increased our awareness of the composition of the nation's food supply and the dietary exposure to GRAS substances, which helps us to ensure the safe use of substances added to food. The ongoing submission of GRAS notices provides evidence that our response to a GRAS notice can support the marketing of a food substance by the regulated industry. Notified substances include substances that are intended to address food safety problems (*e.g.,* antimicrobial substances and substances intended to reduce acrylamide formation) and public health issues (*e.g.,* substances that would reduce levels of sodium chloride in food). In addition, the letters we issue responding to GRAS notices demonstrate that we inform notifiers of any scientific or regulatory issues that call into question a notifier's conclusion of GRAS status, and stakeholders have ready access to those letters. As discussed in Response 81, we intend to increase the transparency of our response letters when a notifier asks us to cease to evaluate a GRAS notice.

In the years since we published the proposed rule, we have taken important public health actions with respect to substances used in food on the basis of the GRAS provision of the FD&C Act. For example, we recently announced an initiative to establish voluntary short-term and long-term goals for sodium reduction in a variety of identified categories of foods to address the excessive intake of sodium in the current population and promote improvements in public health (81 FR 35363, June 2, 2016). In addition, we recently held a public meeting in which we invited public comment on what should be included, changed, or even excluded from our guidance entitled ''Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients'' (79 FR 64603, October 30, 2014); that guidance is intended to help interested parties understand our expectations regarding how to determine which toxicity studies are appropriate and regarding the design, conduct, and reporting of the results of toxicity studies and applies to assessing the safety of GRAS substances. As discussed in section I.D, we also have taken key postmarket actions such as issuing a declaratory order announcing our final determination that there is no longer a consensus among qualified experts that PHOs are GRAS for any use in human food, as well as issuing warning letters regarding the use of caffeine as an added ingredient in alcoholic beverages.

For reasons such as those discussed in this section, and after fully considering comments submitted to this rulemaking, this rule announces that we are replacing the former GRAS affirmation petition process with a GRAS notification procedure.

We strongly encourage any company considering the addition of a substance to any food on the basis of a conclusion of GRAS status to contact us and follow the available procedures for FDA oversight of such decisions. As we move forward to implement the GRAS notification procedure that is the subject of this rulemaking, we intend to continue to closely monitor and assess the ramifications of the use of substances without food additive approval or evaluation by FDA through the GRAS notification procedure. We intend to take action as appropriate, such as we did in the case of PHOs and caffeinated alcoholic beverages, particularly when the available data and information raise a safety concern about the use of a substance.

We advise any company that intends to market a food substance on the basis of an independent conclusion of GRAS status (*i.e.,* a conclusion of GRAS status that would remain with the proponent of the conclusion rather than be submitted to us as a GRAS notice) to carefully consider whether this use fully satisfies the criteria for eligibility for classification as GRAS and to carefully review the discussions in this document relevant to those criteria. Fundamental to all conclusions of GRAS status is the criterion that 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 (see § 170.30(a)). In addition, the criteria for eligibility for classification as GRAS through scientific procedures require that general recognition of safety through scientific procedures be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles (§ 170.30(b)). Although general recognition of safety through scientific procedures may be corroborated by the application of unpublished scientific data, information, or methods (§ 170.30(b)), to satisfy GRAS criteria qualified experts must be able to conclude that the substance is not harmful under the conditions of its intended use without access to ''corroborative'' information (see, *e.g.,* Response 9). For example, as discussed in Response 69 there could be no basis for a conclusion of GRAS status if trade secret information (or other non-public information) is necessary for qualified experts to reach a conclusion that the notified substance is safe under the conditions of its intended use.

We also advise any company who intends to market a food substance on the basis of an independent GRAS conclusion that relies, in whole or in part, on the opinion of a specially convened ''GRAS panel'' to carefully review the discussions in this document regarding whether and how the opinion of a GRAS panel can support an independent conclusion of GRAS status. For example, as discussed in Response 10 and Response 11 whether a published ''GRAS panel'' opinion that discusses data and information that are available to the members of the GRAS panel, but not generally available to qualified experts, could support an independent conclusion of GRAS status would depend on factors such as whether that publication includes details similar to details that would be included in a publication in the primary scientific literature; the subject matter expertise of the members of the GRAS panel; and whether the members of the GRAS panel would be considered representative of experts qualified by scientific training and experience to evaluate the safety of the substance under the conditions of its intended use. For example, a published GRAS panel opinion that includes a very general statement that a study was conducted and reported no adverse findings would not suffice to make the study ''generally available'' as required by the criteria for eligibility for classification as GRAS and would merely be a generally available opinion about data and information that are not generally available. As another example, a ''GRAS panel'' opinion published by scientists without expertise appropriate to address the applicable safety questions could not provide evidence that the conclusions in the publication are ''generally

accepted.'' Unless both criteria, *i.e.,* ''generally available'' as well as ''generally accepted'', are satisfied, there would be no basis for a conclusion of GRAS status.

II. Background

A. The Proposed Rule

We proposed to: (1) Clarify the criteria for eligibility for classification as GRAS; and (2) replace the GRAS affirmation petition process with a notification procedure through which any interested person may notify us of a determination that a particular use of a substance is GRAS (62 FR 18938). In the proposed rule, we:

- Discussed the 1958 amendment, including judicial decisions bearing on GRAS criteria and the burden on the proponent of a conclusion of GRAS status to show that there is a consensus of expert opinion regarding the safety of the use of the substance (62 FR 18938 at 18939);
- Described the history of our approach to the GRAS provision, including: (1) A GRAS list, first established in 1959, in which we clarified the regulatory status of a multitude of food substances that were used in food prior to 1958; (2) opinion letters in which Agency officials rendered an informal, non-binding opinion on the GRAS status of a use of a substance; (3) an FDA-initiated GRAS review to evaluate the available safety information regarding substances presumed to be GRAS; and (4) GRAS criteria and the GRAS affirmation petition process (62 FR 18938 at 18939 to 18940);
- Discussed ''elements of the GRAS standard,'' in which we distinguished the ''technical element'' of the GRAS standard (*i.e.,* safety) from the ''common knowledge element'' of the GRAS standard (*i.e.,* general recognition) (62 FR 18938 at 18940 to 18941);
- Proposed the submission requirements for the GRAS notification procedure, including: (1) A ''GRAS exemption claim,'' in which a notifier would take responsibility for a GRAS determination; (2) information about the identity of the notified substance; (3) information about any self-limiting levels of use; and (4) a comprehensive discussion of the basis for the GRAS determination (proposed §§ 170.36 (c) and 570.36(c));
- Proposed what we would do when we received a GRAS notice, including: (1) Acknowledge receipt of the GRAS notice; (2) evaluate whether the notice provides a sufficient basis for a GRAS determination and respond to the notifier in writing; (3) make readily accessible to the public the notice's ''GRAS exemption claim'' and our response to the notice; and (4) disclose other releasable information in a notice in accordance with our regulations, in part 20 (21 CFR part 20), implementing the FOIA (proposed §§ 170.36 (d) through (f) and 570.36(d) through (f)); and
- Proposed to: (1) Convert any GRAS affirmation petition that was pending on the effective date of the rule establishing the notification procedure to a GRAS notice; and (2) require the petitioner to submit an amendment to the converted petition to satisfy the procedural requirements of the GRAS notification procedure (proposed §§ 170.36(g) and 570.36(g)).

We requested comments on the proposed rule by July 16, 1997.

B. Interim Pilot Program

In the proposed rule, we invited interested persons who determine that a use of a substance is GRAS to notify us of those determinations as described in the proposed rule (62 FR 18938 at 18954). We explained that we would administer the notices as described in the proposed rule (*i.e.,* we would acknowledge receipt of the notice, respond in writing to the notifier, and make publicly accessible a copy of all ''GRAS exemption claims'' and our response). Although we would make a good faith effort to respond within the proposed 90-day timeframe, we would not be bound by such a timeframe. We stated that we would determine whether our experience in administering such notices suggests modifications to the proposed procedure.

CFSAN received its first GRAS notice in 1998. CFSAN wrote a memorandum documenting its experience in evaluating GRAS notices during the period 1998–2009 (Ref. 18, ''CFSAN's 2010 experience document'') and added that memorandum to the docket for this rulemaking in 2010. Unless we say otherwise, the discussions in this document referring to FDA's experience during the Interim Pilot program refer to CFSAN's experience.

During the Interim Pilot program, CFSAN's response to a GRAS notice fell into three categories as shown in table 1 in this document. We refer to these categories of response throughout this document. Table 1 in CFSAN's 2010 experience document shows the category of response for CFSAN's GRAS notices that came to closure by December 31, 2009. CFSAN has now written an updated memorandum showing the category of response for CFSAN's GRAS notices that came to closure by December 31, 2015 (Ref. 19).

TABLE 1—CATEGORIES OF LETTERS RESPONDING TO A GRAS NOTICE DURING THE INTERIM PILOT PROGRAM

Category of response letter	Typical text of the response
''No questions letter''	Based on the information provided by the notifier, as well as other information available to FDA, the Agency has no questions at this time regarding the notifier's conclusion that the notified substance is GRAS under the intended conditions of use. The Agency has not, however, made its own determination regarding the GRAS status of the subject use of the notified substance. As always, it is the continuing responsibility of the notifier to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.
''Insufficient basis letter''	FDA has evaluated the information that the notifier discusses in its GRAS notice as well as other data and information that are available to us. The notice does not provide a sufficient basis for a determination that the notified substance is GRAS under the conditions of its intended use.
''Cease to evaluate letter''	In correspondence dated [month, day, year], you asked that we cease to evaluate your notice. We ceased to evaluate your GRAS notice, effective the date we received your correspondence.

In this document, we frequently cite CFSAN's experience during the Interim Pilot program when responding to comments asking us to clarify how we intend to administer various provisions of the rule, as well as state our intent to continue the applicable practice in the future, because this experience is relevant to our administration of the GRAS notification program. Nonetheless, we intend to adapt our practices, consistent with the provisions of this rule, as circumstances warrant and as necessary to administer the GRAS notification program consistent

with appropriate public health policy, current scientific information, our available resources, and the scientific and regulatory issues raised by specific GRAS notices. For example, as discussed in Response 92 we intend to continue to include standard language such as that shown in table 1 in responding to GRAS notices. However, this language may evolve over time.

CVM established its Interim Pilot program in June, 2010 (75 FR 31800, Docket No. FDA–2010–N–0215) and filed its first GRAS notice in December 2010. CVM did not have any experience to document as of 2010 and, thus, had not written its own experience document at that time. As of December 31, 2015, CVM had responded to 18 GRAS notices, and has now documented its experience with those 18 GRAS notices with respect to some comments specifically directed to the GRAS notification procedure administered by CVM (Ref. 20; ''CVM's experience document''). We discuss CVM's experience with GRAS notices submitted for substances intended for use in animal food in section XXV.

We are ending both the CFSAN Interim Pilot program announced in the proposed rule, and the CVM pilot program announced in Docket No. FDA–2010–N–0215, as of October 17, 2016. On that date, the final rule becomes effective and will govern the GRAS notification procedure.

C. 2010 Report of the Government Accountability Office

As noted in section I.B, from 2008 to 2010 GAO conducted a study related to ingredients used in human food on the basis of the GRAS provision of section 201(s) of the FD&C Act. In 2010, GAO issued a report (Ref. 4) that included a number of recommendations for FDA. We responded to the GAO's recommendations, and that response is also included in the GAO report.

D. 2010 Notice Reopening the Comment Period

As noted in section I.A, we reopened the comment period for the proposed rule to update comments (75 FR 81536). We did so because of the length of time that had elapsed since publication of the proposed rule and because we had identified a number of issues within the scope of the proposed rule that may require further clarification based on CFSAN's experience with GRAS notices during the Interim Pilot program, comments we received on the proposed rule, and GAO's recommendations (75 FR 81536 at 81537). These issues related to the proposed revisions to the criteria for eligibility for classification as GRAS (Issue 1), the proposed establishment of a notification procedure (Issues 2 through 16), and the effect of the proposed notification procedure on existing GRAS affirmation petitions (Issue 17). Accordingly, we requested comments, by March 28, 2011, on the entire proposed rule as well as on the specific issues identified in the 2010 notice.

In Issue 2 in the 2010 notice, we explained our reasons for tentatively concluding that the terms ''conclude'' and ''conclusion'' would be more appropriate in lieu of ''determine'' and ''determination'' and requested comment on these terms. In the remainder of this document, we generally use the terms ''conclude'' and ''conclusion'' in lieu of ''determine'' and ''determination'' except when we are describing provisions of the proposed rule (see Response 41).

E. Public Comments

We received submissions, each containing one or more comments, from diverse members of the public, including manufacturers; trade organizations; consulting firms; law firms; public advocacy groups; non-profit organizations; individuals; a Federal Agency; and other organizations. In the remainder of this document, we describe these comments, respond to them, and explain any revisions we made to the proposed rule.

Some comments address issues that are outside the scope of this rule. For example, some comments ask us to add a new definition to part 170, to define the term ''harm'' that is used in our current definition of ''safe'' or ''safety'' (§ 170.3(e)(i)) (where ''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). We did not propose to add a definition of the term ''harm'' or ask for comment on whether we should do so, and adding a new definition in the final rule for a term that is used in the definition of ''safe'' and ''safety'' would broadly affect our regulations for food additives and GRAS substances without opportunity for public comment. As another example, one comment asks us to prepare an alphabetical index of food additive and GRAS regulations and cites the alphabetical list in our Investigations Operations Manual as evidence that it is feasible to develop such a list. Regardless of whether it is feasible to develop such a list, doing so is not within the scope of our proposal to establish a notification procedure for uses of substances that are not listed in our regulations. We do not discuss such comments in this document.

F. Applicability of Discussions in This Document to Both the Human Food Regulations and the Animal Food Regulations

To simplify the discussion in this document, in general we refer to provisions of the proposed rule and the 2010 notice from the perspective of the regulations that would be established in part 170. Unless we say otherwise, however, the issues discussed also apply to the corresponding provisions for part 570. Any reference to CFSAN documents (such as guidance documents) is specific to CFSAN. See section XXV for a discussion of comments and issues specifically directed to substances used in animal food.

G. Use of Pronouns in This Document

In this document, terms such as ''we,'' ''our,'' and ''us'' refer to FDA. The regulatory text of the final rule for the GRAS notification procedure specifies that the terms ''you'' and ''your'' refer to a notifier (*i.e.,* a person who is responsible for a GRAS notice). To simplify the discussion in this document, in general we use pronouns such as ''you'' and ''your'' to refer to a notifier, even though some persons who read this document may not be notifiers.

H. Summary of Principal Changes to the Proposed Notification Procedure

In table 2, we briefly describe the principal changes to the GRAS notification procedure in the final rule compared to the proposed rule. In the remainder of this document, we discuss each of these changes in more detail, including our response to comments relevant to these changes. See table 28 for principal changes that are specific to the GRAS notification procedure for substances used in animal food in part 570.

TABLE 2—SUMMARY OF PRINCIPAL CHANGES TO THE PROPOSED NOTIFICATION PROCEDURE

Proposed rule	Final rule
Would not define any terms	Defines the terms ''amendment,'' ''GRAS,'' ''GRAS notice,'' ''notified substance,'' ''notifier,'' ''qualified expert,'' ''supplement,'' ''we, our, and us,'' and ''you and your.''
Referred to a ''GRAS determination''	Refers to a ''GRAS conclusion'' or ''conclusion of GRAS status.''
Referred to the statutory GRAS provision as an ''exemption''	Refers to the statutory GRAS provision as an ''exclusion.''
Would not use ''Plain Language'' techniques as outlined in a Presidential Memorandum dated June 1, 1998 (Ref. 21) and in ''Improving Electronic Dockets on Regulations.gov and the Federal Docket Management System: Best Practices for Federal Agencies'' (Ref. 22).	Uses ''Plain Language'' techniques such as pronouns and short regulatory sections.
Was silent on whether you could incorporate into your GRAS notice specifically identified data and information previously submitted to CFSAN or CVM.	Expressly provides for you to incorporate into your GRAS notice specifically identified data and information previously submitted to CFSAN or CVM.
Would not specify individual parts of a GRAS notice	Specifies the seven parts of a GRAS notice.
Would require three paper copies of a GRAS notice	Provides that you may submit a GRAS notice either in electronic format that is accessible for our evaluation or on paper. If you send your GRAS notice on paper, a single paper copy is sufficient.
Referred to dated and signed statements in a GRAS notice as a ''claim''.	Refers to dated and signed statements in a GRAS notice as ''signed statements.''
Assumed that a notice will not contain any information that is protected from public disclosure under the FOIA.	Specifies that you must not include any information that is trade secret or confidential commercial information in certain sections of the signed statements in your GRAS notice, but does not otherwise prohibit the submission of information that is protected from public disclosure under the FOIA.
Would require that you inform us of the ''common or usual name'' of the notified substance.	Requires that you provide an ''appropriately descriptive term'' for the notified substance.
Would not require that you state your view as to whether any data and information in your GRAS notice are exempt from disclosure under the FOIA.	Requires that you state your view as to whether any of the data and information in your GRAS notice are exempt from disclosure under the FOIA (e.g., as trade secret or as commercial or financial information that is privileged or confidential).
Would not expressly require a signed certification regarding the representative and balanced nature of the GRAS notice.	Expressly requires a signed certification that to the best of your knowledge, your GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to you and pertinent to the evaluation of the safety and GRAS status of the use of the substance.
For a notified substance of natural biological origin, would require source information such as genus and species.	For a notified substance of natural biological origin, requires source information that includes applicable data and information at the subspecies level (e.g., variety, strain) in addition to genus and species.
Would require the method of manufacture (excluding any trade secrets)	Requires a description of the method of manufacture of the notified substance in sufficient detail to evaluate the safety of the notified substance as manufactured; you may include trade secret information.
Would not expressly require relevant data and information bearing on the physical or other technical effect the notified substance is intended to produce.	When necessary to demonstrate safety, expressly requires relevant data and information bearing on the physical or other technical effect the notified substance is intended to produce, including the quantity of the notified substance required to produce such effect.
Would require consideration of dietary exposure as part of a comprehensive discussion of the data and information that you rely on to establish safety, using the statutory language of section 409(c)(5)(A) and (B) of the FD&C Act.	Separates the statutory language of section 409(c)(5)(A) and (B) of the FD&C Act into two distinct parts of the GRAS notice: (1) Part 3, which addresses how much of the notified substance consumers would eat as part of the total diet (including exposure from its intended use and all sources in the diet), as well as how much consumers would eat of other substances (e.g., contaminants or by-products); and (2) Part 6, which requires that you address, in your narrative, the safety of the notified substance, considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet.
Would require a ''comprehensive discussion'' of, and citations to, generally available and accepted scientific data, information, methods, or principles that you rely on to establish safety.	Requires a narrative (Part 6 of a GRAS notice) and a list of supporting data and information (Part 7 of a GRAS notice).
Would not require consideration of dietary exposure as part of a comprehensive discussion of the data and information that you rely on to establish safety for a conclusion of GRAS status through experience based on common use in food.	Expressly requires consideration of dietary exposure, regardless of whether your conclusion of GRAS status is through scientific procedures or through experience based on common use in food.
Would require a comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with the GRAS determination.	Requires that you either: (1) Identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status; or (2) state that you have reviewed the available data and information and are not aware of any data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status.
Would not require that you identify data and information that you view as exempt from disclosure under the FOIA.	If you view any of the data and information in your notice as exempt from disclosure under the FOIA, requires that you identify the specific data and information.

TABLE 2—SUMMARY OF PRINCIPAL CHANGES TO THE PROPOSED NOTIFICATION PROCEDURE—Continued

Proposed rule	Final rule
Would not require that you explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to non-public, safety-related data and information.	Requires that you explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to non-public, safety-related data and information.
Would require that the comprehensive discussion include the basis for concluding that there is consensus among qualified experts that there is reasonable certainty that the substance is not harmful under the intended conditions of use.	Uses the term ''generally recognized'' rather than the term ''consensus.''
Was silent on whether you could submit an amendment to a GRAS notice.	Expressly provides for you to submit a timely ''amendment'' to a GRAS notice before we respond to your GRAS notice or cease to evaluate your GRAS notice.
Considered that it was implicit that you could ask us to cease to evaluate a GRAS notice.	Expressly provides that you may ask us to cease to evaluate your GRAS notice, and expressly provides that we will inform you of our decision regarding your request.
We would acknowledge receipt of a GRAS notice within 30 days of receipt.	We will conduct an initial evaluation of your submission to determine whether to file it as a GRAS notice for evaluation of your view that the notified substance is GRAS under the conditions of its intended use. If we file your submission as a GRAS notice, we will send you a letter that informs you of the date of filing. If we do not file your submission as a GRAS notice, we will send you a letter that informs you of that fact and provides our reasons for not filing the submission as a GRAS notice.
We would respond to you in writing within 90 days of receipt of the notice.	Within 180 days of filing, we will respond to you by letter based on our evaluation of your notice. We may extend the 180 day timeframe by 90 days on an as needed basis. If we extend the timeframe, we will inform you of the extension as soon as practicable but no later than within 180 days of filing.
Was silent on procedures that apply when the intended conditions of use of a notified substance include use in a product or products subject to regulation by USDA's FSIS.	Specifies procedures that apply when the intended conditions of use of a notified substance in human food include use in a product or products subject to regulation by USDA's FSIS.
We noted that, although the decision to submit a GRAS notice would be voluntary, the provisions governing the GRAS notification procedure, including the information to be submitted, would be mandatory.	The regulatory text of the final rule specifies that the data and information in a GRAS notice are considered a mandatory, rather than voluntary, submission for purposes of its status under the FOIA and our public information requirements in part 20.
Was silent on whether you could submit additional information to a GRAS notice after we respond to it.	Expressly provides for you to submit a ''supplement'' to a GRAS notice after we respond to your GRAS notice or cease to evaluate it.
Would presumptively convert any filed, pending GRAS affirmation petition to a notice on the effective date of the rule. If we did not receive an amendment from the petitioner within 90 days of the effective date of the rule, with information and statements analogous to those in the proposed ''GRAS exemption claim,'' we would consider the converted petition to be inadequate as a notice and would send the petitioner a letter to that effect..	On the effective date of the rule, we will close the docket for any GRAS affirmation petition that is still pending. Any person who submitted a GRAS affirmation petition that is closed may submit a GRAS notice and request that we incorporate the GRAS affirmation petition.

III. Legal Authority

We are amending our regulations in 21 CFR parts 170 and 570 to replace the voluntary GRAS affirmation petition process with a voluntary GRAS notification procedure and to clarify when the intended conditions of use of a substance are eligible for classification as GRAS under our authority in sections 201, 402, 409, and 701 of the FD&C Act (21 U.S.C. 321, 342, 348, and 371). Section 701(a) of the FD&C Act authorizes the Secretary of the Department of Health and Human Services (the Secretary) to issue regulations for the efficient administration of the FD&C Act; under section 1003(d) of the FD&C Act (21 U.S.C. 393(d)), the Secretary is responsible for executing the FD&C Act, including section 701(a), through the Commissioner of Food and Drugs. The FD&C Act requires that all food additives (as defined by section 201(s) of the FD&C Act) be approved by FDA before they are marketed (sections 402(a)(2)(C) and 409 of the FD&C Act). Section 201(s) excludes from the definition of a food additive a substance 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.

These regulations will help FDA administer efficiently the FD&C Act's various provisions that apply to the use of substances added to food, specifically on the question of whether a substance is GRAS under the conditions of its intended use or is a food additive subject to FDA's premarket review. These regulations provide clarification of the GRAS criteria and provide a more efficient procedure.

As an error, the authority citation that we listed for the proposed amendments to part 570 did not include an existing authority citation, *i.e.,* section 408 of the FD&C Act (21 U.S.C. 346a). Nothing in the proposed rule would alter the citation to section 408. Therefore, the authority citation for 21 CFR part 570 continues to include section 408.

As an error, the authority citation that we listed for the proposed amendments to part 170 stated that we were revising the authority citation. Nothing in the proposed rule would alter the authority citation for part 170. Therefore, the authority citation for 21 CFR part 170 states that the authority citation ''continues to read'' rather than ''is revised to read.''

(Comment 1) Some comments state that the proposed rule violates the 1958 amendment because FDA would not be

fulfilling its statutory duty to oversee food additives, and, therefore, FDA's interpretation of the GRAS provision is arbitrary and capricious. The comments state that the proposed rule violates the 1958 amendment because it would not require companies to notify FDA of a conclusion that the use of a substance is GRAS. One comment states that without mandatory submissions FDA lacks a ''comprehensive catalog'' of such substances and their dietary exposure, and therefore cannot ''police the border between food additives and GRAS substances'' and that FDA and food manufacturers do not have access to accurate exposure data and cannot assess the cumulative effect of similar substances. The comment further states that because the proposed rule ''establishes no real oversight over the safety of GRAS substances'' it violates the 1958 amendment.

(Response 1) We disagree that the voluntary nature of the GRAS notification procedure violates the 1958 amendment. The FD&C Act provides for premarket review by FDA of a food additive, and excludes from this review any substance that is generally recognized, among qualified experts, to be safe under the conditions of its intended use. Although the FD&C Act specifically provides for our review of food additives, it is silent with respect to industry submissions to us on the use of GRAS substances. To administer the provisions of the FD&C Act with respect to the use of GRAS substances, we are retaining the voluntary nature of the GRAS administrative procedure. This rule replaces one longstanding voluntary administrative procedure with a different voluntary administrative procedure.

IV. General Comments on the Proposed Rule

(Comment 2) One comment states that the rule does not give consumers an opportunity to participate in the process before a substance is used in food. Another comment asserts that the lack of an opportunity for public comment or participation is a ''major flaw'' in the rule.

(Response 2) We disagree that the GRAS notification procedure does not allow for public participation. We proactively disclose to the public information about each GRAS notice that we have filed for evaluation, including the name and address of the notifier; the name of the notified substance; the intended conditions of use of the notified substance; and the statutory basis for the conclusion of GRAS status (*i.e.,* through scientific procedures or through experience based on common use in food). In the past, outside parties who have accessed this information have made us aware of dissenting views about whether available data and information support a conclusion that a notified substance is safe under the conditions of its intended use (see sections III.C.2, III.E, and III.I.1 in CFSAN's 2010 experience document) (Ref. 18). We continue to welcome substantive information from stakeholders regarding the safety of a notified substance. We advise stakeholders who wish to provide us with such substantive information to submit it to the same address where a notifier would send a GRAS notice and ask us to add it to the administrative file for the applicable GRAS notice. This administrative file is maintained by the responsible Center (*i.e.,* CFSAN or CVM). We would consider the submitted information, along with other information that is available to us, on a case-by-case basis.

(Comment 3) One comment asks us to require companies to maintain active and accurate registrations for GRAS substances in a public database.

(Response 3) We decline this request. This comment is suggesting a process not within our regulatory framework and does not provide a legal basis whereby we could require companies to maintain registrations in a public database for substances that are used in food on the basis of the GRAS provision in section 201(s) of the FD&C Act. We note, however, that the final rule provides a framework for making the GRAS notices, and our responses to these notices, available to the public.

(Comment 4) One comment asks us to specify whether the notified substance would be for human or animal consumption. Another comment notes that specifying whether the notified substance is intended for human or animal consumption is important because food for humans is not necessarily appropriate for animals and vice versa.

(Response 4) We agree with these comments. This rule establishes requirements for a GRAS notice about the intended use of a notified substance in human food in part 170 and establishes separate requirements for a GRAS notice about the intended use of a notified substance in animal food in part 570. Regardless of whether the notified substance would be used in human food or in animal food, the notifier must specify the intended conditions of use (see §§ 170.225(c)(4) and 570.225(c)(4)). As discussed in Response 90, we include the intended conditions of use in our publicly available letters responding to GRAS notices.

(Comment 5) One comment notes that the experience highlighted in CFSAN's experience document (Ref. 18) can provide valuable learning that can be of benefit to CVM and asks CFSAN and CVM to strive for harmonization of their requirements and policies in all areas, so the process is not more stringent for one industry than the other.

(Response 5) We agree that CFSAN and CVM can learn from each other's experience with the implementation of the GRAS notification procedure and that procedural and scientific requirements should be consistent as much as is feasible and appropriate. As noted in section II.B, CVM has now documented its experience with 18 GRAS notices with respect to some comments specifically directed to the GRAS notification procedure administered by CVM (Ref. 20).

(Comment 6) One comment urges CFSAN and CVM to put forth similar training and resources for staff assigned to evaluate GRAS notices to decrease the time necessary to complete the evaluation of a GRAS notice.

(Response 6) We staff, equip, and train our employees consistent with our priorities and budgets, which are specific to each Center. As a practical matter, our current organizational framework, in which CFSAN and CVM are both components of the Office of Foods and Veterinary Medicine, promotes interactions between staff in the two Centers.

V. Comments on the Definition of Scientific Procedures

We proposed to amend the definition of ''scientific procedures'' to specify that scientific procedures include 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. In the 2010 notice, we described comments relevant to this proposed amendment, including comments that support it and a comment that objected to it because, under the proposed amendment, an ''unpublished principle'' could inappropriately be considered a sufficient scientific procedure for demonstrating the safety of a food substance. We also noted that we had reviewed our use of the term ''study'' in the proposed companion change to the definition of scientific procedures and explained our view that, to be a ''procedure,'' data, information, methods, or principles would need to be acquired or applied. We stated that we were considering whether to revise the

definition of scientific procedures in § 170.3(h) to include the application of scientific data (including, as appropriate, data from human, animal, analytical, and 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 (see Issue 1, 75 FR 81536 at 81537–81538). We requested comment on this issue.

Several comments support the proposed amendment to the definition of scientific procedures as described in the proposed rule, with the potential modifications described in the 2010 notice, because the revised definition would more accurately reflect the state of contemporary science than the definition it would replace. Some comments express the view that specifying that it is ''the application'' of unpublished scientific data, information, or methods that would corroborate GRAS status would make it clear that a submission to us regarding a conclusion of GRAS status may include discussions of unpublished studies. In the following paragraphs, we discuss comments that suggest additional changes to the definition of ''scientific procedures.'' After considering these comments, we are finalizing the definition of scientific procedures as proposed, with the modifications described in the 2010 notice and with editorial changes as shown in table 29.

(Comment 7) One comment that supports the potential modifications to the definition of ''scientific procedures'' as described in the 2010 notice asks us to incorporate an additional clarification that ''scientific principles appropriate to establishing the safety of a substance'' encompass consideration of both the data supporting the safety of the substance and the probable dietary exposure.

(Response 7) To the extent that the comment means that ''scientific procedures'' (rather than ''scientific principles'') encompass consideration of both the data supporting the safety of the substance and the probable dietary exposure, we agree. However, it is not necessary to revise the definition of scientific procedures to make that clear. The definition of ''scientific procedures'' already specifies the application of data from human, animal, analytical, or other scientific studies, and the definition of ''safe'' or ''safety'' in § 170.3(i) includes probable dietary exposure as a factor that must be considered in determining safety.

As discussed in the 2010 notice, ''principle'' can be defined as a fundamental cause or basis of something; a primary element, force, or law determining a particular result; or a fundamental truth or proposition on which others depend. Thus, a principle is a different genre than data, information, and methods. Therefore, although we agree that ''scientific procedures'' encompass consideration of both the data supporting the safety of the substance and the probable dietary exposure, we disagree that the data supporting the safety of the substance and the probable dietary exposure are ''scientific principles.''

VI. Comments on the Criteria for Eligibility for Classification as GRAS

Section 170.30 specifies three types of criteria for eligibility for classification as GRAS: (1) General criteria; (2) criteria for classification as GRAS through scientific procedures; and (3) criteria for classification as GRAS through experience based on common use in food. We proposed to amend all three criteria to: (1) Clarify that the safety standard for a GRAS substance is identical to the safety standard for a food additive; (2) clarify the types of technical evidence of safety that could form the basis for classification as GRAS through scientific procedures, and clarify the role of publication in establishing general recognition of safety through scientific procedures; and (3) make conforming changes to the criteria for eligibility for classification as GRAS through experience based on common use in food. We proposed these amendments in association with our concurrent proposal to replace the GRAS affirmation petition process with a GRAS notification procedure. In the 2010 notice, we stated that we were considering an additional revision to correspond with the revision to the definition of scientific procedures (see section V in this document and Issue 1, 75 FR 81536 at 81537–81538 in the 2010 notice).

In the following sections, we discuss comments that disagree with one or more aspects of our proposal to amend the criteria for eligibility for classification as GRAS, with the potential modifications described in the 2010 notice (see, *e.g.,* Comment 9 and Comment 13); ask us to clarify how we will interpret the revised criteria or offer suggestions for how we should interpret the revised criteria (see, *e.g.,* Comment 12, Comment 16, Comment 17, and Comment 18); or suggest one or more changes to the revised criteria (see, *e.g.,* Comment 10, Comment 19, and Comment 20). After considering these comments, we are establishing the criteria for eligibility for classification as GRAS for use of a substance in human food as proposed, with the modification we described in the 2010 notice and with editorial, clarifying, and conforming changes as shown in table 29. See section XXV.B for a description of additional changes we made to the criteria for eligibility for classification as GRAS for use of a substance in animal food.

A. General Criteria for Eligibility for Classification as GRAS

We proposed to revise the final sentence of § 170.30(a) to specify that 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 intended conditions of use. As discussed in the proposed rule, we proposed this revision to clarify that the safety standard for a GRAS substance is identical to the safety standard for food additives (see § 170.3(i)) and that a GRAS substance is neither more safe, nor less safe, than an approved food additive (62 FR 18938 at 18942). We received no comments that disagreed with this proposed revision and are finalizing § 170.30(a) as proposed with conforming changes as shown in table 29.

See section XXV.B regarding revisions to the general criteria for eligibility for classification as GRAS for a substance used in animal food.

B. Criteria for Eligibility for Classification as GRAS Through Scientific Procedures

We proposed to amend the criteria for eligibility for classification as GRAS through scientific procedures to: (1) Require that the data and information for general recognition of safety be ''generally available and accepted,'' and (2) broaden the types of acceptable data and information by replacing ''studies'' with ''data, information, methods, or principles.'' In the 2010 notice, we stated that we were considering whether to revise these criteria with respect to the types of acceptable data and information to include ''the application'' of generally available and accepted scientific data, information, or methods, as well as ''the application'' of scientific principles'' (see section V in this document and Issue 1, 75 FR 81536 at 81537–81538 in the 2010 notice).

See section XXV.B regarding revisions to the criteria for eligibility for classification as GRAS through scientific procedures for a substance used in animal food.

(Comment 8) One comment asserts that the criterion for the generally available data or information establishing safety to ordinarily be published is artificial. Other comments point out that information that is not published can nonetheless be considered ''generally available.'' Some comments object to the proposed amendment to the criteria for eligibility for classification as GRAS through scientific procedures and assert that it would de-emphasize or eliminate the existing criterion for peer-reviewed studies.

(Response 8) Regardless of whether the data and information are published or unpublished, under the revised criteria a GRAS conclusion must be based on data and information that are generally available and accepted, and as such, are publicly available. As we stated in the proposed rule, the common knowledge element of the GRAS standard precludes a GRAS conclusion if the data and information (*e.g.,* as evaluated by a ''GRAS panel'') are only available in files that are not publicly accessible, such as in confidential industry files (62 FR 18938 at 18943). We disagree that the criterion for the generally available data or information establishing safety to ordinarily be published is artificial. Publication in a peer-reviewed scientific journal is the usual mechanism to establish that scientific information is generally available, provided that the journal is representative of scientific publications accessed by the expert scientific community (62 FR 18938 at 18943). Nonetheless, the revised criteria provide flexibility for supporting a conclusion of GRAS status through the application of scientific data, information, or methods that are generally available through a mechanism other than publication in a peer-reviewed scientific journal, such as publication in a textbook and other sources of technical literature. One example of another source of technical literature is the Joint Expert Committee on Food Additives (JECFA, a joint committee of the Food and Agriculture Organization/World Health Organization). We note, however, that the mere fact that data and information are published or otherwise publicly available does not satisfy the criteria for general recognition of safety. Regardless of the mechanism of making data and information generally available to qualified experts, it must be plausible that qualified experts would be accessing those data and information using that mechanism. For example, scientists who routinely access peer-reviewed journals in electronic form on the Internet may avoid Internet ''publications'' about a scientific topic when the ''publication'' is not associated with a reputable scientific institution.

We have not changed our position on the importance of peer review. The basis for GRAS status continues to be the application of generally available scientific data, information, and methods, which ordinarily are published (and, thus, are subject to peer review as part of the scientific publication process for most journals). We continue to believe that whether scientific data, information, and methods have been peer reviewed before publication in a scientific journal that is representative of scientific publications accessed by the expert scientific community is a factor that bears on the objectivity and scientific merit of study, and is a variable we consider in determining whether experts accept the report of a scientific investigation as a credible report and whether there is general knowledge of the scientific investigation.

CFSAN's 2010 experience document (Ref. 18) provides factual information on how CFSAN already has interpreted the criteria for eligibility for classification of GRAS status through scientific procedures for GRAS notices CFSAN received during the Interim Pilot program (see section III.A.1 of CFSAN's 2010 experience document), and we intend to continue this approach in the future. In most cases, a submitted GRAS notice described a mixture of information published in peer-reviewed journals, information (such as in textbooks) that was generally available in a form other than a peer-reviewed journal, and unpublished information. As shown in table 1 in CFSAN's 2016 experience document, CFSAN had no questions about GRAS status based on this mixture of information in approximately 81 percent of the GRAS notices CFSAN evaluated between 1998 and 2015 (Ref. 19). Importantly, CFSAN's evaluation of the basis for a conclusion that a use of a food substance is GRAS in addition to being safe was a case-by-case evaluation. As discussed in section III.A.4 of CFSAN's 2010 experience document, in some cases it was CFSAN's view that the available data and information were sufficient to demonstrate safety, but not GRAS status, and CFSAN established a food additive regulation for the use of the substance in response to a food additive petition for that use (Ref. 18).

(Comment 9) Some comments state that all available relevant data, including unpublished data, should be used in evaluating GRAS status. Some of these comments cited the placement of the word ''ordinarily'' in the criteria for classification as GRAS through scientific procedures as support for this interpretation. Several comments urge us to interpret, in a flexible manner, the proposed criteria for the scientific data, information, methods or principles that establish safety to be ''generally available and accepted'' and ''ordinarily . . . published.''

(Response 9) We agree that all relevant data should be used in evaluating GRAS status, including unpublished data. However, regardless of whether data and information are published or unpublished, a GRAS conclusion based on scientific procedures must be based on data and information that are generally available and accepted, and as such, are publicly available (see Response 8). The GRAS criteria for scientific procedures, as established in 1976, state that the applicable data and information are ''ordinarily'' published and may be ''corroborated'' by unpublished data and information, and this rule retains these criteria. The common meaning of ''corroborate'' is to make more certain or confirm (Ref. 23). Although unpublished data and information can confirm a conclusion of GRAS status, to satisfy GRAS criteria qualified experts must be able to conclude that the substance is not harmful under the conditions of its intended use without access to ''corroborative'' information (see § 170.30(a)). Under this rule, a notifier is required to explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to non-public safety-related data and information considered in reaching a conclusion of GRAS status (see § 170.250(e)).

Whether data and information are corroborative of safety, rather than establish safety, depends on what those data and information are and how they relate to the safety assessment, not just whether they are published or otherwise publicly available. Whereas unpublished data and information that have a bearing on a safety conclusion, and therefore could help confirm a safety conclusion based on other data and information, in general, can only be considered as corroborative in the context of a GRAS conclusion, published data and information may be either the basis for a safety conclusion or corroborative of a safety conclusion, depending on the nature of the data and information. For example, a published 90-day toxicology study could be the basis for a safety conclusion, but a preliminary toxicology study conducted primarily for the purpose of selecting

the doses to be used in that 90-day toxicology study is unlikely to be the basis for a safety conclusion, regardless of whether that preliminary toxicology study is published.

See also the discussion in Response 58 regarding the requirement for you to submit a signed statement certifying that, to the best of your knowledge, your GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to you and pertinent to the evaluation of the safety and GRAS status of the use of the substance (§ 170.225(c)(9)). See also the discussion in section XVII regarding the requirement for your narrative to identify, and place in context, data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status, regardless of whether those data and information are generally available (§ 170.250(c)).

(Comment 10) One comment asks us to explicitly acknowledge publication of information in the secondary scientific literature as a mechanism to satisfy the standard for general availability.

(Response 10) We decline this request. In general, the secondary scientific literature includes publications (such as review articles, textbooks, and compendia) which disseminate the views of scientists who are critically evaluating a primary body of data and information already published in peer-reviewed scientific journals that are representative of scientific publications accessed by the expert scientific community (*i.e.,* the primary scientific literature). Whether a publication in the secondary scientific literature satisfies the criteria for GRAS status through scientific procedures is a case-by-case determination that depends on the circumstances. See section III.A.1 of CFSAN's 2010 experience document (Ref. 18) for examples of how CFSAN considered publications in the secondary scientific literature during the Interim Pilot program. When the underlying data being reviewed in the secondary scientific literature are themselves generally available, a publication in the secondary scientific literature can provide evidence that the data and information discussed in the publication are generally accepted as well as generally available. If a publication in the secondary scientific literature discusses data and information that are available to the authors, but not previously published in the primary scientific literature, whether that publication could satisfy the ''generally available'' aspect of the criteria for eligibility for GRAS status through scientific procedures would depend on the nature and extent of the discussion in the publication. For example, a very general statement that a study was conducted and reported no adverse findings would not suffice to make the study ''generally available''; instead, such a statement would merely be a generally available opinion about data and information, in that study, that are not generally available. Such a publication may satisfy the ''generally accepted'' aspect of the criteria for GRAS status through scientific procedures for that study, but would be insufficient, by itself, to satisfy the ''generally available'' aspect of those criteria. However, a comprehensive description in the secondary scientific literature of a previously unpublished study, including details similar to details that would be included in a publication in the primary scientific literature, may suffice to make the study published in the secondary scientific literature ''generally available.'' In such circumstances, the publication in the secondary scientific literature may be able to satisfy both the ''generally available'' and ''generally accepted'' aspects of the criteria for eligibility for GRAS status through scientific procedures for certain data and information.

(Comment 11) One comment asks us to recognize that publication of an opinion of a specially convened ''expert panel'' would satisfy the standard for general availability because, in the comment's view, review by such a panel would be equivalent to, or exceed, peer review. (By ''expert panel,'' we assume that the comment is referring to a ''GRAS panel'', *i.e.,* a panel of individuals convened for the purpose of evaluating whether the available scientific data, information, and methods establish that a substance is safe under the conditions of its intended use in food. See the discussion in section III.A.1 of CFSAN's 2010 experience document (Ref. 18).)

(Response 11) We would consider publication of an opinion of a specially convened ''GRAS panel'' to be part of the secondary scientific literature as discussed in Response 10. As with any publication in the secondary scientific literature, when the underlying data being reviewed in a published ''GRAS panel'' opinion are themselves generally available, a published ''GRAS panel'' opinion could provide evidence that the data and information discussed in the publication are generally accepted, depending on factors such as the subject matter expertise of the members of the GRAS panel and whether the members of the GRAS panel would be considered representative of experts qualified by scientific training and experience to evaluate the safety of the substance under the conditions of its intended use. For example, a ''GRAS panel'' opinion published by scientists without expertise appropriate to address the applicable safety questions could not provide evidence that the conclusions in the publication are ''generally accepted.''

If a published ''GRAS panel'' opinion discusses data and information that are available to the members of the GRAS panel, but not generally available to qualified experts, whether that publication could satisfy the ''generally available'' aspect of the criteria for eligibility for GRAS status through scientific procedures would depend on the nature and extent of the discussion in the publication (see Response 10). Unless both criteria, *i.e.,* ''generally available'' and ''generally accepted'', are satisfied, there would be no basis for a conclusion of GRAS status based on a published ''GRAS panel'' opinion.

(Comment 12) One comment states that all available relevant data, including unpublished data, should be used in evaluating GRAS status, as long as any unpublished data are generated by appropriate and valid scientific methods as judged and reviewed by an external qualified GRAS panel and are accessible to FDA for review.

(Response 12) We agree that all available relevant data should be used in evaluating whether a use of a substance in food is GRAS through scientific procedures. By ''all relevant data,'' we mean data that support a conclusion of GRAS status as well as data that are inconsistent with a conclusion of GRAS status, not just whether the data are published. (See §§ 170.225(c)(9) and 170.250(c) and the discussion in Response 58, Response 69, and Response 78.) We also agree that it is appropriate for unpublished data to be generated by valid scientific methods and to be accessible to FDA for review (*e.g.,* when such data are cited in a submission to FDA). In addition, we have acknowledged the practice of convening an external ''GRAS panel'' to evaluate whether the available scientific data, information, and methods demonstrate that a substance is safe under the conditions of its intended use in food (see section III.A.1 of CFSAN's 2010 experience document) (Ref. 18). However, we disagree that information that is not generally available to qualified experts could be used as evidence for a GRAS conclusion merely because a GRAS panel has reviewed it. Such information would need to be considered, but generally would only be

corroborative of safety. (See Response 9 and Response 11.)

(Comment 13) One comment asserts that the proposed rule treats the findings of GRAS panels as equivalent to determinations by authoritative bodies and peer reviewed published articles.

(Response 13) We disagree. In the proposed rule, we noted that the basis for concluding there is expert consensus about the safety of a substance under the conditions of its intended use may be quite varied, and described common mechanisms that have been used to do so. We stated that these common mechanisms included publication in the primary, peer-reviewed scientific literature; publication in the secondary scientific literature; documentation of the opinion of an ''expert panel'' that is specifically convened for this purpose; and the opinion or recommendation of an authoritative body such as the National Academy of Sciences or the Committee on Nutrition of the American Academy of Pediatrics on a broad or specific issue that is related to a conclusion of GRAS status (62 FR 18938 at 18940–18941). We also stated that there could be a basis to conclude that there is expert consensus that the published results of a particular safety study (*i.e.,* the primary scientific literature) establish the safety of a substance for its intended use if the study raises no safety questions that experts would need to interpret and resolve (62 FR 18938 at 18943). In addition, technical literature from JECFA can provide evidence that generally available safety data and information are generally accepted (see section III.A.1 of CFSAN's 2010 experience document (Ref. 18)).

However, acknowledging that the opinion of an ''expert panel'' (which we now refer to as a ''GRAS panel'') has been used to provide evidence that safety data and information are generally accepted does not mean that these mechanisms are ''equivalent.'' Whether the findings of a GRAS panel, a determination by an authoritative body, or a peer-reviewed scientific study provide sufficient evidence that safety data and information are generally accepted would depend on the specific findings of the GRAS panel, the specific determination by the authoritative body, and the data and information in the peer-reviewed scientific study rather than on the classification of the mechanism for providing evidence that safety data and information are generally accepted.

(Comment 14) One comment asks us to develop and publish guidelines regarding specific duties that would be expected of any GRAS panel. This comment suggests that such guidelines could include recommendations for: (1) Number of panel members; (2) measures of ''general acceptance,'' such as a majority (rather than unanimous) opinion and the impact of a dissenting opinion; and (3) the content of a letter from a GRAS panel.

(Response 14) See Response 125. We intend to issue for public comment a draft guidance to address GRAS panels.

(Comment 15) Some comments assert it can be difficult to publish data and information that do not raise an issue of concern.

(Response 15) We infer this comment to refer primarily to toxicology studies. Toxicology studies are designed to provide information about potential adverse effects from exposure to a substance and any dose-response relationship. Although studies that fail to identity any adverse effects may be difficult to publish, some scientific journals report the findings of such studies. (See section III.A.1 of CFSAN's 2010 experience document (Ref. 18)).

(Comment 16) One comment asks us to require that both toxicology and exposure data be published because a safety assessment for the use of a substance in food requires consideration of both.

(Response 16) We agree that a safety assessment for the use of a substance in food requires consideration of both safety information (such as toxicology studies) and dietary exposure (*i.e.,* the amount of the substance that consumers are likely to eat or drink). Toxicology data are ordinarily published.

A premarket exposure assessment typically would be calculated by applying generally available and accepted methods to two types of data and information: (1) Generally available and accepted data about food consumption; and (2) specific food categories, and levels of use in those food categories, projected by the sponsor of a food additive petition or by the proponent of GRAS status (Ref. 24 and Ref. 25). Using generally available and accepted data about food consumption, a qualified expert who has access to the specific food categories and associated levels of use intended by the proponent of GRAS status can calculate an estimated dietary exposure. When the proponent of GRAS status submits a GRAS notice, the proponent must: (1) Provide data and information about dietary exposure (see § 170.235); and (2) include a narrative that addresses the safety of the notified substance, considering all dietary sources (see § 170.250). Those calculations and discussions included in the GRAS notice are subject to the public disclosure provisions of this rule (see § 170.275) and, thus, would be available to the expert scientific community. However, when the proponent of GRAS status does not submit a GRAS notice, the expert scientific community that does not have access to the specific food categories and associated levels of use would not be able to calculate an estimated dietary exposure. When the available data and information suggest that the specific food categories and associated levels of use must be carefully chosen to keep consumption of the substance in a safe range (*e.g.,* when fortifying food with certain vitamins), the expert scientific community that does not have access to the specific food categories and associated levels of use would not be able to reach a conclusion about whether the substance is safe under the conditions of its intended use, and GRAS criteria would not be satisfied.

After market entry of the substance, it may be appropriate to re-assess dietary exposure. For example, dietary exposure may need to be reassessed when a key assumption in the methodology is changed; as dietary consumption patterns change; when there is an unresolved question about consumer intake; when there is a small margin of exposure; or when other new information becomes available. As with a premarket exposure assessment, a postmarket exposure assessment typically would be calculated by applying generally available and accepted methods to two types of data and information: (1) Generally available and accepted data about food consumption; and (2) specific food categories, and levels of use in those food categories. In some cases, postmarket exposure assessments have been published so that the expert scientific community has access to them. For example, exposure assessments have been published for some sweeteners using relative sweetness as the basis of the estimate (Ref. 26). As another example, estimates of dietary exposure to caffeine have been published to address consumer intake and patterns of use (Ref. 27 through Ref. 29). However, as with a premarket exposure assessment, when a postmarket exposure assessment is not publicly available, the expert scientific community that does not have access to the specific food categories and associated levels of use would not be able to reach a conclusion about whether the substance is safe under the conditions of its intended use when the available data and information suggest

that the specific food categories and associated levels of use must be carefully chosen to keep consumption of the substance in a safe range.

(Comment 17) One comment asks us to recognize that published literature does not need to address a specific substance, but could involve publications on a class of substances or a related substance to support a conclusion that the use of a substance is GRAS through scientific procedures.

(Response 17) We agree that published information for a specific substance is not always necessary to support a conclusion that the use of a substance is GRAS through scientific procedures. For example, there may be situations where the safety of the use of the substance in food can be demonstrated by relevant published information on a closely, structurally related compound. In such cases, the analysis leading to the conclusion of GRAS status should explain how the information on the closely, structurally related compound is relevant to the safety assessment of the substance being evaluated. In other cases, there may a body of information published in the primary or secondary literature about a class of substances, which reflect generally available and accepted data and information that can be called to bear on the safety assessment of a specific substance. For example, generally available metabolism information about commonly consumed components of food, such as carbohydrates, lipids, and proteins, could support a conclusion that a specific substance is GRAS under the conditions of its intended use.

To help ensure that the data are, in fact, relevant to the safety assessment of the substance being evaluated, we strongly encourage any person who intends to rely on data and information regarding a class of substances, or a specific substance related to the substance that would be added to food, to submit any conclusion of GRAS status to FDA via the GRAS notification procedure.

(Comment 18) One comment states that the use of an approved food additive can, through the passage of time, become GRAS as the substance becomes widely used and as information about the substance becomes publicly available.

(Response 18) We disagree that widespread use of an approved food additive as time passes has any bearing on the eligibility of this use for classification as GRAS. Eligibility for classification as GRAS through scientific procedures would depend on the status of the information—as generally available and generally accepted—rather than on the amount of time that a food additive has been used in food. However, in general, much of the data submitted for our review of a food additive contains unpublished data and trade secret or confidential information that is neither published nor otherwise generally available. Although the safety data are available for public disclosure under 21 CFR 171.1(h)(1), they typically are based on unpublished studies sponsored by the petitioner.

See also the discussion in Response 19 regarding the impact of the passage of time and the discussion in Response 79 that the qualified experts who evaluate the basis for a conclusion that the notified substance is safe under the conditions of its intended use must not exclusively be ''FDA's experts.''

(Comment 19) One comment asks us to exclude uses of ''novel'' substances from consideration for eligibility for classification as GRAS. The comment asserts that novel or newly discovered uses of substances that are the subject of a conclusion of GRAS status are in conflict with the original intent of the 1958 amendment and the plain meaning of ''generally recognized,'' because there is no history of safe use for these substances. The comment also states that similar ''general recognition'' provisions for new drugs are not interpreted to allow industry-made safety determinations for new or novel drugs.

(Response 19) We do not have a regulatory definition for a ''novel'' substance. As a general matter, section 201(s) of the FD&C Act provides two alternatives for general recognition of safety—through scientific procedures, or through experience based on common use in food. Section 201(s) does not limit eligibility, or otherwise exclude, the use of a substance from classification as GRAS through scientific procedures if there is no history of use. Likewise, section 201(s) does not limit eligibility, or otherwise exclude, the use of a substance from classification as GRAS through scientific procedures based on other criteria, such as whether a substance or its use in food is ''novel'' or ''newly discovered.'' Unlike the definition of a ''new drug'' in section 201(p) of the FD&C Act, section 201(s) does not require that a food ingredient be used ''to a material extent or for a material time under such conditions'' before it can become GRAS. Rather, the criteria for eligibility for classification as GRAS depend on whether generally available and accepted data and information establish that the substance is safe under the conditions of its intended use.

However, a conclusion of GRAS status must be based on common knowledge throughout the scientific community knowledgeable about the safety of substances added to food that there is reasonable certainty that the substance is not harmful under the conditions of its intended use (§ 170.30(a)), and a substance cannot be considered GRAS when its characteristics are known to only a few experts (Final rule establishing GRAS criteria, 41 FR 53600, December 7, 1976). In addition, the passage of time is relevant in an evaluation of whether a substance is GRAS under the conditions of its intended use. In our 1974 proposed rule on general recognition of safety and prior sanctions for food ingredients, we acknowledged that there would be at least some gap between the gathering of the scientific knowledge necessary to provide the toxicological underpinning for general recognition of safety and the dissemination to and assimilation by the scientific community of this material that is necessary for general recognition of safety to exist.'' (39 FR 34194 at 34194, September 23, 1974). More recently, the discussions in sections III.A.4 and IV.K of CFSAN's 2010 experience document (Ref. 18) show our approach to the time gap between the publication of safety data and the use of the published safety data to support a conclusion of GRAS status during the Interim Pilot program. See also Response 67 regarding nanotechnology applications in food substances.

(Comment 20) One comment asserts that we must define the extent of agreement needed to establish a consensus among qualified experts, and that we must exclude from eligibility for classification as GRAS any substance whose safety has been called into question by expert authorities or authoritative entities within the scientific community.

(Response 20) The proponent of a GRAS conclusion for a food substance must demonstrate that the conditions of use of the substance satisfy the definition of ''safe'' in our regulations (*i.e.,* that there is reasonable certainty that the substance is not harmful under the conditions of its intended use (see § 170.3(i)). The proponent of GRAS status also must demonstrate that there is common knowledge about this safety throughout the knowledgeable scientific community (§ 170.30(a)). Although courts have established that general recognition of safety requires a consensus of expert opinion regarding the safety of the use of the substance, (see, *e.g., United States* v. *Western*

Serum Co., Inc., 666 F.2d 335, 338 (9th Cir. 1982) (citing *Weinberger* v. *Hynson, Westcott & Dunning,* 412 U.S. 609, 629–32 (1973)), we disagree that we must define the extent of agreement needed to establish such a consensus. Courts have established that general recognition of safety does not require unanimous agreement. See, *e.g., United States* v. *Articles of Drug * * * 5,906 Boxes,* 745 F.2d 105, 119 n. 22 (1st Cir. 1984); *United States* v. *Articles of Food and Drug (Coli-Trol 80),* 518 F.2d 743, 746 (5th Cir. 1975) (''What is required is not unanimous recognition but general recognition''). Importantly, general recognition of safety does not exist if there is a genuine dispute among qualified experts that the use of a substance is safe. See, *e.g., Premo Pharmaceutical Laboratories* v. *United States,* 629 F.2d 795, 803–4 (2nd Cir. 1980) (''genuine dispute among qualified experts'' precludes finding of general recognition, and no general recognition existed as a matter of law where there was a ''sharp difference'' of expert opinion); *United States* v. *Article of Food * * * Coco Rico,* 752 F.2d 11, 15 n 6 (1st Cir. 1985) (substance was not GRAS as a matter of law based on existence of ''genuine dispute among qualified experts'' regarding safety of use). For discussions of additional judicial decisions bearing on the criteria for eligibility for classification as GRAS, see the notice of declaratory order providing our final determination regarding partially hydrogenated oils (80 FR 34650).

A conclusion of GRAS status must be based on the totality of the publicly available and corroborative evidence about the safety of the substance under the conditions of its intended use, including both favorable and potentially unfavorable information. Thus, reports of expert authorities or authoritative entities within the scientific community may indicate that there is no general recognition of safety when the reports call into question the safety of a substance for use in food. However, we disagree that the outcome of an evaluation of such information can be predetermined as suggested by the comments. Regardless of whether particular scientific data and information lead experts to conclude that a substance is safe under the conditions of its intended use, or raise questions about the safety of the substance under the conditions of its intended use, the evaluation of whether a use of a substance in food is safe, and whether safety is generally recognized, is a case-by-case evaluation. For example, data and information that lead expert authorities or authoritative entities within the scientific community to raise a concern about the safety of the substance under the conditions of its intended use in food would have reduced significance if the concern was related to a contaminant in the substance and scientifically valid data and information supplied by the proponent of GRAS status provide evidence that an improved method of manufacture eliminates that contaminant.

See also Response 77, in which we explain that we proposed to provide the judicial interpretation of section 201(s) of the FD&C Act in the requirement for the comprehensive discussion of the notifier's basis for a conclusion of GRAS status to provide more context to notifiers than merely repeating the statutory language. However, as discussed in Response 77, we have decided to use the statutory language (*i.e.,* ''generally recognized'') rather than the proposed term ''consensus'' in the submission requirements for a GRAS notice to mirror the GRAS criteria in § 170.30, which continue to use the statutory language rather than the consensus standard applied by the courts in applying the statutory language to specific situations.

(Comment 21) In the proposed rule, we asked for comment on the potential for a conclusion of GRAS status through scientific procedures to be based in part on the ''substantial equivalence'' of the applicable substance to a substance that is GRAS through experience based on common use in food. One comment agrees with the view, expressed in a 1996 JECFA Report (Ref. 30) and reported in the proposed rule (62 FR 18938 at 18944), that ''substantial equivalence'' embodies the concept that if a new food component is found to be substantially equivalent to an existing food component, the food component could be considered to be as safe as the existing food component, after taking into account any processing that the food component may undergo as well as the intended use and the intake by the population. Several comments assert that the concept of substantial equivalence, although useful, is nonetheless ambiguous. One comment asks us to clearly state our interpretation of this concept in the final rule.

(Response 21) We have decided not to include the term ''substantial equivalence'' in the regulatory text of this rule, because whether, and to what extent, similarity between two substances could support a conclusion of GRAS status depends on too many situation-specific variables. As discussed in section IV.N of CFSAN's 2010 experience document, GRAS notices filed during the Interim Pilot program that relied on the concept of ''substantial equivalence'' generally addressed alternative sources of enzymes already used in food (Ref. 18). Most of these notices both emphasized the similarities of the new enzyme preparations to existing enzyme preparations and explained the differences between the new enzyme preparation and currently used enzyme preparations. However, none of these GRAS notices relied solely on the concept of ''substantial equivalence.'' Instead, these notices also described other applicable data and information, such as data and information about the biological source of the enzyme preparation; the method of manufacture of the enzyme preparation; constituents of the enzyme preparation that derive from the source organism or the manufacturing process; the technical effect of the enzyme preparation; dietary exposure to the enzyme preparation; specifications for the enzyme preparation; and applicable safety studies.

C. Criteria for Eligibility for Classification as GRAS Through Experience Based on Common Use in Food

We proposed to amend the criteria for eligibility for classification as GRAS through experience based on common use in food (§ 170.30(c)(2)) to state that persons who claim that use of a substance is GRAS through experience based on its common use in food outside of the United States should notify FDA of that claim in accordance with the GRAS notification procedure. We received no comments that disagreed with this proposed amendment and are finalizing it as proposed, with conforming changes as shown in table 29.

See section XXV.B regarding revisions to the criteria for eligibility for classification as GRAS through experience based on common use in food for a substance used in animal food.

D. Other Comments on the Criteria for Eligibility for Classification as GRAS

(Comment 22) One comment asserts that the proposed rule would add unnecessary complexity to continued use of substances currently presumed to be GRAS. This comment also asserts that the proposed rule would remove the ''pre-1958 exemption'' and, as a result, would place an unnecessary burden on food producers and processors with respect to substances

that are the subject of previous conclusions of GRAS status.

(Response 22) These comments are unclear. By ''pre-1958 exemption'' these comments could mean a conclusion of GRAS status through experience based on common use in food, which requires common use in food before January 1, 1958. Alternatively, these comments could be referring to the statutory exception from the definition of ''food additive'' for a substance that is the subject of a prior sanction within the meaning of section 201(s)(4) of the FD&C Act and part 181 (21 CFR part 181). Either way, nothing in this rule would affect a lawful use of a food substance that is GRAS based on common use in food prior to January 1, 1958 or that is the subject of a prior sanction. This rule does not remove GRAS status based on common use in food prior to January 1, 1958. Likewise, the lawful use of a substance listed in part 181 as being the subject of a prior sanction is not affected by this rule.

However, any person who relies on a conclusion of GRAS status through experience based on common use in food prior to 1958 or on a prior sanction within the meaning of section 201(s)(4) of the FD&C Act needs to consider 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, are within the scope of these statutory provisions. As discussed in section I.D, in 2010 we issued warning letters informing four companies marketing caffeinated alcoholic beverages that caffeine, as used in the companies' products, is an unsafe food additive, and therefore the products are adulterated under section 402(a)(2)(C) of the FD&C Act, and the companies subsequently ceased distribution of these products. Thus, we advise any manufacturer or distributor to carefully consider whether there is adequate support for concluding that a substance is GRAS under the conditions of its intended use and to submit a GRAS notice to us if it intends to manufacture or distribute a food product containing a substance that has been used in food as a GRAS substance under conditions of use different from those in the manufacturer's or distributor's product.

In addition, new data and information may call into question the safety of a substance used in food as a GRAS substance, whether the basis for a conclusion of GRAS status is through experience based on common use in food or through scientific procedures. As discussed in section I.A, in 1969 we deleted various cyclamate salts from the GRAS list because they were implicated in the formation of bladder tumors in rats; as discussed in section I.D, we recently issued a declaratory order making a final determination that there is no longer a consensus among qualified experts that PHOs are GRAS for any use in human food (80 FR 34650).

(Comment 23) One comment asks us to require minimum safety or short-term toxicology studies for all conclusions of GRAS status, regardless of whether the conclusion is through scientific procedures or through experience based on common use in food before 1958. This comment explains that such studies could corroborate safety when GRAS status is based on common use on food, *e.g.,* by taking into account any impact of the manufacturing process on food safety.

(Response 23) We decline this request. We agree that the method of manufacture can impact safety, regardless of whether GRAS status is through experience based on common use on food or through scientific procedures. See, *e.g.,* our guidance entitled ''Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives'' (Ref. 6). The rule requires submission of a description of the method of manufacture in sufficient detail to evaluate the safety of the notified substance as manufactured, regardless of whether the basis for the conclusion of GRAS status is through scientific procedures or through experience based on common use in food (see § 170.230(b)). If the method of manufacture has changed over time, a new evaluation of GRAS status based on scientific procedures may be warranted. We advise any manufacturer of a substance that is used in food based on a conclusion of GRAS status to carefully consider the impact of its method of manufacture on the safety of the substance before introducing the substance into commerce.

We disagree that the rule must require minimum safety or short-term toxicology studies for all conclusions of GRAS status because the kinds of data and information needed to demonstrate safety (or that could be used to corroborate safety) will vary based on the substance and its intended use. A conclusion of GRAS status based on scientific procedures must be based on the same quantity and quality of scientific evidence as is required to obtain approval of a food additive (§ 170.30(b)). We have issued guidance on the types of data and information in support of a food additive petition, and these types of data and information would be useful in the evaluation of the safety of a substance when the proponent of the substance seeks to demonstrate that the substance is GRAS under the conditions of its intended use (see Response 37 and Response 66).

For a safety assessment of a chemical, the specific types of data and information generally follow from the chemical structure and estimated dietary exposure of the substance. For example, chemistry data, including manufacturing information, as well as information sufficient to estimate exposure, are necessary to consider in arriving at a conclusion of GRAS status. Whether toxicological studies are necessary to demonstrate safety depends on the properties of the substance such as the presence or absence of chemical alerts, physical properties, and physiological fate of the substance. For example, well understood and accepted metabolism information about a substance that is a component of commonly consumed foods (such as vegetables or fruits) may provide sufficient safety information to arrive at a conclusion of GRAS status at a specified level of the use of that substance in food. As discussed in section III.A.2 of CFSAN's 2010 experience document, during the Interim Pilot program it was CFSAN's view that toxicological studies were not necessary to evaluate the safety of substances such as carrot fiber and dried orange pulp (Ref. 18). Likewise, for simple substances (such as minerals and their salts) that are readily dissociated to components that have long been viewed as GRAS (*e.g.,* by a listing in part 182 or by a GRAS affirmation regulation in part 184), toxicological studies would likely not be necessary. As discussed in section III.A.2 of CFSAN's 2010 experience document, during the Interim Pilot program it was CFSAN's view that toxicological studies were not necessary to evaluate the safety of substances such as potassium bisulfate and seaweed-derived calcium (with calcium carbonate as the major component) (Ref. 18).

For a safety assessment of a substance produced from a microorganism, the specific types of data and information generally follow from the identity of the microorganism and how the substance is produced from that microorganism in addition to the substance itself. For example, the safety of a substance produced from a microorganism generally considers generally available microbiological data and information about the potential toxigenicity and

pathogenicity of the microorganism. Whether toxicological studies would be necessary to demonstrate the safety of the substance as manufactured would depend on what the substance is and its intended use in food.

E. GRAS Status of Certain Food Substances

We proposed to remove § 170.30(f), which expresses our intent to review the GRAS status of certain food substances. We received no comments that disagreed with our proposal to remove § 170.30(f) and are removing it as proposed.

VII. Comments on the Substitution of a GRAS Notification Procedure for the GRAS Affirmation

Petition Process

Our regulations specify procedures for us to affirm the GRAS status of the use of a food substance, whether on our own initiative (§ 170.35(a) and (b)) or on the petition of an interested person (§ 170.35(c)). We proposed to eliminate the GRAS affirmation petition process in § 170.35(c) and replace it with a GRAS notification procedure (proposed § 170.36) in which any person may notify us of a claim that a particular use of a substance is exempt from the statutory premarket approval requirements based on the notifier's determination that such use is GRAS. Under the proposed notification procedure, we would evaluate whether the submitted notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to us raises issues that lead us to question whether use of the substance is GRAS. We also proposed to presumptively convert any filed GRAS affirmation petition that is pending on the date that the petition process is replaced with a notification procedure (''pending petition'') to a GRAS notice and provide an opportunity for the person who had submitted a pending petition (''affected petitioner'') to amend the petition to meet the requirements for a GRAS notice.

In the 2010 notice, we discussed several issues broadly applicable to the proposed substitution of a GRAS notification procedure for the GRAS affirmation petition process (see table 3).

TABLE 3—ISSUES IN THE 2010 NOTICE BROADLY APPLICABLE TO THE PROPOSED SUBSTITUTION OF A GRAS NOTIFICATION PROCEDURE FOR THE GRAS AFFIRMATION PETITION PROCESS

Issue No.	Description of our request for comment	Reference
N/A	Our intent to use ''Plain Language'' tools such as pronouns in the final rule	75 FR 81536 at 81537.
2	Our reasons for tentatively concluding that the terms ''conclude'' and ''conclusion'' would be more appropriate in lieu of ''determine'' and ''determination''.	75 FR 81536 at 81538.
17	Alternative approach to administering pending GRAS affirmation petitions	75 FR 81536 at 81542–81543.

Several comments support the proposed replacement of the GRAS affirmation petition process with a GRAS notification procedure. For example, several comments support the expectation we expressed in the proposed rule (62 FR 18938 at 18941) that the substitution of a GRAS notification procedure for the GRAS affirmation petition process would result in our increased awareness of the composition of the nation's food supply and the cumulative dietary exposure to GRAS substances. Most of these comments agree that such increased awareness could be an advantage of the notification procedure if manufacturers view our response to a GRAS notice as an incentive to participate in the program. Many comments that support the proposed replacement of the GRAS affirmation petition process with a GRAS notification procedure nonetheless raise questions about how we would administer the pending GRAS affirmation petitions. We discuss those comments in section XXIII.

In the following sections, we discuss comments that disagree with one or more aspects of our proposal to replace the GRAS affirmation petition process with a GRAS notification procedure (see, *e.g.,* Comment 24, Comment 25, and Comment 32); ask us to clarify how we generally will administer the proposed GRAS notification procedure (see, *e.g.,* Comment 31); or suggest one or more general changes to the proposed GRAS notification procedure (see, *e.g.,* Comment 27, Comment 28, Comment 30, Comment 31, and Comment 36). After considering these comments, we are replacing the GRAS affirmation petition process with a GRAS notification procedure, using the terms ''conclude'' and ''conclusion'' as described in the 2010 notice. As noted in the 2010 notice, the final rule uses Plain Language tools such as pronouns.

To improve clarity and readability we used another Plain Language tool, *i.e.,* the use of short regulatory sections that have limited subparagraph designations. To do so we redesignated the single proposed section (*i.e.,* proposed § 170.36) into several distinct, short sections of regulatory text in a newly established subpart E (GRAS Notice), with editorial changes associated with the new structure of the redesignated regulations. See table 4 for the section numbers and titles of the regulatory text in subpart E. Many provisions of the regulatory text in subpart E use singular nouns when discussing the intended use of the notified substance, *e.g.,* the definition of ''GRAS notice'' means a submission that informs us of your view that a specified use of a substance is not subject to the premarket approval requirements of the FD&C Act based on your conclusion that such use is GRAS. The singular term ''use'' is employed for a simple and consistent presentation in the regulatory text and does not mean, for example, that you are limited to notifying us about a single use of the notified substance.

We also are establishing in new subpart E the process we described in the 2010 notice for administering pending GRAS affirmation petitions. Finally, we made editorial, clarifying, and conforming changes as shown in table 29. Because the editorial changes associated with the redesignation of the notification procedure in subpart E are extensive, we do not list them in table 29.

A. Affirmation on the Initiative of the Commissioner

We proposed to amend current § 170.35(a) to clarify that the Commissioner would affirm the GRAS status of a use of a substance, rather than the substance itself, and to include a grammatical change to place § 170.35(a) in the singular. The single

comment that expressly addressed this proposed amendment concurred with us on this point and we are finalizing it as proposed.

We also proposed to amend current § 170.35(a) to remove the provision that we may review the GRAS status of a substance added to food in response to a petition from an interested party. Under current § 170.35, such a petition would be submitted in accordance with the provisions of the GRAS affirmation petition process established in current § 170.35(c). We are deleting this provision as proposed. The comments we received relevant to our proposed deletion of the petition-related provision in § 170.35(a) are directed to our proposed deletion of the GRAS affirmation petition process in current § 170.35(c), and we discuss those comments in section VII.B.

B. Deletion of the GRAS Affirmation Petition Process

We proposed to eliminate the GRAS affirmation petition process in current § 170.35(c).

(Comment 24) Several comments oppose our proposal to eliminate the GRAS affirmation petition process. In general, these comments assert that we should provide manufacturers the option of seeking GRAS affirmation even though we would be establishing a new notification procedure. The comments assert that such an option is essential to support the marketing of a product in certain situations, such as when recognition of GRAS status is needed by international standard-setting bodies.

(Response 24) We acknowledge that a regulation listing the use of a substance in food could provide some support for marketing a product in certain situations, but disagree that we should retain the GRAS affirmation petition process. We note that CFSAN filed more than 600 GRAS notices during the time period 1998 through 2015 (Ref. 19), for an average of approximately 34 GRAS notices per year, including 69 GRAS notices filed during 2014 and 51 GRAS notices filed during 2015. By contrast, during that time CFSAN finalized six GRAS affirmation regulations. We believe that the ongoing submission of GRAS notices is evidence that our response to a GRAS notice can support the marketing of a food substance.

(Comment 25) Some comments assert that the proposed GRAS notification procedure would be less protective of food safety than the GRAS affirmation petition process it would replace. Some comments assert that our role in ensuring the safety of food ingredients is best carried out by a review of the data supporting the safety of the ingredient and that the public should also have access to these data. These comments also assert that the GRAS affirmation petition process, in which we conduct a review of supporting data, provides an incentive to manufacturers to fully research each substance and that removing this incentive would compromise safety. Other comments assert that the GRAS notification procedure would be less thorough than the GRAS affirmation petition process. One comment states that consumers are concerned about the safety and wholesomeness of substances added to food and criticizes the proposed rule as not being ''rigorous enough'' and as not creating a ''meaningful process for adequately reviewing the safety of substances used in human and animal food.''

(Response 25) We disagree that the notification procedure is less protective of food safety than the affirmation petition process. In the proposed rule, we stated that our response to a GRAS notice would not be equivalent to an agency affirmation of GRAS status because we would neither receive nor review the detailed data and information that support the GRAS determination (62 FR 18938 at 18951). These comments may have misinterpreted that statement to mean that we would not conduct a substantive evaluation of the summary information that we receive in a GRAS notice. This is not the case. CFSAN's 2010 experience document (Ref. 18) demonstrates that we have conducted a substantive evaluation of the GRAS notices that we received during the Interim Pilot program. For example, section III.C.1 of CFSAN's 2010 experience document describes examples of situations in which we contacted a notifier to request clarification about data and information in the notice. CFSAN's 2010 experience document also demonstrates that during the period 1998–2009 CFSAN had questions about 21 percent of GRAS notices, such that CFSAN either responded to the notifier that the submitted GRAS notice did not provide a basis for a conclusion of GRAS status or the notifier asked us to cease to evaluate the GRAS notice (see section III.B of CFSAN's 2010 experience document). Furthermore, we believe that the GRAS notification procedure provides us with greater flexibility to respond to safety concerns that may arise about a substance that is the subject of a GRAS notice, compared to a substance that is the subject of a GRAS affirmation regulation, which would require rulemaking to revoke.

We acknowledge that the term (*i.e.,* ''evaluate'') we use to describe our actions when we receive a GRAS notice is different from the term (*i.e.,* ''review'') we use to describe our actions when we receive a petition (whether a food or color additive petition or a GRAS affirmation petition). We decided to use a different term because, as already noted, the data and information we will receive in a GRAS notice (*i.e.,* summary data and discussions) are different from the data and information we receive in a petition (which generally includes the underlying data from studies described in the petition).

As discussed in Response 120, we currently make a hyperlink to an electronic copy of each GRAS notice accessible from our Internet site and, thus, the public has access to each GRAS notice. We also make our response to each GRAS notice accessible from our Internet site (see § 170.275(b), Response 115, and Response 116). We acknowledge that supporting data and information that are provided to us in the form of a petition can provide the public with ready access to such data and information (*e.g.,* through a FOIA request), but disagree that substitution of the GRAS notification procedure for the GRAS affirmation petition process has a fundamental impact on the public's access to supporting data and information, because a conclusion of GRAS status must be based on generally available data and information. Under the notification procedure, the publicly accessible GRAS notice both summarizes the available data and information and provides a list of publicly available data and information (see §§ 170.250 and 170.255). Under the GRAS affirmation petition process, we placed a copy of each publication provided by the petitioner to support a conclusion of GRAS status in the public docket for that petition, but our current practice with respect to copyrighted publications is to refer the public to the primary records (see § 20.51, Referral to primary source of records).

We cannot say whether a petition process would provide an incentive for a manufacturer to more fully research the safety of a substance before sending a GRAS notice to us. However, we advise a manufacturer who intends to submit a GRAS notice to expect a substantive evaluation of that GRAS notice by us. Likewise, we advise a manufacturer who reaches a conclusion that a substance is GRAS under the conditions of its intended use, but does not submit a GRAS notice to us, that when a substance is not GRAS under

the conditions of its intended use (or is not otherwise excepted from the definition of ''food additive'' in section 201(s) of the FD&C Act), that use of the substance is a food additive use subject to our premarket review as mandated by the FD&C Act. In such circumstances, we can take various actions, including issuing a warning letter (which we make public on our Web site) to companies that manufacture or distribute the food additive and/or food containing the food additive; issuing a public alert; taking enforcement action to stop distribution of the food substance and foods containing it on the grounds that such foods are or contain an unlawful food additive; and issuing a declaratory order determining that the substance is not GRAS under the conditions of its intended use and is a food additive subject to section 409 of the FD&C Act. For example, as already discussed in section I.D, we recently issued a declaratory order making a final determination that there is no longer a consensus among qualified experts that PHOs are GRAS for any use in human food (80 FR 34650). As another example discussed in section I.D, we have issued warning letters informing four companies marketing caffeinated alcoholic beverages that caffeine, as used in the companies' products, is an unsafe food additive, and therefore the products are adulterated under section 402(a)(2)(C) of the FD&C Act (Ref. 10 through Ref. 13), and the companies subsequently ceased distribution of these products. Thus, we advise any manufacturer or distributor to carefully consider whether there is adequate support for concluding that a substance is GRAS under the conditions of its intended use and to submit its conclusion of GRAS status to us in the form of a GRAS notice.

(Comment 26) A few comments express skepticism that the substitution of a GRAS notification procedure for the GRAS affirmation petition process would result in our increased awareness of the composition of the nation's food supply and the cumulative dietary exposure to GRAS substances. These comments assert that the proposed notification procedure offered a risk (*i.e.,* the risk of a publicly available ''insufficient basis letter'') without the potential benefit that was available under the petition process (*i.e.,* a regulation affirming GRAS status). These comments predict that, unless we modify the proposed rule substantially, we likely would have less awareness of GRAS substances under the notification procedure than we currently have under the GRAS affirmation petition process.

One comment asserts that the notification procedure would in no manner be equivalent to the GRAS affirmation petition process, and the substitution of a notification procedure for a petition process would be anything but neutral. This comment asserts that the proposed substitution of a notification process for the affirmation process would actually reduce the incentive for producers to notify FDA, because notification would invite regulatory scrutiny without requiring FDA to attest to a conclusion of GRAS status.

(Response 26) We disagree that the notification procedure we are establishing in this rule will reduce the incentive for producers to notify us. As already noted in Response 24, CFSAN has filed more than 600 GRAS notices between 1998 and 2015, for an average of approximately 34 GRAS notices per year. In contrast, as discussed in section IV.L of CFSAN's 2010 experience document (Ref. 18), between 1987 and 1996 CFSAN received a total of fewer than 100 GRAS affirmation petitions, with an average of approximately 8 GRAS affirmation petitions per year. These data support the expectation we expressed in the proposed rule that the substitution of a GRAS notification procedure for the GRAS affirmation petition process would result in our increased awareness of the composition of the nation's food supply and the cumulative dietary exposure to GRAS substances.

The comments that predict that we would need to modify the final rule substantially to achieve increased awareness of the nation's food supply did not suggest specific modifications for this purpose. However, this document discusses the changes we have made to the proposed notification procedure as a result of comments, described in this document and the 2010 notice, that raised specific issues and concerns regarding the proposed notification procedure. For example, the final rule defines the term ''amendment'' (§ 170.203) and expressly provides that a notifier may submit a timely amendment to address our questions (§ 170.260(a)). As another example, the final rule expressly provides that a notifier may ask us to cease to evaluate a GRAS notice (§ 170.260(b)). In addition, see Response 80 regarding our willingness to engage with a notifier to clarify particular aspects of the notice and Response 96 and Response 97 regarding comments that raise concerns about a publicly available insufficient basis letter. For a summary of the principal changes to the notification procedure in this final rule relative to the proposed rule, see table 2.

(Comment 27) One comment asks us to require the submission of a GRAS affirmation petition on a random basis for 20 percent of the GRAS notices we receive. This comment states that such a requirement would be essential in light of our concurrent proposal to broaden the types of safety information that could support GRAS status in the criteria for eligibility for classification as GRAS through scientific procedures. The comment refers to this procedure as a ''verification audit'' and describes a ''verification audit'' as a detailed evaluation of the scientific data and other technical information. The comment asks that the final rule give FDA such ''verification authority'' and asserts that such a verification system would give consumers greater confidence that the new notification system was not just a system of deregulation.

(Response 27) We decline this request. Both the GRAS notification procedure and the GRAS affirmation petition process that it is replacing are voluntary procedures and, thus, the comment's position that we could require a GRAS affirmation petition—on a random or any other basis—is incorrect. Moreover, we disagree that the revised criteria for eligibility for GRAS status through scientific procedures have any bearing on whether we should evaluate a conclusion of GRAS status through a notification procedure or a petition process. The revised criteria reflect the nature of substances being added to food, and the fact that the quantity and quality of scientific evidence required to demonstrate safety vary considerably depending upon the estimated dietary exposure to the substance and the chemical, physical, and physiological properties of the substance. See Response 23.

C. General Comments on the Proposed GRAS Notification Procedure

(Comment 28) Some comments ask us to require that companies notify us of a conclusion of GRAS status and assert that we have implied legal authority to require such notification. These comments express concern that potentially dangerous substances could enter the food supply without our knowledge or supervision. Other comments emphasize that the GRAS notification procedure should remain voluntary and assert that we lack express statutory authority to require companies to submit GRAS notices.

(Response 28) We agree that we lack express statutory authority to require

companies to submit GRAS notices. In creating the premarket approval requirement for food additives in the 1958 amendment, Congress excluded a substance that is GRAS under the conditions of its intended use from the definition of food additive. The creation of this GRAS provision reflected Congress' determination that many substances intentionally added to food for a specific use do not need premarket review by FDA to ensure their safety, either because their safety has been established by a long history of use in food, or because their safety has been established by information that is generally available to and accepted by qualified experts, regarding the intended conditions of use of a substance in food. Subsequently, in 1997, the Food and Drug Administration Modernization Act (FDAMA) amended section 409 of the FD&C Act to require the establishment of a mandatory food contact notification program for human food. By contrast, Congress has not amended section 409 of the FD&C Act to require the establishment of a premarket GRAS notification procedure—either voluntary or mandatory.

We did not propose to require the submission to FDA of notices concerning all conclusions of GRAS status. We recognize that some comments suggest that such a requirement might be within our legal authority, even if not expressly required by the FD&C Act. We will consider these comments and our experience under this final rule in evaluating what, if any, further action is needed with respect to ensuring the safety of the food supply. However, mandating submission of GRAS notices would need to be done in a separate rulemaking to ensure adequate notice and comment.

(Comment 29) One comment notes that the proposed rule did not specifically ask members of the food industry to notify us of all conclusions of GRAS status. This comment suggests that the final rule include such a request, explaining that such a provision would help us to achieve our goal of increasing our awareness of substances added to food.

(Response 29) We view our establishment of the GRAS notification procedure in this final rule, as well as our announcement of the Interim Pilot program in the proposed rule, as an invitation to industry to submit GRAS notices to us for evaluation. See also § 170.205, entitled ''Opportunity to submit a GRAS notice.'' The ongoing submission of GRAS notices during the Interim Pilot program demonstrates that the food industry is actively submitting GRAS notices. As already noted in Response 26, we believe that our filing of more than 600 GRAS notices for substances used in human food is evidence that we have increased our awareness of the composition of the nation's food supply and the dietary exposure to GRAS substances.

(Comment 30) Some comments ask us to require certain postmarket submissions of exposure and safety data related to all GRAS substances, to require submissions for conclusions of GRAS status that predate the final rule, and to require any notifier who ''withdraws'' a GRAS notice or receives an ''insufficient basis letter'' to notify us about any use of that substance.

(Response 30) We decline this request for the same reasons that we discuss in Response 28. See also the discussions in Response 25 and Response 35 regarding the responsibility of a manufacturer to ensure that a substance added to food complies with the FD&C Act, and the potential that we may disagree with a conclusion of GRAS status and take regulatory action against use of the food substance when we do so.

(Comment 31) Some comments ask us to clarify all the information we expect to be submitted in a GRAS notice. One comment states its opposition for the proposed GRAS notification procedure, but also states that if we implement such a program we should establish the framework and criteria for the voluntary submission of GRAS notices. Another comment asks us to include core requirements in the final rule. Another comment asks us to provide more explicit instructions concerning the level of detail necessary within the required elements of a GRAS notice.

(Response 31) Subpart E of part 170 (subpart E) establishes a comprehensive framework for the submission of GRAS notices, describing in detail ''core requirements'' such as the seven distinct parts of a GRAS notice. Subpart E also includes provisions that will govern what we will do when we receive a GRAS notice, as well as provisions that will govern disclosure of a GRAS notice. Section 170.30 establishes the revised criteria for eligibility for classification of the food use of a substance as GRAS.

(Comment 32) One comment expresses concern that the proposed GRAS notification procedure would be viewed as a ''fast-track'' option that would tempt a company that should submit a food additive petition to submit a GRAS notice instead.

(Response 32) We recognize that there is a possibility that some manufacturers of food ingredients may decide that they do not need to submit a food additive petition because they have concluded that the substance is GRAS under the conditions of its intended use; this possibility exists regardless of how we structure the GRAS notification procedure. However, a manufacturer's decision that a food additive petition is not required must be based on the extent to which the manufacturer has information both that the intended conditions of use of a substance in food are ''safe,'' and that there is ''general recognition'' of that safety. In this rule, we clarify the criteria (§ 170.30) that govern when the intended conditions of use of a substance in food are more properly the subject of a food additive petition than a GRAS notice.

The record of our actions during the Interim Pilot program demonstrates that we will, when appropriate, issue an ''insufficient basis letter'' or a ''cease to evaluate letter'' signaling that a petition to obtain a regulation is more appropriate than a GRAS notice. As described in sections III.A.4 and III.N.2 of CFSAN's 2010 experience document (Ref. 18), in several cases during the Interim Pilot program the outcome of CFSAN's review of a GRAS notice was the notifier's subsequent submission of a food additive petition.

(Comment 33) One comment expresses the opinion that a GRAS notice could be an appropriate mechanism to inform us of a view that an additional use of an approved food additive is GRAS.

(Response 33) We agree, provided that the available data and information demonstrate that the criteria for GRAS status are satisfied. Whether an additional use of a food additive is GRAS depends on both whether that additional use is safe and on whether the safety of that additional use is generally recognized by qualified experts. To support a conclusion of GRAS status for the additional use of the substance, there must be evidence that qualified experts generally (not solely FDA experts who conducted a premarket review of a food additive petition) have evaluated generally available data and information about the intended conditions of use of the substance, and reached agreement that those generally available data and information establish the safety of the additional use of the substance. During the Interim Pilot program, CFSAN received several GRAS notices informing CFSAN of a conclusion that an additional use of an approved food additive is GRAS. As discussed in section III.A.4 of CFSAN's 2010 experience document (Ref. 18), CFSAN's response to these GRAS notices has been a case-by-case response

that depends on the circumstances. In several cases, CFSAN had no questions about the notifier's conclusion of GRAS status for an additional use of a food additive; in one case, the GRAS notice did not support GRAS status for the additional use of the food additive, and the notifier subsequently submitted a food additive petition for the additional use of the substance.

(Comment 34) One comment suggests that the GRAS notification procedure would shift the burden of proof to FDA to demonstrate that a use of a substance is not safe or not GRAS after the substance is already on the market.

(Response 34) We disagree. Under the FD&C Act, the burden of supporting a conclusion that a substance is GRAS under the conditions of its intended use is on the proponent of this conclusion. *United States* v. *An Article of Food,* 752 F.2d 11, 15 (1st Cir. P.R. 1985). This burden of proof remains after the substance is on the market regardless of whether the proponent asks FDA to evaluate that GRAS conclusion, and our rule does not change this. By establishing a process for the submission of GRAS notices for FDA to review, our rule encourages firms to seek our evaluation of their conclusions, before they introduce the substance into the market.

(Comment 35) A few comments note that a notifier who markets a food substance before we issue our letter responding to the notice runs the risk that we may disagree with the conclusion of GRAS status. One comment expresses concern that we would take regulatory action to remove the substance from the food supply rather than discuss our concerns with the notifier.

(Response 35) The comments are correct that a notifier who markets a food substance before we issue our letter based on our evaluation of the notice runs the risk that we may disagree with the conclusion of GRAS status. (We note that a manufacturer who markets a food substance without submitting a GRAS notice runs a similar risk.) However, we make every effort to evaluate the data and information submitted on a timely basis, and in this rule we commit to responding to a GRAS notice within 180 days after filing the notice, with the option to extend an additional 90 days as needed. Because a substance that is GRAS under the conditions of its intended use is not subject to premarket review as a food additive under the FD&C Act, a notifier could decide to introduce the substance into the market without waiting for the letter; we could subsequently determine that the substance is an unapproved food additive, and we may take action to remove the substance from the food supply.

See also the discussion in Response 80. Our experience during the Interim Pilot program demonstrates that we are willing to contact a notifier to clarify particular aspects of a GRAS notice. As also discussed in Response 80, under the final rule, we intend to contact a notifier when we identify a safety concern. However, whether the purpose of the contact is to provide an opportunity to address that concern (*e.g.,* in an amendment or in a newly submitted GRAS notice), or to alert the notifier to our concerns while we prepare an ''insufficient basis letter,'' has been, and will continue to be, a matter committed to our discretion depending on the totality of the circumstances.

(Comment 36) One comment suggests that we ask notifiers who previously received a ''no questions letter'' under the Interim Pilot program to review their prior submissions and align them with the requirements of the final rule.

(Response 36) We decline this suggestion. The final rule does not pose any substantially different data requirements than did the Interim Pilot program in terms of data quality and quantity to support the conclusion of GRAS status. We do not anticipate, as a general matter, the need to ask previous notifiers who received a ''no questions letter'' to provide any supplemental information. However, if we become aware of data or information that questions the GRAS status of the use of a substance that has been the subject of a ''no questions letter,'' we may send the notifier a subsequent letter advising the notifier of those questions (see § 170.265(c)). Because we would make the subsequent letter readily accessible to the public (see § 170.275(b)(2)), other stakeholders would have ready access to those questions.

(Comment 37) One comment states that GRAS ''determinations'' must be evaluated based on adequate science and recommends that GRAS ''determinations'' comply with our guidance on food additive testing.

(Response 37) We agree that safe use(s) of a substance must be supported by adequate science. We do have extensive guidance on food additive testing (Ref. 31 through Ref. 35), and we agree that this guidance on food additive testing can be useful in the evaluation of the safety of a substance when the proponent of the substance seeks to demonstrate that the substance is GRAS under the conditions of its intended use. As discussed in Response 128, as resources allow we intend to re-visit these scientific guidance documents to determine whether and how to modify them to clarify that our guidance on evaluating the safety of a food substance generally applies regardless of whether the substance would be used in food as a food additive or as a GRAS substance.

Recently, we issued a notice (79 FR 64603, October 30, 2014) announcing a public meeting, and requesting comments, on our intent to update our guidance entitled ''Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients'' (Ref. 35; commonly referred to as our ''Redbook''). In that notice, we reiterated that general recognition of safety based upon scientific procedures requires the same quantity and quality of evidence as is required to approve a food additive. We also asked for comment on how we should balance the desire for transparency and consistency in risk assessment, as described in the Redbook, with the goal of flexibility in applying the most appropriate analysis for specific contexts.

(Comment 38) One comment states that the resource-intensive petition process would be reserved for ingredients not eligible to meet GRAS criteria, or those which pose questions necessitating indepth review by FDA scientists, even though the safety standard for GRAS ingredients and food additives is the same.

(Response 38) The comment is correct that a food additive petition would be required for an ingredient that is not eligible for classification as GRAS and is not otherwise excepted from the statutory definition of a food additive. We agree that indepth review of the safety of a substance under the conditions of its intended use in food by FDA scientists is necessary when there is no basis for a conclusion that the intended conditions of use have GRAS status. However, see Response 25. Our evaluation of a GRAS notice is a substantive evaluation even though we respond to a GRAS notice by letter rather than by establishing a regulation.

(Comment 39) One comment asserts that we tentatively concluded that the proposed notification procedure would allow us to direct our resources to the more significant questions about GRAS status, without further explaining what these ''more significant questions'' are. This comment further asserts that the obvious conclusion is that we will simply reduce the Federal layer of oversight in the interests of efficiency and in doing so ignore the history of food law, which has repeatedly shown

that the public suffers when FDA declines to regulate.

(Response 39) See the actions we describe in section I.D, on PHOs and caffeinated alcoholic beverages, for examples of what we mean by ''more significant questions.'' We disagree that directing our resources in such a manner reduces our oversight; on the contrary, such actions demonstrate that we will take appropriate steps to address concerns about the safety of substances marketed under the GRAS provision of the FD&C Act. The comment provides no basis for its assertion that the notification procedure ignores the history of food law or that the public will suffer.

(Comment 40) One comment points out that our response to a GRAS notice addresses the question of whether a particular use of a notified substance is GRAS, without limiting that question to production of that food substance by a specific manufacturer (*e.g.,* the notifier who submitted the GRAS notice). This comment asks us to require that any other food producer who uses the substance in food on the basis of a GRAS conclusion submitted to FDA in a GRAS notice meet all requirements and specifications in the submitted GRAS notice, including use of the same source for the production of the food substance.

(Response 40) The comment is correct that our response to a GRAS notice would not limit a food producer other than the notifier from relying on the submitted GRAS notice, and our response to that GRAS notice, when that food producer concludes that a substance is GRAS under the conditions of its intended use in food. The method of manufacture (including any source specified for the production of the notified substance) and specifications identified in a GRAS notice are relevant to both the identity of the substance and its safety for use in food. We advise any food producer who relies on a GRAS notice submitted by another person to carefully consider whether its production process, and/or the intended conditions of use of the notified substance, fall within the parameters, such as method of manufacture (including a specified source) and specifications, addressed by the submitted GRAS notice. We recently issued guidance to help food producers to do so. See our guidance entitled ''Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives'' (Ref. 6).

D. Comments on Certain Terms Used in the Proposed Regulatory Text

1. Replacing the Terms ''Determine'' and ''Determination'' With the Terms ''Conclude'' and ''Conclusion''

In the 2010 notice, we explained our reasons for tentatively concluding that the terms ''conclude'' and ''conclusion'' would be more appropriate in lieu of ''determine'' and ''determination'' and requested comment on these terms (see Issue 2, 75 FR 81536 at 81538).

(Comment 41) Many comments support replacing the terms ''determine'' and ''determination'' with the terms ''conclude'' and ''conclusion.'' One comment disagrees with changing the terms ''determine'' and ''determination.'' This comment asserts that the terms ''determine'' and ''determination'' are more appropriate because a determination is made based on the sum of the total assembled data and conclusions. This comment also disagrees with changing the terms because individuals who already are involved in the GRAS notification procedure as a result of the Interim Pilot program are already familiar with the terms and meanings of ''determine'' and ''determination.''

One comment observes that the terms ''determined'' and ''determination'' are used in § 170.30 of our regulations within the context of establishing GRAS status. This comment asks us to clarify how we would apply the terms ''determined,'' ''determination,'' ''conclude,'' and ''conclusion'' and whether we would limit how some terms apply depending on whether a substance is the subject of a GRAS notice. This comment expresses concern that such a distinction in terms could lead to a misperception that a substance that is the subject of a GRAS notice has a more authoritative and/or superior legal standing than a substance that does not.

(Response 41) We are replacing the term ''determination'' with ''conclusion,'' and referring to a ''conclusion of GRAS status'' rather than to a ''GRAS determination,'' throughout the regulatory text for the GRAS notification procedure. We recognize that notifiers involved with the GRAS notification procedure may be more familiar with the terms ''determine'' and ''determination.'' Nevertheless, we believe that as notifiers gain more experience with the GRAS notification procedure set forth in this final rule, notifiers will adjust to using ''concludes'' and ''conclusion.''

We are making conforming changes to current regulations regarding the use of GRAS substances in food to no longer use the terms ''determine'' and ''determination'' (see the changes to §§ 170.3(k), 170.30(c)(1), and 170.30(e) in table 29). We are making these conforming changes to clarify that there would be no distinction between a conclusion of GRAS status submitted to us as a GRAS notice and a conclusion of GRAS status that remains with its proponent as an independent conclusion (formerly referred to as a ''self-determination'') of GRAS status.

2. The Terms ''Exempt,'' ''Exemption,'' and ''Claim''

Several provisions in the proposed rule would use terms such as ''exempt,'' ''exemption,'' and ''claim.''

(Comment 42) Several comments object to some terms used in the proposed procedure for submitting a GRAS notice. Some comments object to proposed title for the GRAS notification procedure, *i.e.,* ''Notice of a claim for exemption based on a GRAS determination.'' Most of these comments also object to our characterization of one of the proposed provisions (proposed § 170.36(c)(1)) as a ''GRAS exemption claim.'' In general, these comments assert that nothing in the FD&C Act or in the legislative history of the FD&C Act supports designation of GRAS status as an ''exemption.'' In addition, several comments object to our use of the term ''claim'' in various proposed provisions because our use of this term implies that we have legal authority to deny a claim or that GRAS status is not operative unless a claim is filed.

(Response 42) We have made the following editorial changes throughout the regulatory text to no longer use terms such as ''exempt,'' ''exemption,'' and ''claim.'' First, we replaced the term ''exempt'' with the phrase ''not subject to.'' Section 201(s) of the FD&C Act provides that a substance that is GRAS under the conditions of its intended use is not within the definition of food additive. Whether the statutory GRAS provision in section 201(s) is an ''exemption,'' or, is an ''exclusion,'' is not essential to this rulemaking and, thus, we need not include any variations of the term ''exempt'' in the final rule. Second, we replaced the term ''claim'' (when used as a noun) with the term ''view.'' In the past, we have used the term ''view'' when describing a statement or assertion that a use of a substance is GRAS (see, *e.g.,* 62 FR 36749, July 9, 1997). Finally, we simplified the title of the regulatory text to ''Generally Recognized as Safe (GRAS) Notice.''

E. Comments on the Use of ''Plain Language'' in the Regulatory Text

In the 2010 notice, we noted our intent to use ''Plain Language'' tools such as pronouns in the final rule (75 FR 81536 at 81537). The use of ''Plain Language'' tools in government writing, now called ''plain writing,'' is consistent with the government-wide initiative to promote transparency, public participation, and collaboration throughout the Federal Government's programs and activities as set out in ''Improving Electronic Dockets on Regulations.gov and the Federal Docket Management System: Best Practices for Federal Agencies'' (Ref. 22).

(Comment 43) One comment recommends that we use Plain Language throughout the regulatory text to foster greater understanding about the regulatory requirements and expectations for the notification procedure, leading to a more effective program.

(Response 43) We have used ''Plain Language'' tools (such as short sections and the use of pronouns) throughout the regulatory text of subpart E, which establishes the requirements for the GRAS notification procedure. See table 4 for the section numbers and titles of the redesignated regulatory text in subpart E.

TABLE 4—REDESIGNATION OF THE GRAS NOTIFICATION PROCEDURE IN SUBPART E

Section	Title
170.203	Definitions.
170.205	Opportunity to submit a GRAS notice.
170.210	How to send your GRAS notice to FDA.
170.215	Incorporation into a GRAS notice.
170.220	General requirements applicable to a GRAS notice.
170.225	Part 1 of a GRAS notice: Signed statements and certification.
170.230	Part 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect.
170.235	Part 3 of a GRAS notice: Dietary exposure.
170.240	Part 4 of a GRAS notice: Self-limiting levels of use.
170.245	Part 5 of a GRAS notice: Experience based on common use in food before 1958.
170.250	Part 6 of a GRAS notice: Narrative.
170.255	Part 7 of a GRAS notice: List of supporting data and information in your GRAS notice.
170.260	Steps you may take before FDA responds to your GRAS notice.
170.265	What FDA will do with a GRAS notice.
170.270	Procedures that apply when the intended conditions of use of a notified substance include use in a product or products subject to regulation by FSIS.
170.275	Public disclosure of a GRAS notice.
170.280	Submission of a supplement.
170.285	Disposition of pending GRAS affirmation petitions.

VIII. Definitions Applicable to a GRAS Notice

A. Definitions We Described in the 2010 Notice

In the 2010 notice, we requested comment on definitions for the terms ''amendment,'' ''notified substance,'' ''notifier,'' ''qualified expert,'' and ''supplement'' (see Issue 3, 75 FR 81536 at 81538). We received several comments that generally support adding definitions for these terms, and we are establishing a section in the regulatory text of subpart E to define these and other terms (see § 170.203).

B. Definition of ''GRAS Notice''

(Comment 44) Some comments express concern about the potential for confusion between the proposed GRAS notification procedure and another FDA ''notification program'', *i.e.,* the premarket notification program for food contact substances (in part 170, subpart D) that we established under FDAMA. These comments assert that this confusion can lead to uncertainty about the nature of the proposed GRAS notification procedure, such as with respect to market ''exclusivity'' for the notified substance. One comment states that the terms ''GRAS notice'' and ''GRAS notification'' appear to be used interchangeably in the 2010 notice and asks whether it is our intention to use ''notice,'' ''notification,'' or both terms with regard to the proposed procedure for submission of a conclusion of GRAS status for a use of a food substance.

Another comment notes that the proposed rule to establish a GRAS notification procedure was followed soon thereafter by the rulemaking to establish the premarket notification program for food contact substances as authorized by FDAMA (the FCN program; proposed rule 65 FR 43269, July 13, 2000; final rule 67 FR 35724, May 21, 2002). This comment asserts that although the proposed GRAS notification procedure and the established FCN program are distinct, industry reasonably relied on the close temporal proximity of the 1997 proposed rule to establish a GRAS ''notification'' procedure, and the rulemaking to establish the FCN program, as contemporaneous guidance for the meaning of the term ''notification'' under FDAMA. Because the FCN program provides market ''exclusivity'' for the food contact substance, the comment asserts that it is understandable why regulated industry would think that submitting a GRAS notice likewise implies ''exclusivity'' for the substance. The comment notes that FDA is not responsible for misinterpretations made by industry, but asks us to recognize this lack of transparency and clarity and remedy it in a fair and equitable manner.

(Response 44) In the proposed rule and in this final rule, we use the term ''notice'' as a noun to refer to the submission that you send to us and we use the term ''notification'' as an adjective, *e.g.,* to modify the noun ''procedure.'' In contrast, the FCN program uses the term ''notification'' as a noun in addition to using the term as an adjective, consistent with FDAMA's use of the term as a noun. We continue to use the term ''notification'' as an adjective (*e.g.,* GRAS notification procedure) in this preamble discussion of the requirements for submitting a GRAS notice. However, in the regulatory text we only use the term ''notice,'' and we have added a definition of the term ''GRAS notice'' to the regulatory text (see § 170.203).

The ''exclusivity'' within the FCN program is provided by section 409(h)(2)(C) of the FD&C Act. See also our implementing regulation at

§ 170.100(a), which provides that a FCN is effective for the food contact substance manufactured or prepared by the manufacturer or supplier identified in the FCN submission. There is no similar provision in the FD&C Act or our regulations providing exclusivity for a substance that is used in food based on a conclusion that the substance is GRAS under the conditions of its intended use.

C. Other Terms We Are Defining in the Rule

We are defining the abbreviation ''GRAS'' to mean ''generally recognized as safe'' so that we can use that abbreviation throughout the regulatory text without defining it in each section where it appears. To clarify how pronouns apply in the regulatory text, we also are specifying in the definition section that ''you'' and ''your'' refer to a notifier, and that ''we,'' ''our,'' and ''us'' refer to FDA.

IX. Opportunity To Submit a GRAS Notice

We proposed to provide that any person may notify FDA of a claim that a particular use of a substance is exempt from the statutory premarket approval requirements based on the notifier's determination that such use is generally recognized as safe (GRAS) (proposed § 170.36(a)). We are establishing this statement of an opportunity to submit a GRAS notice in § 170.205, with the editorial changes described in Response 41 and Response 42.

X. Comments on Administrative Procedures for Submission of a GRAS Notice

We proposed that a notice of a ''GRAS exemption claim'' be submitted in triplicate to a specified address (proposed § 170.36(b)). We also asked for comment on whether it would be appropriate to require or recommend that the submission include an electronic copy in addition to the three paper copies (62 FR 18938 at 18946) or, at a minimum, an electronic copy of the proposed ''GRAS exemption claim'' (proposed § 170.36(c)(1); final § 170.225 (part 1 of a GRAS notice).

In the 2010 notice, we described comments asking us to permit a notifier to reference a previously submitted GRAS notice to support a view that an additional use of the applicable substance is GRAS. We also discussed a coordinated evaluation process with FSIS when the use of a notified substance includes use in products subject to regulation by FSIS. (Note that the discussion in the 2010 notice referred to a ''coordinated review process.'' As discussed in Response 25, we are using the term ''evaluation'' rather than ''review'' in connection with GRAS notices. In addition, in a Memorandum of Understanding (MOU) between FDA and FSIS (Ref. 36), we specify that we will inform the notifier in writing that the notice will also be ''evaluated'' by FSIS to determine the suitability of the use of the substance in the production of meat, poultry, or egg products. Given the discussion in Response 25 and the terms of the MOU with FSIS, in this document, we use the term ''coordinated evaluation'' rather than ''coordinated review.'') We asked for comment relevant to these administrative procedures (see table 5).

TABLE 5—ISSUES IN THE 2010 NOTICE RELEVANT TO PROCEDURES FOR ADMINISTERING A GRAS NOTICE

Issue No.	Description of our request for comment	Reference
4	Whether the final rule should include a provision to expressly permit a notifier to incorporate into a GRAS notice data and information that were previously submitted by the notifier, or public data and information submitted by another party, when such data and information remain in our files.	75 FR 81536 at 81538.
13	Whether a notifier who submits a GRAS notice for such a substance should provide an additional paper copy or an electronic copy of the GRAS notice that we could send to FSIS.	75 FR 81536 at 81541–81542.

Several comments support the administrative procedures that we proposed or described in the 2010 notice. For example, several comments support adding a provision to allow a notifier to incorporate information into a GRAS notice, including data and information previously submitted by the notifier and public data and information submitted by another party, because such a provision would be practical, promote administrative efficiency, or reduce paper. In the following sections, we discuss comments that disagree with one or more aspects of the administrative procedures that we proposed or described as potential modifications in the 2010 notice (see, *e.g.,* Comment 45); ask us to clarify these administrative procedures (see, *e.g.,* Comment 48 and Comment 49); or suggest one or more changes to these administrative procedures (see, *e.g.,* Comment 47). After considering these comments, we are providing that you may submit a GRAS notice either in electronic format that is accessible for our evaluation or on paper; for paper submissions, a single paper copy of a GRAS notice is sufficient.

We also are finalizing a provision to allow for incorporation into a GRAS notice of data and information as described in the 2010 notice, with clarification that the referenced data and information must be specifically identified. As discussed in the 2010 notice, the provision specifies that incorporation into a GRAS notice applies only when data and information remain in our files. We do not retain records indefinitely; rather, records may be retired to a Federal Records Center and subsequently disposed of in accordance with our Records Control Schedule.

A. How To Send a GRAS Notice to FDA

We proposed to specify in the regulatory text the address where you would send a GRAS notice. We are finalizing this administrative provision with updates to reflect the current mailing address and the editorial changes described in Response 42. See the regulatory text in § 170.210(a).

(Comment 45) One comment asserts that a single GRAS notice to either CFSAN or CVM should suffice to inform both Centers of a conclusion of GRAS status.

(Response 45) We disagree. Our regulations directed to human food are established in subchapter B of 21 CFR (*i.e.,* Food For Human Consumption, parts 100–199), whereas our regulations directed to animal food are established in subchapter E of 21 CFR (*i.e.,* Animal Drugs, Feeds, And Related Products, parts 500–599). We have separately established requirements applicable to GRAS substances for use in human food in subchapter B of 21 CFR (*e.g.,* in parts 170, 182, 184, and 186) and requirements applicable to GRAS substances for use in animal food in subchapter E of 21 CFR (*e.g.,* in parts 570, 582, and 584). We also had separately established requirements for the GRAS affirmation petition process

(which the GRAS notification procedure is replacing) for substances for use in human food in subchapter B of 21 CFR (*i.e.,* in § 170.35(c)) and requirements applicable to the GRAS affirmation petition process for substances for use in animal food in subchapter E of 21 CFR (*i.e.,* in § 570.35(c)). We address food substances separately for human use and for animal use because the safety evaluation of a food substance relates to the conditions of its intended use, and the conditions of use of a substance in human food can raise different safety questions than the conditions of use of that same substance in animal food. For example, a substance containing copper can be safely used in human food and in food for many animal species, but even small amounts of copper can be toxic to sheep. As another example, FDA has affirmed that several uses of propylene glycol in human food are GRAS (§ 184.1666), but propylene glycol is known to be toxic to cats and FDA has prohibited its use in cat food (see § 589.1001). Therefore, the final rule establishes separate (albeit parallel) requirements for submission of a GRAS notice to CFSAN for the use of a substance in human food and for submission of a GRAS notice to CVM for the use of a substance in animal food.

B. Option for Submission of Electronic or Paper Copies of a GRAS Notice

(Comment 46) Most of the comments that responded to our request for comment on the submission of an electronic copy of a GRAS notice encourage us to recommend, but not require, submission of an electronic copy, explaining that an electronic copy would make our administration of the notification procedure more efficient. However, one comment notes that electronic technology may not be universally available. As discussed in Comment 47, another comment expresses concern about protection for confidential information in an electronic copy. One comment suggests that if we use an electronic means to make GRAS notices readily accessible to the public, then we should require that the submission include an electronic copy. Comments that address Issue 13 support requiring the notifier to provide an additional paper copy that we would send to FSIS as part of this procedure.

(Response 46) We agree that an electronic copy will make our administration of the GRAS notification procedure more efficient. For example, an electronic copy generated from a word processing format generally is searchable without the need for Optical Character Recognition techniques, but an electronic copy generated by scanning a paper document into ''Portable Document Format'' (''pdf'') requires Optical Character Recognition before it can be searched electronically. Furthermore, the Government Paperwork Elimination Act of 1998 (Pub. L. 105–277, Title XVII) requires Federal agencies to give persons who correspond with these agencies the option of doing so electronically when practicable as a substitute for paper, and to use electronic authentication (electronic signature) methods to verify the identity of the sender and the integrity of the electronic content. We acknowledge that technology may not be available to every notifier and, thus, the final rule does not require the submission of an electronic copy. Instead, the final rule provides that when you submit your GRAS notice, you may do so either in electronic format that is accessible for our evaluation or on paper (see § 170.210(b)). Because you have an option to submit a GRAS notice either electronically or on paper, an electronic copy will essentially replace the need for a paper copy. In 2010, CFSAN issued draft guidance for how to transmit a submission, including a GRAS notice, in electronic format (Ref. 37).

We used electronic means to make submitted GRAS notices accessible to the public during the Interim Pilot program, and intend to continue to do so under the final rule. However, we decline the request to require that the submission include an electronic copy solely because we are doing so. We acknowledge that an electronic copy will improve the efficiency with which we make GRAS notices available to the public (see the public disclosure provisions of this rule in § 170.275). However, during the Interim Pilot program we made an electronic copy of a submitted GRAS notice available on the Internet by scanning the paper GRAS notice to create an electronic pdf document, and we intend to continue to do so when you submit a GRAS notice on paper under the final rule.

We have decided that a single copy of a GRAS notice that is submitted on paper is acceptable (rather than the three copies that we proposed to require) and have specified that a single paper copy is sufficient in the regulatory text (§ 170.210(b)). We proposed to require three copies of a submitted GRAS notice to make it easier to provide a paper copy of the GRAS notice to all members of our staff who will evaluate the GRAS notice. However, in practice during the Interim Pilot program we developed internal procedures in which we scan a GRAS notice submitted on paper to create an electronic pdf version of the GRAS notice, and we make the electronic pdf document available to all staff who will evaluate the GRAS notice. This procedure has reduced the resources needed to distribute the GRAS notice to our staff, and we intend to continue to use this procedure when we receive a GRAS notice on paper. When we coordinate our evaluation of a GRAS notice with FSIS, we send an electronic copy to FSIS and, thus, an additional paper copy for use by FSIS is not necessary.

(Comment 47) One comment expresses concern about the security of confidential information in an electronic submission. This comment asks us to allow a notifier to edit an electronic copy to remove confidential information and present that information only in the paper copy. Another comment asks us to provide the same protections that would apply to confidential information in written records to confidential information in electronic records.

(Response 47) We decline the request to allow you to edit an electronic copy of your GRAS notice such that the electronic copy would differ from the paper copy. If you have concerns about the security of confidential information in an electronic submission, you have the option to send the GRAS notice on paper (see Response 46). The protections applicable to confidential information are the same regardless of whether the information is in written or electronic form (see part 20, ''Public Information''). In particular, under § 20.20(e), ''Policy on disclosure of Food and Drug Administration records,'' the term ''record'' (as well as any other term used in § 20.20 in reference to information) includes any information that would be an agency record maintained by the Agency in any format, including an electronic format.

In addition, the final rule requires you to state in writing your view as to whether any of the data and information in your GRAS notice are exempt from disclosure under FOIA (*e.g.,* as trade secret or as commercial or financial information that is privileged or confidential) (see § 170.225(c)(8)). The final rule also requires that if you view any of the data and information in your GRAS notice as exempt from disclosure under FOIA, you must identify the specific data and information (§ 170.250(d)). Together, these provisions will give us notice as to whether we will need to evaluate specific data and information under the FOIA and take steps to protect applicable data and information from public disclosure.

C. Incorporation Into a GRAS Notice

(Comment 48) One comment supports adding a provision to allow a notifier to incorporate data and information into a GRAS notice as long as the notifier has explicit first-hand knowledge of the referenced files. Other comments address the limitation, discussed in the 2010 notice, that data and information that are submitted by a person other than the notifier must be public, noting that it would be difficult to prevent the use of public information by others or that incorporating such data and information into a GRAS notice would be consistent with the criteria for general recognition of safety.

(Response 48) A notifier must have sufficient knowledge of data and information submitted by another party to be able to identify the specific data and information that would be incorporated into a GRAS notice. To make this clear, the provision we are adding to the rule to allow for incorporation of data and information into a GRAS notice requires that such data and information be specifically identified. For example, we expect you to provide a specific file number (*e.g.,* for a GRAS notice or a food additive petition) that contains the referenced data and information, and to identify the specific data and information in that file (rather than to broadly incorporate into a GRAS notice the entire file without explaining which data and information to incorporate). Although you may also incorporate into a GRAS notice a ''food master file'' (provided that you specifically identify both the file number and the data and information in that file that you are asking us to incorporate into a GRAS notice), the regulatory text does not include ''food master file'' as an example of the type of file that you may reference because we do not have a regulatory definition for ''food master file.'' See the discussion of ''food master file'' in Response 49.

A notifier also must have sufficient knowledge of data and information submitted by another party to be able to discuss these data and information in the narrative that is required in part 6 of a GRAS notice (see § 170.250). This narrative must explain the basis for the notifier's view that the notified substance is safe under the conditions of its intended use and that GRAS criteria—for both general availability and general acceptance—are satisfied. In other words, a GRAS notice must present the independent conclusions of the notifier regarding the basis for GRAS status, even if the data and information on which the notifier relies were submitted by another person.

Consistent with the discussion in the 2010 notice, the provision we are adding to allow for incorporation of data and information into a GRAS notice specifies that data and information submitted by another party must be ''public.'' By ''public,'' we mean data and information that we have provided (or would provide) in response to a request under the FOIA, or that are otherwise publicly available (*e.g.,* in a docket). Consistent with the views expressed in the comments, we see no reason to preclude you from referring us to such public information when we already have such information in our files, provided that you identify the specific data and information and the file(s) containing these data and information. We would not, for example, search our files to look for the referenced data and information. However, if you intend to incorporate into a GRAS notice data and information that were submitted by another party, and that you believe to be public information, we recommend that you explain the basis for your view that the data and information are public. If we need to evaluate the status of the data and information under the FOIA (*e.g.,* because the data and information have not previously been disclosed to the public), we may decline to file the GRAS notice until we have evaluated the status of the referenced data and information under the FOIA. Doing so would be appropriate in light of the perspective of the comments, as discussed in the 2010 notice, that the process of incorporation would be administratively efficient (75 FR 81536 at 81538) and the limited time (*i.e.,* 180 days) that we have to respond after we file a submission as a GRAS notice (see § 170.265(b)). A notifier who intends to incorporate data and information that we must evaluate under the FOIA before we determine whether the data and information can be disclosed under the FOIA may find it advantageous to request those data and information under our public information procedures (see part 20), and then either include the data and information we disclose in response to that request in the submitted GRAS notice, or refer us to administrative information identifying the completed FOIA request when asking us to incorporate the data and information into a GRAS notice.

(Comment 49) One comment states its presumption that a ''food master file'' is not available for public viewing, referring to a ''long-standing center policy'' that such files are confidential. This comment asks us to continue to provide that a ''food master file'' be a confidential repository for proprietary data, such as utility and manufacturing information.

(Response 49) We establish a ''food master file'' for a variety of reasons. For example, a person who submits a food additive petition may need us to evaluate data and information regarding a substance that the petitioner purchases from another party for use in the manufacture of the food additive. The petitioner may ask the manufacturer of that substance to provide the applicable data and information to us, and we then place the submitted data and information in a food master file. Although some or all of the data in such a food master file may be exempt from public disclosure (*e.g.,* as trade secret information or confidential commercial information), a determination of whether specific data and information in a food master file is exempt from public disclosure is based on the status of the data and information under FOIA rather than on the type of file in which we place the data and information. We do not limit the type of data and information that may be included in a food master file to proprietary data and information.

See also § 170.215 and Response 48. Data and information submitted by a party other than a notifier must be public information. If you previously submitted a food master file to us, and you view the data and information in your food master file as proprietary, you must explain in part 6 of your GRAS notice how GRAS criteria are satisfied (see § 170.250(e)).

XI. General Requirements Applicable to a GRAS Notice

The final rule specifies two general provisions applicable to a GRAS notice (see § 170.220). As discussed in Response 43, we have redesignated the single proposed section (*i.e.,* proposed § 170.36) into several distinct, short sections of regulatory text in a newly established subpart E (GRAS Notice). The first general provision specifies that a GRAS notice has seven parts, refers the user to the regulatory text for each of these parts, and specifies that you must submit the information specified in each of these parts on separate pages or sets of pages (§ 170.220 (a)). Submitting the information on separate pages or sets of pages is consistent both with the guidance we developed for preparation of a GRAS notice in electronic format (Ref. 37) and with long-standing requirements for other regulatory submissions, such as a food additive petition (see § 171.1(f)) and a health claim petition (see § 101.70(g)).

The second general provision specifies that you must include each of the seven parts; if a part is not included, you must include an explanation of why that part does not apply to your GRAS notice (§ 170.220 (b)). We added this provision because some parts of a GRAS notice (*e.g.,* Part 4 (self-limiting levels of use) and Part 5 (experience based on common use in food before 1958)) would not apply to most GRAS notices. Specifying that Parts 4 and 5 do not apply to a particular GRAS notice will make it clear that a notifier is aware of the requirements of those parts and has acknowledged that they do not apply.

XII. Comments on Part 1 of a GRAS Notice: Signed Statements and Certification

We proposed that a GRAS notice must include a dated and signed claim that a particular use of a substance is exempt from the premarket approval requirements of the FD&C Act because the notifier has determined that such use is GRAS. The proposed ''GRAS exemption claim'' would include: (1) The name and address of the notifier; (2) the common or usual name of the notified substance; (3) the applicable conditions of use of the notified substance, including the foods in which the substance is to be used, levels of use in such foods, and the purposes for which the substance is used, including, when appropriate, a description of the population expected to consume the substance; (4) the basis for the GRAS determination (*i.e.,* through scientific procedures or through experience based on common use in food); and (5) a statement that the data and information that are the basis for the notifier's GRAS determination are available for our review and copying at reasonable times at a specific address set out in the notice or will be sent to us upon request (proposed § 170.36(c)(1)). In the 2010 notice, we requested comment on several issues relevant to the proposed ''GRAS exemption claim'' (see table 6).

As discussed in Response 42, we have made editorial changes throughout the rule to replace the term ''exempt'' with the phrase ''not subject to'' and to replace the term ''claim'' (when used as a noun) with the term ''view.'' In light of these editorial changes, in the remainder of this section we generally use the term ''proposed signed statements'' (rather than ''GRAS exemption claim'') when referring to the provisions that we had proposed to include in proposed § 170.36(c)(1)).

TABLE 6—ISSUES IN THE 2010 NOTICE REGARDING THE PROPOSED SIGNED STATEMENTS IN A GRAS NOTICE

Issue No.	Description of our request for comment	Reference
6a	How to best ensure that the identity and authority of the person who is signing the GRAS notice is made clear.	75 FR 81536 at 81539.
6b	Whether to require that a notifier submit a statement that to the best of his knowledge, the GRAS notice is a representative and balanced submission that includes unfavorable information, as well as favorable information, known to him and pertinent to the evaluation of the safety of the substance.	75 FR 81536 at 81539.
6b	Whether to require a notifier to certify to the statement (described in Issue 6a) regarding the representative and balanced nature of the GRAS notice.	75 FR 81536 at 81539.
7	Whether to require that the GRAS notice include the name of the notified substance, using an appropriately descriptive term, instead of the ''common or usual name'' of the notified substance.	75 FR 81536 at 81539.
8	Whether to explicitly require that the information submitted in the ''GRAS exemption claim'' exclude non-public information.	75 FR 81536 at 81539.
9b*	Whether to require that a notifier who identifies one or more trade secret(s) in the GRAS notice explain why it is trade secret information and how qualified experts could conclude that the intended use of the notified substance is safe without access to the trade secret(s).	75 FR 81536 at 81540.
9c*	Whether to require that a notifier who identifies confidential commercial or financial information in the GRAS notice explain why it is confidential commercial or financial information and how qualified experts could conclude that the intended use of the notified substance is safe without access to such information.	75 FR 81536 at 81540.
13	Whether to make our coordinated evaluation process with FSIS explicit in the final rule	75 FR 81536 at 81541–81542.

*In the 2010 notice, Issues 9b and 9c asked how qualified experts could conclude that the intended use of the notified substance is ''GRAS'' rather than ''safe.'' However, the qualified experts evaluate safety rather than GRAS status; the person who is responsible for the conclusion of GRAS status considers the view of the qualified experts on safety in reaching the conclusion that GRAS criteria are satisfied. In the remainder of this document, we describe Issues 9b and 9c with respect to whether qualified experts could conclude that the intended use of the substance is ''safe'' rather than ''GRAS.''

In general, comments directed to the proposed signed statements agree that we should modify the provisions as discussed in Issues 6a, 6b, 7, 8, 9a, 9b, 9c, and 13 in the 2010 notice. In the following sections, we discuss comments that address the issues discussed in the 2010 notice (see, *e.g.,* Comment 50, Comment 51, Comment 57, Comment 58, and Comment 59); address provisions of the proposed signed statements that we did not discuss in the 2010 notice (see, *e.g.,* Comment 53); ask us to clarify how we will interpret the provisions of the proposed signed statements and potential modifications (see, *e.g.,* Comment 54 and Comment 55); or suggest one or more changes to the proposed signed statements and potential modifications (see, *e.g.,* Comment 52, Comment 56, and Comment 59). After considering these comments, we are establishing requirements for Part 1 of a GRAS notice to include certain signed statements and a certification as shown in table 7, with editorial, clarifying, and conforming changes as shown in table 29. (See § 170.225.) Table 7 identifies changes we made relative to the proposed rule or the description in the 2010 notice other than the editorial, clarifying, and conforming changes shown in table 29 and the additional editorial changes associated with the redesignation of proposed § 170.36(c)(1) as § 170.225.

We did not receive comments disagreeing with the proposed requirement for a GRAS notice to: (1) Be dated and signed by a responsible official of your organization, or by your attorney or agent; (2) provide your name and address; and (3) provide the applicable conditions of use of the notified substance. Therefore, we are establishing those requirements in the rule (see § 170.225(c)(1), (2), and (4)).

See Comment 42 for our discussion of comments on the terms used in final § 170.225(c)(6), in which you inform us of your view that the notified substance is not subject to the premarket approval requirements of the FD&C Act based on your conclusion that the substance is GRAS under the conditions of its intended use; see Response 42 for the editorial changes we made in response to those comments.

TABLE 7—FINAL REQUIREMENTS FOR SIGNED STATEMENTS AND A CERTIFICATION IN PART 1 OF A GRAS NOTICE

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description. Part 1 of your GRAS notice:	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.225(a)	170.36(c)(1)	N/A	Must be dated and signed by a responsible official of your organization, or by your attorney or agent.	N/A.
170.225(b)	N/A	8	Must not include any information that is trade secret or confidential commercial information.	Makes an exception for § 170.225(c)(8), which requires you to state your view as to whether any of the data and information in Parts 2 through 7 of your GRAS notice are exempt from disclosure under the FOIA.
170.225(c)(1)	N/A	N/A	Informs us that you are submitting a GRAS notice in accordance with subpart E.	N/A.
170.225(c)(2)	170.36(c)(1)(i)	N/A	Provides the name and address of your organization.	N/A.
170.225(c)(3)	170.36(c)(1)(ii)	7	Provides the name of the notified substance, using an appropriately descriptive term.	N/A.
170.225(c)(4)	170.36(c)(1)(iii)	N/A	Describes the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purposes for which the substance will be used, including, when appropriate, a description of a subpopulation expected to consume the substance.	Uses the term ''subpopulation'' rather than ''population''.
170.225(c)(5)	170.36(c)(1)(iv)	N/A	Informs us of the statutory basis for your conclusion of GRAS status (*i.e.,* through scientific procedures or through experience based on common use in food).	• Specifies that a conclusion of GRAS status through scientific procedures is in accordance with both § 170.30(a) and (b). • Specifies that a conclusion of GRAS status through experience based on common use in food is in accordance with both § 170.30(a) and (c).
170.225(c)(6)	170.36(c)(1)	2	States your view that the notified substance is not subject to the premarket approval requirements of the FD&C Act based on your conclusion that the substance is GRAS under the conditions of its intended use.	See Response 42.
170.225(c)(7)	170.36(c)(1)(v)	N/A	States your agreements regarding making data and information available to us upon our request.	You agree to a procedure in which we can access data and information ''during customary business hours'' rather than ''at reasonable times''.
170.225(c)(8)	N/A	9	States your view as to whether any of the data and information in Parts 2 through 7 of your GRAS notice are exempt from disclosure under the FOIA.	N/A.
170.225(c)(9)	170.36(c)(4)	6b	Certifies that, to the best of your knowledge, your GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to you and pertinent to the evaluation of the safety and GRAS status of the use of the substance.	Specifies that your GRAS notice is ''complete'' in addition to ''representative'' and ''balanced''.
170.225(c)(10)	170.36(c)(1)	6a	States both the name and position or title of the person who signs the GRAS notice.	N/A.

TABLE 7—FINAL REQUIREMENTS FOR SIGNED STATEMENTS AND A CERTIFICATION IN PART 1 OF A GRAS NOTICE—Continued

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description. Part 1 of your GRAS notice:	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.225(c)(11)	N/A	13	When applicable, states whether you: (1) Authorize us to send any trade secrets to FSIS; or (2) ask us to exclude any trade secrets from the copy of the GRAS notice that we will send to FSIS.	We added a statement communicating how you want us to handle trade secret information in a copy of a GRAS notice that we send to FSIS.

A. Exclusion of Trade Secret and Confidential Commercial Information From the Signed Statements

(Comment 50) Several comments support a provision specifying that information submitted in the signed statements exclude non-public information. One of these comments states that the information in the signed statements should be publicly disclosed because public disclosure is critical to the continued success of the GRAS program, and that for the use of a substance to be ''generally recognized as safe'' the data and research supporting a conclusion of GRAS status must be available for public view. Other comments disagree that non-public information should be excluded from the signed statements and assert that the final rule should allow for the submission of limited amounts of non-public information at the discretion of the notifier or when necessary to clarify the safety of the notified substance for the purposes of our evaluation. These comments emphasize we should take care to remove such non-public information from any public disclosure or, or at a minimum, discuss or clear our intent to disclose non-public information with the notifier before disclosing it.

(Response 50) Some of these comments appear to misinterpret the reach of our request for comment in Issue 8 in the 2010 notice. We narrowly directed Issue 8 to the signed statements that would provide the name and address of the notifier; the name of the notified substance; the applicable conditions of use of the notified substance; the statutory basis for the conclusion of GRAS status; and agreement to make the data and information that are the basis for the notifier's conclusion of GRAS status available for our review and copying. The signed statements provide administrative information rather than safety information and, as discussed in the 2010 notice, we extract notice-specific information from the signed statements for the purpose of informing the public about GRAS notices that we are evaluating. However, some comments seem to be addressing the issue of whether other sections of a GRAS notice (*e.g.,* Part 2 of a GRAS notice (in which a notifier describes the method of manufacture of the notified substance) and Part 6 of a GRAS notice (in which a notifier discusses the safety of the notified substance)) can include non-public information.

Consistent with our request for comment in Issue 8, the final rule specifies that a notifier must not include any information that is trade secret or confidential commercial information in Part 1 of a GRAS notice, except in the statement in § 170.225(c)(8) (see § 170.225(b) and the discussion of § 170.225(c)(8) in Response 57). This provision does not preclude a notifier from including non-public information in other parts of a GRAS notice. However, if a notifier views any submitted data and information as exempt from disclosure under the FOIA then that notifier must identify the specific data and information, and explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to those data and information (see § 170.250(d) and (e)). Section 170.250(d) and (e) is consistent with the criteria for eligibility for classification as GRAS, because: (1) The criteria provide that general recognition of safety may be corroborated by unpublished information; and (2) the notifier has a burden to explain how GRAS criteria are satisfied given that certain data and information in the GRAS notice are trade secret or confidential commercial information.

See section XIII.B for a discussion of comments regarding including non-public information in part 2 of a GRAS notice (particularly with respect to the method of manufacture). Regarding whether we would ''clear our intent'' to disclose non-public information with the notifier before disclosing it, see Response 70. Regarding how we treat non-public information in a GRAS notice, see section XXI regarding the provisions of the final rule regarding public disclosure of information in a GRAS notice. Under § 170.275(c), we will disclose information that is not exempt from public disclosure in accordance with part 20.

B. Name of the Notified Substance, Using an Appropriately Descriptive Term

(Comment 51) Some comments agree that the signed statements should identify the name of the notified substance using an ''appropriately descriptive term'' instead of the ''common or usual name,'' and also agree with our statement in the 2010 notice that the ''appropriately descriptive term'' may be the same as the common or usual name of the substance in some circumstances (75 FR 81536 at 81539). One comment disagrees and asks us to continue to specify that the signed statements in a GRAS notice identify the name of the notified substance using the common or usual name of the notified substance. This comment recommends that a notifier work with us to establish the common or usual name of the notified substance if the common or usual name is not known or well defined. This comment also asks us to include the common or usual name of the notified substance in any ''no questions letter'' from us to make the common our usual name clear to the public. A few comments support requiring that the signed statements include both the common or usual name of the notified substance, as well as an appropriately descriptive term for the notified substance. One comment asks us to continue the practice, described in the 2010 notice (75 FR 81536 at 81539), of reminding notifiers that our response to a GRAS notice should not be considered an endorsement for any given term for the purpose of complying with the labeling provisions of the FD&C Act.

(Response 51) The final rule requires that you provide the name of the notified substance, using an appropriately descriptive term, in Part 1 of your GRAS notice (§ 170.225(c)(3)). The appropriately descriptive term may be the same as the common or usual name of the substance under our labeling regulations (see 21 CFR 102.5). We decline the request to use resources that we are directing to the evaluation of the safety and regulatory status of food substances under sections 201 and 409 of the FD&C Act to also address the labeling requirements of the FD&C Act given the limited time (*i.e.,* 180 days) that we have to respond (see § 170.265(b)). You may consult with our staff in operating divisions that address the labeling requirements of the FD&C Act, currently CFSAN's Office of Nutrition and Food Labeling (for human food); however, doing so would be a separate process from the GRAS notification procedure. (See section XXV.C for contact information for CVM.)

C. Intended Conditions of Use of the Notified Substance

We did not receive comments disagreeing with the proposed requirement for the signed statements in a GRAS notice to include the applicable conditions of use of the notified substance, including the foods in which the substance is to be used, levels of use in such foods, and the purposes for which the substance is used, including, when appropriate, a description of the population expected to consume the substance, and we are establishing this requirement in the final rule (see § 170.225(c)(4)). As noted in table 29, the final rule refers to the ''intended conditions of use'' rather than the ''applicable conditions of use'' for consistency with other provisions in the rule. The final rule also uses the term ''subpopulation'' rather than ''population'' to provide more context about when it would be appropriate to specify the expected consumers of a food. Most foods are broadly available to all consumers; a few are more specifically targeted to particular subpopulations, such as persons with specific dietary needs (such as persons on liquid diets or persons with conditions like phenylketonuria), infants consuming infant formula, and persons seeking alternatives to commonly used food ingredients (such as persons on a gluten-free diet).

D. Statutory Basis for the Conclusion of GRAS Status

(Comment 52) Some comments ask us to modify the rule to provide that the statutory basis for a conclusion of GRAS status may be through scientific procedures, through experience based on common use in food, or through both scientific procedures and experience based on common use in food. These comments assert that many conclusions of GRAS status are based on both statutory criteria.

(Response 52) We disagree that this modification is needed. The final rule does not prevent you from basing your conclusion of GRAS status on both statutory criteria. Importantly, if you assert that your conclusion of GRAS status is based on both statutory criteria, you must fully support each conclusion and address all requirements of the rule regarding each conclusion; partial support for each of the two statutory criteria for a conclusion of GRAS status is not adequate. You could not, for example, assert that a substance is GRAS under the conditions of its intended use through scientific procedures, but ''fill in data gaps'' by also asserting that the substance was commonly used in food before 1958. Likewise, you could not assert that a substance is GRAS under the conditions of its intended use through experience based on common use in food if you cannot provide evidence of a substantial history of consumption of the notified substance for food use by a significant number of consumers prior to January 1, 1958.

These comments highlight the importance of fully supporting a conclusion of GRAS status through each of the statutory criteria. Because the general criteria in § 170.30(a), as well as the specific criteria in § 170.30(b) or (c), must be satisfied to support a conclusion of GRAS status, the final rule specifies that a conclusion of GRAS status through scientific procedures is in accordance with both § 170.30(a) and (b) and that a conclusion of GRAS status through experience based on common use in food is in accordance with both § 170.30(a) and (c).

E. Agreement To Make Data and Information Available Upon Request

(Comment 53) Some comments recommend that there be a means for us to request non-public information if we deem it necessary for our evaluation of the intended conditions of use of the notified substance, provided that the information can be considered as confidential and protected from disclosure.

(Response 53) These comments appear to misinterpret the reach of the proposed requirement to agree to provide us access to data and information that a notifier relies on to support a conclusion of GRAS status. Some of the data and information that we may ask to see during our evaluation of a GRAS notice may be ''public'' data and information in that it would be data and information that we would provide in response to a request under the FOIA (see Response 48), even though it may not have been disseminated to the public (*e.g.,* in the scientific literature or on the Internet (*e.g.,* when a science-based organization uses the Internet to disseminate scientific or technical information or recommendations)). If we receive data and information that are non-public, such data and information would be protected from public disclosure in accordance with part 20.

(Comment 54) One comment states that the phrase ''at reasonable times'' refers not only to hours of a day, but also to a reasonable amount of time following the submission of a GRAS notice. This comment recommends that ''several years (for example, five years)'' after submission of a GRAS notice would be a reasonable time for notifiers to retain such data and information in their active files.

(Response 54) By ''at reasonable times,'' we meant the time of day that we would have access to data and information you retained but did not include in your GRAS notice. To clarify that the requirement relates to the time of day rather than to the timeframe for retaining the data and information, the final rule specifies that you agree to a procedure in which we can access data and information ''during customary business hours'' rather than ''at reasonable times.''

As previously discussed (62 FR 18938 at 18951), we may, at some point after our response to a GRAS notice, receive additional information about a notified substance that raises questions about the safety of that substance. To address this possibility, the rule specifies that we will send you a subsequent letter about your GRAS notice if circumstances warrant (see § 170.265(c)). Although the rule does not specify any timeframe to retain the data and information that support your conclusion of GRAS status, preservation of the data and information that are the basis for the conclusion of GRAS status represents prudent practice for those who claim an exclusion from a statutory requirement regardless of whether the person subsequently notifies us (62 FR 18938 at 18947).

(Comment 55) One comment asks us to clarify that electronic records are acceptable for documenting the data and information that support a conclusion of GRAS status.

(Response 55) Electronic records are acceptable for documenting the data and information that support a conclusion of GRAS status. If we ask you to send us such data and information for a notified substance that would be used in human food, we recommend that you do so by following the instructions in CFSAN's guidance entitled ''Guidance for Industry: Providing Regulatory Submissions in Electronic or Paper Format to the Office of Food Additive Safety'' (Ref. 37), which includes instructions for making an electronic submission through our Electronic Submission Gateway, as well as on media that we can access on our network computers. CFSAN's procedures for making an electronic submission through our Electronic Submission Gateway use a form that CFSAN developed for a GRAS notice when a substance would be used in human food (*i.e.,* Form FDA 3667) (Ref. 38). Form FDA 3667 prompts a notifier to include certain elements of a GRAS notice in a standard format. The form, and elements that would be prepared as attachments to the form, may be submitted in electronic format via the Electronic Submissions Gateway, as electronic files on physical media, or in paper format. At this time, we cannot accept media such as thumb drives, which can present a security risk.

(Comment 56) One comment asks us to develop criteria for the required documentation underlying industry conclusions of GRAS status.

(Response 56) We are not establishing criteria in the rule for the documentation a notifier would have regarding a conclusion of GRAS status. Regardless of whether a person who concludes that a use of a food substance is GRAS notifies us, the applicable documentation would address the safety of the substance as described in the definition of ''safe'' or ''safety'' (see § 170.3(i)); as applicable, the definition of ''common use in food'' (see § 170.3(f) and/or the definition of ''scientific procedures'' (§ 170.3(h)); and the criteria for general recognition of safety (see § 170.30)).

F. Statements and Any Applicable Explanation Regarding Data and Information That a Notifier Views as Exempt From Disclosure Under FOIA

In Issue 9 in the 2010 notice (75 FR 81536 at 81539–81540), we discussed three issues regarding confidential data and information that are included in a GRAS notice. See table 8. Most of the comments that address Issue 9 address Issue 9a, particularly with respect to how we would protect trade secret or confidential commercial information from public disclosure. See sections XIII.B and XXI.C for a discussion of those comments, and our response to those comments. In the following paragraphs, we discuss comments on Issues 9b and 9c, and respond to those comments.

TABLE 8—ISSUES IN THE 2010 NOTICE REGARDING CONFIDENTIAL DATA AND INFORMATION IN A GRAS NOTICE

Issue No.	Description of our request for comment	Reference
9a	Whether the final rule should stipulate that the method of manufacture exclude any trade secrets, as we proposed.	75 FR 81536 at 81539–81540.
9b	Whether to require that a notifier who identifies one or more trade secret(s), as defined in § 20.61(a), in the GRAS notice explain why it is trade secret information and how qualified experts could conclude that the intended use of the notified substance is safe without access to the trade secret(s).	75 FR 81536 at 81539–81540.
9c	Whether to require that a notifier who identifies confidential commercial or financial information, as defined in § 20.61(b), in the GRAS notice explain why it is confidential commercial or financial information and how qualified experts could conclude that the intended use of the notified substance is safe without access to such information.	75 FR 81536 at 81539–81540.

(Comment 57) One comment supports the recommendation we made in the proposed rule for a notifier who considers that certain information in a submission should not be available for public disclosure to identify as confidential the relevant portions of the submission for our consideration (62 FR 18938 at 18952). Those comments that address Issues 9b and 9c agree with the outcome of our discussion, in the 2010 notice, that we should require that a notifier who identifies a trade secret or confidential commercial information explain why it is a trade secret or confidential commercial information and how qualified experts can conclude that the use of a substance is safe without access to the trade secret or confidential commercial information.

(Response 57) The final rule requires a notifier to state his view as to whether any of the data and information in Parts 2 through 7 of a GRAS notice are exempt from disclosure under the FOIA (*e.g.,* as trade secret or as commercial or financial information that is privileged or confidential) (§ 170.225(c)(8)). Requiring this statement in Part 1 of a GRAS notice will give us notice as to whether we will need to evaluate specific data and information under the FOIA and take steps to protect applicable data and information from public disclosure. See also § 170.250(d), which requires that Part 6 of a GRAS notice (a narrative) identify specific data and information that a notifier views as exempt from disclosure under the FOIA. Whereas Part 1 of a GRAS notice only requires that the signed statements in a GRAS notice state the notifier's view as to whether any of the data and information in Parts 2 through 7 of a GRAS notice are exempt from disclosure under the FOIA, in Part 6 of a GRAS notice the notifier would specifically identify the applicable data and information.

During the Interim Pilot program, we sometimes received a curriculum vitae (*e.g.,* of a GRAS panel member) containing personal privacy information that we needed to redact before we could make the GRAS notice available to the public. The rule does not require that a notifier submit such information, and redaction of unnecessary privacy information takes resources that we would otherwise use to evaluate the GRAS notice. We ask that notifiers exclude personal privacy information from a GRAS notice whenever possible. If a notifier does include such information, in Part 1 of a GRAS notice the notifier should state his view that the GRAS notice contains personal privacy information. In Part 6 of a GRAS notice, the notifier should identify the personal privacy information.

G. Certification Statement

(Comment 58) Several comments support a requirement for a GRAS notice to include a certification statement similar to the certification statement that had been required in a GRAS affirmation petition. One

comment agrees that the notifier should submit a statement that the notice is a representative and balanced submission, but does not agree that the notifier needs to certify the statement.

(Response 58) The final rule requires a certification statement as described in the 2010 notice, with one modification (see § 170.225(c)(9)). We added that the statement certify that the GRAS notices is ''complete'' in addition to ''representative'' and ''balanced,'' to emphasize your responsibility to identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with a conclusion of GRAS status, regardless of whether those data and information are generally available (see the requirements of the narrative in Part 6 of a GRAS notice (§ 170.250, in particular § 170.250(c))). The certification is appropriate and necessary to underscore your legal responsibility for the conclusion of GRAS status. As discussed in the 2010 notice, the specific text of the certification statement that you must include in a GRAS notice is consistent with the specific text of the certification statement in the GRAS affirmation petition process that the notification procedure is replacing. The use of certification statements has become routine in other submissions to FDA for food programs (see, *e.g.,* the certification statement in Part V of Form FDA 3480 (for a food contact notification submission) (Ref. 39); and the certification statement in Section 13 of Form FDA 3537 (for registration of a food facility) (Ref. 40)).

By ''complete,'' we also mean that your GRAS notice identifies, and places in context, unpublished data and information that you believe corroborate GRAS status. For example, if you conduct six toxicology studies, but only publish three of the studies, it may be that you consider the remaining three studies to be corroborative of safety. As an example, it may be that you were dissatisfied with the study design of one study, repeated that study with an improved study design, and published the study with the improved study design. If you consider that the findings of the unpublished studies corroborate safety, even if they do not establish it, a ''complete, representative, and balanced'' submission would briefly describe the unpublished studies. In addition, we expect that you would describe, and place in context, unpublished data and information if you consider that the findings of the unpublished data and information warrant sharing with any ''GRAS panel'' that you convene. See also the discussion in Response 69 and Response 78.

(Comment 59) One comment asks us to specify that the statement include the date the statement was certified.

(Response 59) The rule requires that Part 1 of a GRAS notice be dated and signed by a responsible official of your organization, or by your attorney or agent (see § 170.225(a)). The certification statement is included in Part 1 of the GRAS notice; it is not necessary to date each statement included in Part 1.

H. Person Signing Part 1 of the GRAS Notice

(Comment 60) Several comments support a provision to require a GRAS notice to clearly identify the person signing the GRAS notice, such as by printing or stating the name and the title of the person signing the GRAS notice.

(Response 60) The final rule requires you to state both the name and position or title of the person who signs the GRAS notice (see § 170.225(c)(10)).

I. Authorization for FDA To Send Trade Secret Information to FSIS

In the 2010 notice, we described some of the terms of a MOU, between FDA and USDA's FSIS, that provides for a coordinated evaluation process with FSIS when the intended conditions of use of a notified substance include use in a product or products subject to regulation by USDA under statutes that it administers (75 FR 81536 at 81541–81542); in 2015 we amended that MOU to include more details about the procedures FDA and FSIS will follow to do so (Ref. 36). We also asked for comment on whether to make our coordinated evaluation process with FSIS explicit in the final rule (see Issue 13, 75 FR 81536 at 81541–81542).

In accordance with our public information regulations in § 20.85 (Disclosure to other Federal government departments and agencies), we can share confidential commercial information with another Federal agency pursuant to a written agreement that the record will not be further disclosed. The amended MOU between FDA and USDA's FSIS now provides for FDA to share with FSIS confidential commercial information in a submission such as a GRAS notice (Ref. 36). We generally cannot share trade secret information with other Federal agencies under section 301(j) of the FD&C Act (21 U.S.C. 331(j)), and therefore we would need your authorization to share this information with FSIS. For efficiency in administering the coordinated evaluation of a GRAS notice with FSIS, we have added a requirement for a notifier who submits a GRAS notice that we would send to FSIS to include in part 1 of the GRAS notice a statement as to whether the notifier: (1) Authorizes us to send any trade secrets to FSIS; or (2) asks us to exclude any trade secrets from the copy of the GRAS notice that we will send to FSIS (see § 170.225(c)(11)). Under the provisions that make the coordinated evaluation of a GRAS notice with FSIS explicit, we will exclude any trade secrets unless you have authorized us to send trade secret information to FSIS (see § 170.270). These provisions will enable us, with your authorization, to share a GRAS notice that includes trade secret information with FSIS without first redacting the GRAS notice to remove the trade secret information and, thus, will reduce the time it takes for us to provide FSIS with a copy of the GRAS notice. These provisions also will clarify your expectations regarding whether we should share trade secret information with FSIS and, thus, require us to redact the trade secret information from the copy we send to FSIS when consistent with your express wishes.

Note that our rule establishing the requirements of the GRAS notification procedure does not specify the data and information that FSIS will need to evaluate whether the intended use of the notified substance complies with applicable statutes and regulations, or, if not, whether the use of the substance would be permitted in products under FSIS jurisdiction under specified conditions or restrictions. We recommend that you contact the appropriate staff at FSIS regarding the data and information that FSIS will need you to provide. FSIS provides contact information for its programs on its Web site (Ref. 41).

XIII. Comments on Part 2 of a GRAS Notice: Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

We proposed to require that a GRAS notice include detailed information about the identity of the notified substance, including, as applicable, its chemical name, Chemical Abstracts Service (CAS) Registry Number, Enzyme Commission number, empirical formula, structural formula, quantitative composition, method of manufacture (excluding any trade secrets and including, for a substance of natural biological origin, source information such as genus and species), characteristic properties, any content of potential human toxicants, and specifications for food-grade material (proposed § 170.36(c)(2)). In the 2010 notice, we requested comment on

several issues relevant to the proposed requirements for detailed information about the identity of the notified substance (see table 9).

TABLE 9—ISSUES IN THE 2010 NOTICE REGARDING THE PROPOSED REQUIREMENTS FOR DETAILED INFORMATION ABOUT THE IDENTITY OF THE NOTIFIED SUBSTANCE

Issue No.	Description of our request for comment	Reference
9a	Whether the final rule should continue to stipulate that the method of manufacture exclude any trade secrets, as proposed.	75 FR 81536 at 81539–81540.
10a	What scientific information would be sufficient to identify the biological source	75 FR 81536 at 81540.
10b	Whether to require that information about the identity of the notified substance specify any known toxicants that could be in the source.	75 FR 81536 at 81540.
10c	Whether the final rule should address, as part of identity, particle size and other chemical and physical properties that may be used to characterize engineered materials.	75 FR 81536 at 81540.

Some comments support the proposed requirements, with the potential modifications described in the 2010 notice, without change. For example, most of the comments that address the issue of scientific information sufficient to identify a biological source support requiring both taxonomic information and the part of any animal or plant used as a source. As another example, several comments that address the issue of scientific information sufficient to identify a biological source support requiring that this information specify toxicants that could be in the source.

Most of the comments regarding our proposal to require that a GRAS notice include detailed information about the identity of the notified substance address the issues discussed in 2010 notice. In the following sections, we discuss these and other comments. After considering these comments, we are establishing requirements for Part 2 of a GRAS notice to include information about the identity, method of manufacture, specifications, and physical or technical effect of the notified substance as shown in table 10, with editorial, clarifying, and conforming changes as shown in table 29. (See § 170.230). Table 10 identifies changes we made relative to the proposed rule or the description in the 2010 notice other than the editorial, clarifying, and conforming changes shown in table 29 and the additional editorial changes associated with the redesignation of proposed § 170.36(c)(2) as § 170.230.

TABLE 10—FINAL REQUIREMENTS FOR DETAILED INFORMATION IN PART 2 OF A GRAS NOTICE ABOUT THE IDENTITY OF A NOTIFIED SUBSTANCE

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description. Part 2 of your GRAS notice:	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.230(a)(1)	170.36(c)(2)	N/A	Must include scientific data and information that identifies the notified substance.	N/A.
170.230(a)(1)	170.36(c)(2)	10a	Must include data and information sufficient to identify a biological source of a notified substance.	• Must provide taxonomic information at the sub-species level (*e.g.,* variety, strain) in addition to genus and species. • Must specify the part of any plant or animal used as the source.
170.230(a)(2)	170.36(c)(2)	10b	Must include data and information sufficient to identify any known toxicants that could be in the source.	N/A.
170.230(b)	170.36(c)(2)	9a	Must include the method of manufacture of the notified substance in sufficient detail to evaluate the safety of the notified substance as manufactured.	• No longer requires that the method of manufacture exclude any trade secrets. • Requires ''sufficient detail to evaluate the safety of the notified substance as manufactured'' rather than ''detailed information.''
170.230(c)	170.36(c)(2)	N/A	Must include specifications for food-grade material.	N/A.
170.230(d)	N/A	N/A	When necessary to demonstrate safety, must include relevant data and information bearing on the physical or other technical effect the notified substance is intended to produce, including the quantity of the notified substance required to produce such effect.	New requirement based on comments that addressed experience during CVM's Interim Pilot program (see section XXV.E).

A. Scientific Information About the Identity of a Notified Substance

1. Scientific Information Sufficient To Identify a Biological Source

(Comment 61) One comment asserts that the scientific information, beyond the standard taxonomic information, that is sufficient to identify a biological source for a notified substance should be determined on a case-by-case basis consistent with established practice and publicly available guidance. Another comment asserts that identifying the source organism by the genus and species (without additional information such as strain or variety) is sufficient when the notified substance is an enzyme preparation produced by a microorganism. However, this comment also asserts that if safety concerns for a specific genus and species have been addressed (*i.e.,* by genetic modification to remove a characteristic of concern) for a specific strain within that species then information about the strain would be appropriate. This comment emphasizes that the description of the source of a biological material should be based on the safety of that source and consider all relevant information related to safety.

(Response 61) The information, beyond the standard taxonomic information, that we discussed in the 2010 notice is consistent with established practice (see section III.J.1 of CFSAN's 2010 experience document (Ref. 18)) and the final rule specifies that when the source of a notified substance is a biological material, your GRAS notice must include both taxonomic information (*e.g.,* genus, species), including as applicable data and information at the sub-species level (*e.g.,* variety, strain) and the part of any plant or animal used as the source (see § 170.230(a)(2)). We agree that the specific scientific information, beyond the standard taxonomic information, that is sufficient to identify a biological source is determined on a case-by-case basis, and section III.J.1 of CFSAN's 2010 experience document demonstrates that the specific scientific information included in a GRAS notice to describe a biological source varied on a case-by-case basis. For example, when the notified substance was derived from a microorganism, the notifier specified a particular strain or subspecies or stated the strain was a nontoxigenic and nonpathogenic strain; when the notified substance was derived from a plant, the notifier identified the specific part(s) of the plant used as the starting material, such as fruit, seeds or seed husks, expressed oil, flowers, roots, leaves, pulp, wood, or bark. However, we disagree that we should use guidance, rather than the regulatory text of this rule, to describe the types of data and information that are necessary to sufficiently identify the biological source because the types of information we are specifying are necessary—rather than merely recommended—information. For example, data and information at the sub-species level (*e.g.,* variety, strain) is necessary for source microorganisms because so many microorganisms (*e.g., Escherichia coli* and *Saccharomyces cerevisiae*) have multiple strains, and although some strains are both non-toxigenic and non-pathogenic, others are not. For example, there are several pathogenic strains of *Saccharomyces cerevisiae,* even though nonpathogenic strains are commonly used in food and in the production of enzyme preparations. As another example, both *Aspergillus oryzae* and *Aspergillus niger* naturally produce mycotoxins, but strains that do not produce mycotoxins have been developed and are used for production of enzyme preparations. In addition, for phage production some host strains have been pathogens (*e.g., Listeria monocytogenes*) and produce toxins. Likewise, data and information about the part of a plant used as a source is necessary because some plants that have edible parts also secrete toxins in non-edible parts. For example, the leaf stalks (petioles) of rhubarb (*Rheum rhaponticum*) are edible, but the leaves contain notable quantities of oxalic acid. As another example, the leaves and stems of tomato (*Solanum lycopersicum*) contain solanine.

We agree that the description of a biological source should be based on the safety of that source and consider all relevant information related to safety. The regulatory text requires taxonomic information beyond genus and species, such as variety or strain, ''when applicable'' for a source microorganism such as those used to produce enzyme preparations. Examples of when information such as variety or strain would be applicable are those microbial sources, such as some fungi, for which there are multiple strains or subspecies that have different properties with respect to the ability to produce toxins, antibiotics, or other substances that are not suitable for use in food.

(Comment 62) One comment asks us to specify that information identifying a substance derived from a biological source must include the breed of animal or plant.

(Response 62) During the Interim Pilot program we did not evaluate any GRAS notices in which the breed of an animal or plant source was a taxonomic descriptor necessary to sufficiently identify that animal or plant source. Therefore, although breed may be an appropriate taxonomic descriptor in some circumstances, the circumstances are rare enough that we have not seen it as necessary information in more than 15 years. Therefore, we are not specifying it as an example of applicable taxonomic information in the rule. In a specific circumstance where breed is necessary to adequately identify a particular animal or plant source, and you do not specify the breed, we intend to ask you to amend your GRAS notice to identify the breed.

(Comment 63) One comment asks us to address substances produced from microorganisms, particularly bioengineered microorganisms. This comment explains that the development of a production microorganism through bioengineering is, for the most part, highly confidential and cannot be disclosed publicly. In addition, the production microorganism often is modified on an ongoing basis, *e.g.,* to improve yield. This comment asks us to specify the point at which subsequent modification of a production microorganism would trigger submission of a new GRAS notice and notes that in some cases subsequent modification of a production organism could be incorporated into the original GRAS notice by ''amendment'' or by reference. This comment also asserts that submission of a new GRAS notice should not be needed in the case of safe strain lineage as described in the scientific literature (Ref. 42).

Another comment asks us to specify that information identifying a substance derived from a biological source must specify whether the plant or animal is genetically engineered or cloned.

(Response 63) We recommend that notifiers consult our guidance entitled ''Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives'' (Ref. 6). That guidance lists a change in the source microorganism (including a change in strain) used for a food substance derived from fermentation of a microorganism as an example of a significant manufacturing process change. Whenever there has been a significant manufacturing process change for a food substance that is the subject of a previous conclusion of GRAS status, the guidance recommends that the manufacturer consider whether the GRAS status of the use of the food substance would be affected; consult

with us regarding the conclusions about the impact of the significant manufacturing change on the safety and regulatory status of the use of the food substance; and make an appropriate regulatory submission to us as circumstances warrant. In the specific circumstance of a production microorganism that is modified on an ongoing basis, a modification that results in a new strain would no longer fall within the description of the source, which must include information at the sub-species level (see § 170.230(a)(2)(i)). If a notifier concludes that a modification that results in a new strain has no impact on the conclusion of GRAS status, one approach could be to submit a supplement to the GRAS notice. Doing so would be consistent with CFSAN's 2010 experience during the Interim Pilot program. See section IV.J of CFSAN's 2010 experience document (Ref. 18), in which CFSAN discusses a GRAS notice in which a notifier consulted with CFSAN about mechanisms to inform CFSAN about its conclusion that additional uses of the notified substance are also GRAS. The notifier supplemented its original GRAS notice with a letter informing CFSAN of the additional conclusion of GRAS status and CFSAN issued a second ''no questions letter'' to the notifier as additional correspondence.

We decline the request to require that information identifying a substance derived from a biological source specify whether the plant or animal is ''genetically engineered'' or ''cloned.'' We consider that the more general requirement to identify a biological source at the sub-species level is adequate to identify the source. In practice during the Interim Pilot program, notifiers routinely informed us about the use of such techniques in describing production microorganisms, particularly for GRAS notices about the intended conditions of use of enzyme preparations. (See, *e.g.,* the list of enzyme preparations in section IV.N of CFSAN's 2010 experience document (Ref. 18).) The source microorganisms for several of the listed enzyme preparations were developed using bioengineering techniques.

When confidential data and information about the development of a production microorganism through bioengineering are necessary to provide evidence that a notified substance produced from that production organism is safe under the conditions of its intended use, the use of the notified substance would not satisfy GRAS criteria. See the discussion in Response 69, where we explain that it may be possible to explain that confidential information (whether included in a GRAS notice, or provided privately to a GRAS panel) is corroborative of safety, rather than necessary to demonstrate safety, if, for example, the method of manufacture included in a GRAS notice meets the requirements of the rule to provide sufficient detail to evaluate the safety of the notified substance as manufactured. Alternatively, the notifier could describe the development of the production microorganism in sufficient detail to address any safety issues associated with use of that production microorganism. For enzyme preparations that would be used in human food, we recommend that notifiers consult our guidance entitled ''Guidance for Industry: Enzyme Preparations: Recommendations for Submission of Chemical and Technological Data for Food Additive Petitions and GRAS Notices'' (Ref. 33), and ''Food-Processing Enzymes From Recombinant Microorganisms—A Review'' (Ref. 43), for details about our recommendations for safety information regarding enzyme preparations derived from bioengineered microorganisms.

2. Potential Toxicants in the Source of the Notified Substance

(Comment 64) One comment agrees that a review of known toxicants that could be produced by the biological source of a notified substance should be part of the safety review, but recommends that the depth of the review be addressed on a case-by-case basis and be tailored to the substance and the source of the substance. This comment asserts that it would be difficult and impractical to define a method for this review or to define the specific toxicants that are required to be reviewed for each particular substance.

(Response 64) We agree that the safety review should be tailored to the substance and its source because of the diversity of toxicants that could be in the biological source. It is your responsibility to determine how to conduct the safety review; the rule does not prescribe any method for this review or any specific toxicants that must be reviewed for a particular substance or source. In some cases (*e.g.,* when it is well established in the scientific community that a source is non-toxigenic), citations to publicly available information about a biological source may be sufficient to address the safety of the notified substance with respect to potential toxicants in the source. In other cases (*e.g.,* when a source is known to be toxigenic), the information about the toxigenic source would lead you to a discussion, in the narrative required in Part 6 of a GRAS notice, of how the method of manufacture and specifications for the notified substance lead you to conclude that the notified substance as manufactured is safe and that the criteria for general recognition are satisfied.

(Comment 65) One comment refers to a statement we made, in the 2010 notice, that we have found that information about substances known to be toxicants is relevant regardless of the state of the science regarding the specific toxicity of the substance to humans (75 FR 81536 at 81540). This comment asserts that specifying that the identity of the notified substance include any known toxicants that could be in the source does not fully address whether the toxicants cause a safety concern. Another comment states that the ''GRAS process'' should contain a safety/risk assessment for known toxicants, not just identify the toxicants.

(Response 65) We agree that a GRAS notice must address the safety concerns associated with toxicants known to be in a biological source, not just identify the toxicants. See the requirements for a GRAS notice to include the method of manufacture of the notified substance (§ 170.230(b)), specifications for food-grade material (§ 170.230(c)), and a narrative explaining why the data and information in a GRAS notice provide a basis for the notifier's view that the notified substance is safe under the conditions of its intended use (§ 170.250).

(Comment 66) One comment recommends using our guidance entitled ''Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions'' (Ref. 31) as a more ''holistic'' approach to addressing potential safety concerns regarding known toxicants in a biological source, because the guidance describes how to use the manufacturing process to control, reduce, or concentrate toxicant levels and explains the importance of establishing limits for any known natural toxicants in or on food additives derived from a natural source. The comment asserts that this guidance should apply to GRAS substances as well as food additives because general recognition of safety through scientific procedures requires the same quantity and quality of evidence as is required to establish a food additive regulation for the use of the substance, and therefore the information about the identity of the substance should be consistent with the requirements for food additives. This comment notes that section III.A of ''Recommendations for Submission of Chemical and Technological Data for

Direct Food Additive Petitions'' clearly outlines the information needed for ''allowing the unequivocal identification and characterization of the food additive'' and that the principles in specific sections in section III.A of the guidance apply to GRAS substances even though they are written to specifically address food additives.

(Response 66) We agree that many of the recommendations in our guidance entitled ''Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions'' (Ref. 31) could be useful to a person who assesses whether a substance is GRAS under the conditions of its intended use. As the comment points out, the guidance currently is structured to address the specific requirements in § 171.1 (particularly § 171.1(c)) for food additive petitions. Consistent with available resources, we will consider revising that guidance to clarify how its recommendations apply to an evaluation of whether a substance is GRAS under the conditions of its intended use.

3. Particle Size

In the 2010 notice, we noted that substances that have a small particle size often have chemical, physical, or biological properties that are different from those of their larger counterparts (75 FR 81536 at 81540). We requested comment on whether the final rule should address, as part of identity, particle size and other chemical and physical properties that may be used to characterize engineered materials (see table 9).

(Comment 67) Some comments recommend that a GRAS notice discuss particle size only if it is relevant to the safety or effectiveness of the notified substance. One comment recommends that the rule not address particle size, at least until this area is better understood. Another comment asks us to clarify what we mean by the term ''small particle size'' if we include that term in the rule.

One comment asks us to require information about particle size and other physical/chemical properties that may be used to characterize engineered materials. This comment asserts that nanoparticles are not simply smaller versions of materials; instead nanoparticles are specifically engineered to create new properties and behaviors that give products certain attributes and highly reactive nanoparticles can exhibit a toxic reaction with their environments, including the cells of living organisms. This comment also notes that the U.S. Environmental Protection Agency (EPA) has already made case-by-case rulings on the safety of certain nanoparticles.

Several comments assert that any requirement for a GRAS notice to address particle size and other chemical or physical properties should apply only to engineered nanomaterials, and that it is not typically necessary to address such properties for non-engineered materials. One comment asserts that engineered nanomaterials could never be eligible for classification as GRAS because they either are new materials with unfamiliar properties or represent a significant new use of a material.

(Response 67) The final rule requires that a GRAS notice include scientific information that identifies the notified substance, and includes ''characteristic properties'' in a list of examples of appropriate information that a notifier would include. We agree that data and information about particle size, and any chemical and physical properties attributable to small particle size, are appropriate for engineered nanomaterials; a GRAS notice about an engineered nanomaterial likely would not provide an adequate basis for a conclusion of GRAS status without such information. We also agree that data and information about particle size may not be relevant for non-engineered materials and, thus, we are including the broad example of ''characteristic properties'' in the final rule without adding the narrow example of ''particle size'' (see § 170.230(a)(1)).

We note that we have several guidances applicable to significant manufacturing changes in food, including nanotechnology (Ref. 6; Ref. 8; and Ref. 44). Our guidance entitled ''Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives'' (Ref. 6) states: ''At present, for nanotechnology applications in food substances, there are questions related to the technical evidence of safety as well as the general recognition of that safety, that are likely to be sufficient to warrant formal premarket review and approval by FDA, rather than to satisfy criteria for GRAS status.'' However, that guidance reflects the generally available data and information at present, and we disagree that data and information supporting the safety of engineered nanomaterials could never satisfy GRAS criteria. Whether the generally available data and information supporting the safety of the intended conditions of use of any substance—including an engineered nanomaterial—satisfy GRAS criteria is a case-by-case conclusion that depends on whether the generally available data and information support a conclusion that the substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use. Section 201(s) of the FD&C Act does not limit the eligibility of a substance for classification as GRAS based on factors such as its characteristic properties.

4. Other Comments About the Identity of the Notified Substance

(Comment 68) One comment asserts that the criteria used to conclude that a particular substance is GRAS, including details regarding biological source, known toxicants, particle size, etc., should be based on what qualified experts determine to be necessary.

(Response 68) We disagree that the role of qualified experts in a conclusion of GRAS status means that the requirements for a GRAS notice should be silent on the types of data and information that generally apply to any conclusion of GRAS status—in this case, data and information regarding the identity of the substance. In the narrative required by part 6 of a GRAS notice, a notifier must explain why the data and information in the notice provide a basis for the notifier's view that the notified substance is safe under the conditions of its intended use (§ 170.250(a)(1)); identify what specific data and information that the notifier discusses to support his view that the notified substance is safe under the conditions of its intended use are generally available, and what specific data and information that the notifier discusses are not generally available (§ 170.250(a)(2)); and explain how the generally available data and information that a notifier relies on to establish safety provide a basis for the notifier's conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use (§ 170.250(b)). The narrative is the appropriate mechanism for a notifier to explain how the view of qualified experts supports his view that the notified substance is GRAS under the conditions of its intended use.

B. Method of Manufacture

(Comment 69) Several comments address Issue 9a, *i.e.,* whether the final rule should continue to stipulate that the method of manufacture exclude any trade secrets, as proposed. Some of these comments support stipulating that the method of manufacture exclude any trade secrets. The stated reasons varied.

For example, some comments state that in the past experience of notifiers, it is generally possible to include sufficient information on the manufacturing process without disclosing trade secrets. One comment states that transparency, by both FDA and industry, and the use of publicly available information is critical to the continued success of the GRAS notification procedure. One comment states that the common knowledge element of the GRAS standard inherently limits the submission of confidential information and/or trade secrets by the notifier to substantiate a conclusion of GRAS status.

Other comments point to the proposed requirement that a GRAS notice include ''detailed information about the . . . method of manufacture (excluding any trade secrets . . .)'' and question whether a method of manufacture that excludes trade secrets can be sufficiently detailed to meet the requirements of a GRAS notice. One comment recommends that we clarify the rule by requiring that the notice include appropriate information on the method of manufacture, sufficient to conduct an adequate safety review, so that confidential information would not be submitted when a very general and non-confidential description suffices.

Several comments acknowledge that there may be situations where trade secret information is necessary to complete the description of the method of manufacture and recommend that the final rule provide flexibility for a notifier to provide trade secret information when appropriate (*e.g.,* to help us evaluate the GRAS notice), and for FDA to protect trade secrets or other confidential information in a GRAS notice from public disclosure, just as we would in the case of submissions such as food additive petitions. To promote clarity and transparency, some of these comments recommend revising the rule to require that a notifier who includes trade secret information explain why the information is trade secret and why the trade secret information has a corroborative role in the safety assessment. Some comments emphasize that a notifier who submits trade secret information must mark the information as non-public. Other comments assert that information identified as trade secret or confidential information should only be allowed if the information is not critical to a conclusion of GRAS status.

One comment suggests that a notifier could provide trade secret information to a GRAS panel for review on a confidential basis because deliberations of the panel would not necessarily be subject to public disclosure. One comment notes that supporting information can be valuable to a GRAS panel and allowing submission of confidential information in a GRAS notice could inform FDA of the full range of information taken into consideration by a GRAS panel.

Some comments cite our regulations for new drugs, premarket notification for medical devices, and premarket approval of medical devices as evidence that our regulations implementing FOIA specifically regard methods of manufacture as confidential and urge us to adopt a similar approach for GRAS notices.

See also Comment 57.

(Response 69) See table 11, and the regulatory text in §§ 170.230(b), 170.225(c)(8), 170.250(d), and 170.250(e), for a series of changes we made to the rule to address these comments about the method of manufacture included in a GRAS notice, including comments about trade secret information associated with the method of manufacture. Although the changes in Parts 1 and 6 of a GRAS notice broadly apply to any non-public information, in this response we focus on how these provisions apply to trade secret information that you may include in the description of the method of manufacture. Collectively, these changes: (1) Emphasize that the description of the method of manufacture must be in sufficient detail to evaluate the safety of the notified substance as manufactured, without stipulating that the method of manufacture exclude any trade secrets (§ 170.230(b)); (2) require the notifier to include a signed statement with his view as to whether the method of manufacture includes trade secret information (§ 170.225(c)(8)); (3) require the notifier to identify any trade secret information in the method of manufacture (§ 170.250(d)); and (4) require the notifier to explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to trade secret information that the notifier considered in concluding that the substance is safe under the conditions of its intended use (§ 170.250(e)). See also Response 57, Response 78, and section XVII.

TABLE 11—REQUIREMENTS THAT APPLY WHEN A NOTIFIER INCLUDES TRADE SECRET OR OTHER NON-PUBLIC INFORMATION IN A GRAS NOTICE

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Description	Revision
170.230(b)	170.36(c)(2)	In Part 2 of your GRAS notice, you must include a description of the method of manufacture in sufficient detail to evaluate the safety of the notified substance as manufactured.	• We replaced ''detailed'' with ''sufficient detail to evaluate the safety of the notified substance as manufactured''. • We no longer stipulate that the description of the method of manufacture must exclude trade secret information.
170.225(c)(8)	N/A	In Part 1 of your GRAS notice, you must state your view as to whether any of the data and information in Parts 2 through 7 of your GRAS notice are exempt from disclosure under the FOIA (*e.g.,* as trade secret or as commercial or financial information that is privileged or confidential).	Requires a notifier who includes information that the notifier views as non-public information to make FDA aware of that view. See Response 57.
170.250(d)	N/A	In Part 6 of your GRAS notice (the narrative), if you view any of the data and information in your notice as exempt from disclosure under the FOIA, you must identify the specific data and information.	Requires a notifier who includes information that the notifier views as non-public information to identify the non-public information. See section XVII.

TABLE 11—REQUIREMENTS THAT APPLY WHEN A NOTIFIER INCLUDES TRADE SECRET OR OTHER NON-PUBLIC INFORMATION IN A GRAS NOTICE—Continued

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Description	Revision
170.250(e)		In Part 6 of your GRAS notice (the narrative), you must explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to non-public, safety-related data and information.	Requires a notifier to place non-public information in the context of a conclusion of GRAS status. See section XVII.
170.275(c)	170.36(f)(1)	We will disclose all remaining data and information that are not exempt from public disclosure in accordance with part 20.	Uses active voice to emphasize that we will apply the protections from public disclosure under the FOIA to non-public information included in a GRAS notice.

This rule establishes requirements for the information that a notifier submits to FDA in a GRAS notice. GRAS criteria require that any conclusion of GRAS status be based on common knowledge (see § 170.30(a)) and, thus, there could be no basis for a conclusion of GRAS status if trade secret information (or other non-public information) is necessary for qualified experts to reach a conclusion that the notified substance is safe under the conditions of its intended use. In the particular case of a conclusion of GRAS status through scientific procedures, GRAS criteria require that the conclusion of GRAS status be based on data, information, and methods that are generally available (see § 170.30(b)). Non-public information may be used to corroborate safety but cannot be used to establish safety; as discussed in Response 9, qualified experts must be able to conclude that the substance is not harmful under the conditions of its intended use without access to ''corroborative'' information (see § 170.30(a)).

We believe that it will be rare for a GRAS notice to include trade secret information. Likewise, we expect it will be rare that trade secret information would warrant sharing with members of a GRAS panel, because a notifier must write a non-confidential description of the method of manufacture to include in the GRAS notice and could share this non-confidential description, rather than trade secret information, with the GRAS panel. If the GRAS panel had questions about that description of the method of manufacture, we expect that the notifier would revise the description to address those questions rather than provide the GRAS panel with trade secret information to address those questions. If, however, a notifier does provide the GRAS panel with trade secret information, we agree that the notifier should inform us of the full range of information taken into consideration by the GRAS panel, consistent with the signed statement that the GRAS notice is a complete, representative, and balanced submission (see Response 58 and § 170.225(c)(9)). The notifier could do so either by including in his GRAS notice a non-confidential description of the trade secret information that was shared, or by providing the trade secret information shared with a GRAS panel. Importantly, the notifier would be required to explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to non-public, safety related data and information (see Response 78 and § 170.250(e)). If the public description of the method of manufacture that a notifier includes in a GRAS notice cannot provide sufficient detail to evaluate the safety of the notified substance as manufactured, there could be no basis to support a conclusion of GRAS status. However, if that public description meets the requirements of the rule to provide sufficient detail to evaluate the safety of the notified substance as manufactured (see § 170.230(b)), it may be possible to explain that trade secret information that a GRAS panel evaluated is corroborative of safety rather than necessary to demonstrate safety.

Under § 20.61, trade secrets and commercial or financial information which is privileged or confidential are exempt from public disclosure. Under §§ 20.100(c)(7) and 171.1(h)(2)(i), manufacturing methods or processes, including quality control procedures, are exempt from public disclosure unless they have been previously disclosed to the public (as defined in § 20.81) or they relate to a product or ingredient that has been abandoned. If a notifier believes that all information about the method of manufacture should be non-public, it is unlikely that the notifier has a basis to conclude that the notified substance is GRAS under the conditions of its intended use. The use of the substance would be a food additive use and, if the notifier submits a food additive petition for that use, our regulations governing a food additive petition would protect the information from public disclosure, as do our regulations for new drugs, premarket notification for medical devices, and premarket approval of medical devices.

(Comment 70) Several comments express concern about the possibility that we would determine that information a notifier identifies as a trade secret or as confidential commercial information is available for public disclosure. One comment asserts that if we choose to allow the submission of confidential information in a GRAS notice, we should not be the party who determines whether information should be publicly disclosed. Another comment asks us to provide an opportunity for a notifier to make a ''cease to evaluate'' request before we disclose confidential information.

One comment asks us to allow the submission of limited confidential information to supplement (or corroborate) the publicly available information in a GRAS notice, such as by providing sufficient information in a GRAS notice to support a conclusion of GRAS status but also including additional, corroborating information in a food master file. The comment explains that the public GRAS notice would be complete and sufficient to form a conclusion of GRAS status, but we would have access to additional, confidential information that would ensure that we are informed of new manufacturing or technological developments. This comment points out that we have for many years employed food, drug, and medical device master files for the submission of confidential information.

(Response 70) We disagree that we should not be the party who determines whether information should be publicly disclosed. Under our public information regulations in part 20, we have the responsibility to determine whether information should be publicly disclosed, regardless of whether a person who submits the information has marked it as non-public. Marking records submitted to us as confidential, or with any other similar term, raises no obligation by FDA to regard such records as confidential, to return them to the person who has submitted them, to withhold them from disclosure to the public, or to advise the person submitting them when a request for their public disclosure is received or when they are in fact disclosed (see § 20.27). We also disagree that providing an opportunity for a notifier to ask us to cease to evaluate a GRAS notice would impact the public disclosure of data and information that do not satisfy the criteria in part 20 for exemption from disclosure; under § 20.29 a GRAS notice is available for public disclosure in accordance with part 20.

Data and information submitted to us are available for public disclosure based on the nature of the data and information, not the name of the file where we store the data and information. Thus, asking us to store data and information that you view as confidential in a specific type of file, such as a ''food master file,'' would not automatically protect the information from public disclosure. Furthermore, in Part 6 of your GRAS notice you would be required to explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to the confidential data and information in the separate file. We also would expect that you provide a statement in Part 1 of your GRAS notice with your view that the additional data and information in the separate file are exempt from disclosure under the FOIA (see § 170.225(c)(8)). Because part 20 already provides protection of non-public information from disclosure, and because your GRAS notice would need to both acknowledge the data and information in the separate file and explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to these data and information, we consider it administratively inefficient to maintain the data and information submitted in support of a conclusion of GRAS status in two separate files, and we may decide to decline to file a GRAS notice that is accompanied by a separate file containing data and information that you view as non-public.

(Comment 71) Some comments assert that many manufacturers will choose not to notify us of a conclusion of GRAS status because they expect that we will determine that all information submitted in a GRAS notice is available for public disclosure in most circumstances.

(Response 71) Our experience during the Interim Pilot program does not support the assertions in these comments. As noted in Response 24 and Response 26, CFSAN has filed more than 600 GRAS notices between 1998 and 2015, for an average of approximately 34 GRAS notices per year.

(Comment 72) One comment states that commercial and financial information are not relevant to the determination of safety of a notified substance.

(Response 72) Confidential commercial information may on occasion be used to corroborate safety. One example is an article that has been accepted for publication, but has not yet been published. This article would likely be considered confidential until it is published, but it could be used to corroborate other published information.

C. Specifications for the Notified Substance

We received no comments that disagreed with our proposed requirement for a GRAS notice to include specifications for food-grade material and we are finalizing it as proposed for a substance used in human food. See table 29 for an editorial change we made to the regulatory text for specifications for a substance used in animal food.

D. Data and Information Bearing on the Physical or Other Technical Effect of the Notified Substance

As discussed in section XXV.E, several comments discuss their experience with CVM's practice, during the Interim Pilot program, of asking a notifier to provide data or information demonstrating the effectiveness, or utility, of the notified substance. After considering these comments, we have added a requirement for Part 2 of a GRAS notice to include relevant data and information bearing on the physical or other technical effect the notified substance is intended to produce, including the quantity of the notified substance required to produce such effect, when necessary to demonstrate safety (see § 170.230(d) and Response 144). Data and information bearing on the physical or other technical effect the notified substance is intended to produce are only necessary when they bear on safety. This relationship to safety is consistent with the requirements of the FD&C Act for a petition to establish the safety of a food additive (see section 409(b)(2)(C) of the FD&C Act). An example of when such data and information would be relevant to safety is when the intended use of the notified substance is as an antimicrobial agent. For example, an antimicrobial agent may change the microbiological profile of food such that it suppresses one group of pathogenic microorganisms while allowing others to proliferate, thereby creating a potential health problem (Ref. 32).

XIV. Comments on Part 3 of a GRAS Notice: Dietary Exposure

We proposed that a notice regarding a conclusion of GRAS status through scientific procedures include a comprehensive discussion of, and citations to, generally available and accepted scientific data, information, methods, or principles that the notifier relies on to establish safety, including a consideration of the probable consumption of the substance and the probable consumption of any substance formed in or on food because of its use and the cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substances in such diet (proposed § 170.36(c)(4)(i)(A)). In the 2010 notice, we requested comment on several issues relevant to the proposed requirements for a comprehensive discussion that considers the probable consumption of the substance and the probable consumption of any substance formed in or on food because of its use and the cumulative effect of the substance in the diet, and noted that the simple term ''dietary exposure'' could be used in place of the statutory language (*i.e.,* derived from section 409(c)(5) of the FD&C Act) we used in the proposed rule (see table 12). See table 27 for issues in the 2010 notice regarding dietary exposure when a notified substance would be added to animal food.

TABLE 12—ISSUES IN THE 2010 NOTICE REGARDING DIETARY EXPOSURE WHEN A NOTIFIED SUBSTANCE WOULD BE ADDED TO HUMAN FOOD

Issue No.	Description of our request for comment	Reference
11a	Whether the final rule should continue to restate the statutory language of section 409(c)(5) of the FD&C Act or whether this provision should be stated more clearly, for example, by requiring information about dietary exposure (*i.e.,* the amount of the notified substance that consumers are likely to eat or drink as part of a total diet).	75 FR 81536 at 81540–81541.
11b	Whether a GRAS notice should be required to include information about dietary exposure to contemporary consumers regardless of whether the determination of GRAS status is through scientific procedures or through experience based on common use in food.	75 FR 81536 at 81540–81541.

In the following sections, we discuss comments on the proposed requirements applicable to dietary exposure and the issues discussed in the 2010 notice. After considering these comments, we are establishing requirements for Part 3 of a GRAS notice as shown in table 13, with editorial, clarifying, and conforming changes as shown in table 29. (See § 170.235). Table 13 identifies changes we made relative to the proposed rule or the description in the 2010 notice other than the editorial, clarifying, and conforming changes shown in table 29 and the additional editorial changes associated with the redesignation of some of the regulatory text of proposed § 170.36(c)(4)(i)(A) as § 170.235.

TABLE 13—FINAL REQUIREMENTS FOR DATA AND INFORMATION ABOUT DIETARY EXPOSURE IN PART 3 OF A GRAS NOTICE

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.235	170.36(c)(4)(i)(A) ...	11a 11b	In Part 3 of your GRAS Notice, you must provide data and information about dietary exposure (*i.e.,* the amount of relevant substances that consumers are likely to eat or drink as part of a total diet), regardless of whether your conclusion of GRAS status is through scientific procedures or through experience based on common use in food.	• Uses the term ''dietary exposure'' and describes it as meaning ''the amount of relevant substances that consumers are likely to eat or drink as part of a total diet.'' • Requires data and information about dietary exposure regardless of whether your conclusion of GRAS status is through scientific procedures or through experience based on common use in food.
170.235(a)	170.36(c)(4)(i)(A) ...	11a	In Part 3 of your GRAS Notice, you must provide data and information about dietary exposure to the notified substance that includes exposure from its intended use and all sources in the diet.	Uses the term ''dietary exposure.''
170.235(b)	170.36(c)(4)(i)(A) ...	11a	When applicable, in Part 3 of your GRAS Notice you must provide data and information about dietary exposure to any other substance that is expected to be formed in or on food because of the use of the notified substance (*e.g.,* hydrolytic products or reaction products).	• Uses the term ''dietary exposure.'' • Gives examples of substances that could be formed in or on food because of the use of the notified substance.
170.235(c)	170.36(c)(4)(i)(A), 170.36(c)(2).	11a	When applicable, in Part 3 of your GRAS Notice you must provide data and information about dietary exposure to any other substance that is present with the notified substance either naturally or due to its manufacture (*e.g.,* contaminants or by-products).	Requires an estimate of dietary exposure to substances such as contaminants and by-products as a means to establish specifications for applicable contaminants and by-products.
170.235(d)	170.36(c)(4)(i)(A) ...	11a	In Part 3 of your GRAS notice, you must describe the source of any food consumption data that you use to estimate dietary exposure.	Specifies a necessary aspect of the proposed ''comprehensive discussion'' of scientific data, information, and methods.
170.235(e)	170.36(c)(4)(i)(A) ...	11a	In Part 3 of your GRAS notice, you must explain any assumptions you made to estimate dietary exposure.	Specifies a necessary aspect of the proposed ''comprehensive discussion'' of scientific data, information, and methods.

TABLE 13—FINAL REQUIREMENTS FOR DATA AND INFORMATION ABOUT DIETARY EXPOSURE IN PART 3 OF A GRAS NOTICE—Continued

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.250(a)(1)	170.36(c)(4)(i)(A) ...	N/A	In Part 6 of your GRAS notice, you must explain why the data and information in your notice provide a basis for your view that the notified substance is safe under the conditions of its intended use, considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet.	N/A.

See section XXV.F for a discussion of comments on the issues listed in table 27 regarding dietary exposure when a notified substance would be added to animal food and for changes we made to the regulatory text regarding dietary exposure when a notified substance would be added to animal food.

(Comment 73) Some comments support retaining the statutory language derived from section 409(c)(5) of the FD&C Act when stating the requirement for a comprehensive discussion in a GRAS notice that considers dietary exposure. One of these comments states that the proposed statutory language regarding dietary exposure is consistent with the criteria for general recognition of safety through scientific procedures, which requires the same quantity and quality of scientific evidence necessary for a food additive petition. Other comments support revising the proposed requirement as a means of clarifying that the comprehensive discussion in a GRAS notice must consider dietary exposure.

(Response 73) We agree that: (1) The requirements of the rule regarding what a notifier must include in a GRAS notice regarding dietary exposure must be clear; and (2) the statutory language of section 409(c)(5)(A) of the FD&C Act is consistent with the criteria for general recognition of safety through scientific procedures, which requires the same quantity and quality of scientific evidence necessary for a food additive petition. To meet both of these goals, the final rule requires information about dietary exposure (*i.e.,* the amount of relevant substances that consumers are likely to eat or drink as part of a total diet), as we suggested in the 2010 notice, but also retains the detailed statutory direction as proposed (see § 170.235(a) through (c), § 170.250(a)(1), and table 13). In addition to requiring an estimate of dietary exposure to the notified substance (§ 170.235(a)), the rule requires, when applicable, that a notifier provide data and information about dietary exposure to any other substance that is expected to be formed in or on food because of the use of the notified substance (*e.g.,* hydrolytic products or reaction products) (§ 170.235(b)). Example of such substances are benzoates (which react with ascorbic acid (such as in beverages) to form benzene) and sulfur dioxide (which reacts irreversibly with thiamine, such that we have prescribed limitations on the use of sulfur dioxide in some food products (see § 182.3862)). The rule also requires, when applicable, that a notifier provide data and information about dietary exposure to any other substance that is present with the notified substance either naturally or due to its manufacture (*e.g.,* contaminants or by-products). An estimate of dietary exposure to substances such as contaminants and by-products is necessary to establish specifications for applicable contaminants and by-products (see § 170.230(c), which requires that a GRAS notice include specifications for food-grade material). See also Response 75.

(Comment 74) One comment asks us to allow for a reasonable methodology that does not overestimate dietary exposure in the extreme.

(Response 74) The rule neither prescribes the methodology you would use to estimate dietary exposure nor requires that you overestimate dietary exposure. Consistent with the proposed requirement for the consideration of dietary exposure to be a ''comprehensive discussion,'' the rule requires you to describe the source of any food consumption data that you use to estimate dietary exposure and any assumptions you made to estimate dietary exposure; such information is necessary for the estimates of dietary exposure to be scientifically sound and provides an opportunity for you to explain why the methodology you used is reasonable (see § 170.235(d) and (e) and table 13). Our guidance entitled ''Estimating Dietary Intake of Substances in Food'' provides general recommendations for calculating and submitting estimates of dietary intake to support the documentation of the safety of substances introduced into food either intentionally to accomplish a technical effect, adventitiously as a component of an added substance, or inadvertently through contamination resulting from processing (Ref. 25).

(Comment 75) One comment emphasizes that the requirement for consideration of dietary exposure must discuss the potential cumulative effect of the notified substance.

(Response 75) We agree. We are specifying that the narrative included in Part 6 of a GRAS notice must address the safety of the notified substance, considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet (see § 170.250(a)(1)).

(Comment 76) Some comments support requiring that a GRAS notice include information about dietary exposure to contemporary consumers when the conclusion of GRAS status is through experience based on common use in food prior to 1958, *e.g.,* because dietary exposure to contemporary consumers serves as a baseline for future studies/assessment. Other comments do not support such a requirement and assert that it is not critical to update the exposure data if consumption of the GRAS substance was already widespread before 1958, or that information about dietary exposure to contemporary consumers would only be necessary if the exposure has significantly changed since 1958.

One comment questions the value of requiring information about contemporary dietary intake of an ingredient that is GRAS through experience based on common use in foods. This comment asserts that the

FD&C Act deems an ingredient to be GRAS if it was commonly used in foods prior to January 1, 1958, and that FDA has long recognized that a conclusion of GRAS status through experience based on common use in food may be made without the quantity or quality of scientific procedures required for establishment of a food additive regulation. This comment asserts that there is no requirement for a GRAS ingredient to be consumed at the same use level as in 1958 and that imposition of such a new requirement may be impracticable, *e.g.,* because there may not be any databases that would allow for the calculation of dietary exposures prior to 1958. This comment also asserts that in many instances there may be insufficient information to establish an acceptable daily intake (ADI) for the ingredient because studies that can be used to calculate ADIs may not be available for many of these ingredients, and that without information about the ADI it would be difficult to imagine the relevance of the estimated daily intake, which would be calculated through dietary exposure.

Another comment asserts that §§ 170.30(c) and 170.3(f) clearly provide that for a substance to be GRAS through experience based on common use in food there must be a substantial history of consumption of the substance in food by a significant number of people prior to 1958 and that the requirements for information about consumption data in a GRAS notice should be consistent with those regulatory provisions. This comment also asserts that requiring information about dietary exposure to contemporary consumers would represent an additional regulatory burden that would not impact the original conclusion of GRAS status through experience based on common use in food if there are no safety concerns when the notified substance is used in accordance with the intended conditions of use.

(Response 76) We are requiring that a notifier provide data and information about dietary exposure, regardless of whether the conclusion of GRAS status is through scientific procedures or through experience based on common use in food (see § 170.235). The FD&C Act and our regulations do not provide that a substance is necessarily GRAS under the conditions of its intended use merely because it was commonly used in food prior to 1958. Rather, the FD&C Act provides that such a substance must be generally recognized, among experts qualified by scientific training and experience to evaluate its safety, through experience based on common use in food, to be safe under the conditions of its intended use. Under both the FD&C Act and the definition of ''safe'' in our regulations, relevant factors must be considered, including the ''probable consumption of the substance and of any substance formed in or on food because of its use'' (see section 409(c)(5)(A) of the FD&C Act and § 170.3(i)(1)). We recognize that a conclusion of GRAS status through experience based on common use in food does not require the same quantity or quality of scientific information required for establishment of a food additive regulation; however, this means that a conclusion of GRAS status through experience based on common use in food is not necessarily supported by the same testing data as would be required to support establishment of a food additive regulation. See, for example, the 1976 final rule establishing GRAS criteria, which provides, ''for those substances that were widely used before 1958, under the terms of the statute FDA must consider available data and may not prohibit use of a substance merely because tests that would be required for new food additives have not been performed.'' (41 FR 53600, December 7, 1976). Like a conclusion of GRAS status based on scientific procedures, a conclusion of GRAS status through experience based on common use in food requires that the substance be ''safe,'' as defined in 21 CFR 170.3(i), under the conditions of its intended use.

The rule requires that a notifier provide evidence of substantial history of consumption of the substance for food use by a significant number of consumers prior to January 1, 1958, but does not require an estimate of dietary exposure prior to 1958 (see § 170.245). The rule requires that the narrative in Part 6 of a GRAS notice explain why the data and information in the notice provide a basis for the notifier's view that the notified substance is safe under the conditions of its intended use, considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet (§ 170.250(a)); to do so, the notifier must consider the estimated dietary exposure (which this comment refers to as ''estimated daily intake''). However, the rule does not specify that a notifier must determine an ''acceptable daily intake'' as part of the narrative.

XV. Comments on Part 4 of a GRAS Notice: Self-Limiting Levels of Use

We proposed that a GRAS notice must include information on any self-limiting levels of use (proposed § 170.36(c)(3)). We did not receive comments disagreeing with this proposed requirement. Therefore, we are establishing a requirement for you to include in Part 4 of your GRAS notice data and information on self-limiting levels of use in circumstances where the amount of the notified substance that can be added to food is limited because food containing levels of the notified substance above a particular level would become unpalatable or technologically impractical (see § 170.240). We included an explanation of the circumstances in which the level of use is self-limiting for clarity.

XVI. Comments on Part 5 of a GRAS Notice: Common Use in Food Before 1958

We proposed that a GRAS notice include a comprehensive discussion of, and citations to, generally available data and information that the notifier relies on to establish safety, including evidence of a substantial history of consumption of the substance by a significant number of consumers, for a conclusion of GRAS status through experience based on common use in food (proposed § 170.36(c)(4)(ii)(A)). During the Interim Pilot program, we received fewer than a dozen GRAS notices where the statutory basis was through experience based on common use in food (Ref. 45).

We did not receive comments disagreeing with this proposed requirement and we are establishing a requirement for you to include in Part 5 of your GRAS notice evidence of a substantial history of consumption of the notified substance for food use by a significant number of consumers prior to January 1, 1958 if the statutory basis for your conclusion of GRAS status is through experience based on common use in food (see § 170.245). See table 29 for conforming changes for a substance used in animal food.

XVII. Comments on Parts 6 and 7 of a GRAS Notice: Narrative and List of Supporting Data and Information

We proposed that a GRAS notice must include a detailed summary of the basis for the notifier's determination that a particular use of the notified substance is exempt from the premarket approval requirements of the FD&C Act because such use is GRAS (proposed § 170.36(c)(4)). Regardless of whether the conclusion of GRAS status was based on scientific procedures or through experience based on common use in food, we proposed to require: (1) A comprehensive discussion of, and citations to, generally available and accepted scientific data and information that the notifier relies on to establish

safety (proposed § 170.36(c)(4)(i)(A) and 170.36(c)(4)(ii)(A)); (2) a comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with the GRAS determination (proposed § 170.36(c)(4)(i)(B) and (c)(4)(ii)(B)); and (3) the basis for concluding, in light of the data and information in the GRAS notice, that there is consensus among experts qualified by scientific training and experience to evaluate the safety of substances added to food that there is reasonable certainty that the substance is not harmful under the intended conditions of use (proposed § 170.36(c)(4)(i)(C) and (c)(4)(ii)(C)). When the conclusion of GRAS status is based on scientific procedures, we also proposed that the discussion of generally available and accepted information that the notifier relies on to establish safety include methods and principles, and include a consideration of the probable consumption of the substance and the probable consumption of any substance formed in or on food because of its use and the cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substances in such diet (proposed § 170.36(c)(4)(i)(A)).

In the 2010 notice, we requested comment on issues relevant to the applicability of confidential data and information to a conclusion that a substance is GRAS under the conditions of its intended use (see table 14).

TABLE 14—ISSUES IN THE 2010 NOTICE REGARDING THE APPLICABILITY OF CONFIDENTIAL DATA AND INFORMATION TO A CONCLUSION OF GRAS STATUS

Issue No.	Description of our request for comment	Reference
9b	Whether to require that a notifier who identifies one or more trade secret(s), as defined in § 20.61(a), in the GRAS notice explain why it is trade secret information and how qualified experts could conclude that the intended use of the notified substance is safe without access to the trade secret(s).	75 FR 81536 at 81539–81540.
9c	Whether to require that a notifier who identifies confidential commercial or financial information, as defined in § 20.61(b), in the GRAS notice explain why it is confidential commercial or financial information and how qualified experts could conclude that the intended use of the notified substance is safe without access to such information.	75 FR 81536 at 81539–81540.

In the following paragraphs, we discuss comments on the proposed requirements applicable to a detailed summary of the basis for the notifier's conclusion of GRAS status and the issues discussed in the 2010 notice. After considering these comments, we are establishing requirements for Part 6 of a GRAS notice to include a narrative as shown in table 15, and for Part 7 of a GRAS notice to include a list of supporting data and information as shown in table 16, with editorial, clarifying, and conforming changes as shown in table 29. (See §§ 170.250 and 170.255.)

Table 15 and table 16 identify changes we made relative to the proposed rule or the description in the 2010 notice other than the editorial, clarifying, and conforming changes shown in table 29 and the additional editorial changes associated with the redesignation of proposed § 170.36(c)(4) as §§ 170.250 and 170.255.

TABLE 15—FINAL REQUIREMENTS FOR A NARRATIVE IN PART 6 OF A GRAS NOTICE

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description. Part 6 of your GRAS notice:	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.250	170.36(c)(4)	N/A	You must include a narrative that provides the basis for your conclusion of GRAS status.	N/A.
170.250(a)(1)	170.36(c)(4)	N/A	You must explain why the data and information in your notice provide a basis for your view that the notified substance is safe under the conditions of its intended use, considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet.	N/A.
170.250(a)(2)	170.36(c)(4)	9a, 9b, and 9c	You must identify what specific data and information are generally available, and what specific data and information are not generally available, by providing citations to the list of data and information that you include in Part 7 of your GRAS notice.	Requires that your narrative clarify the status of all data and information that you rely on to establish safety.

TABLE 15—FINAL REQUIREMENTS FOR A NARRATIVE IN PART 6 OF A GRAS NOTICE—Continued

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description. Part 6 of your GRAS notice:	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.250(b)	170.36(c)(4)	N/A	You must explain how the generally available data and information that you rely on to establish safety provide a basis for your conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use.	Uses the term ''generally recognized'' rather than the term ''consensus.''
170.250(c)	170.36(c)(4)	6b	You must either: (1) Identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status, regardless of whether those data and information are generally available; or (2) State that you have reviewed the available data and information and are not aware of any data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status..	When applicable, requires an affirmative statement that you have reviewed the available data and information and are not aware of any data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status.
170.250(d)	N/A	9b and 9c	In Part 6 of your GRAS notice (the narrative), if you view any of the data and information in your notice as exempt from disclosure under the FOIA, you must identify the specific data and information.	N/A.
170.250(e)	N/A	9b and 9c	In Part 6 of your GRAS notice (the narrative), you must explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access non-public, safety-related data and information.	Your explanation must address all non-public safety-related data and information, not just confidential data and information included in your GRAS notice.

TABLE 16—FINAL REQUIREMENTS FOR A LIST OF SUPPORTING DATA AND INFORMATION IN PART 7 OF A GRAS NOTICE

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description. Part 7 of your GRAS notice:	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.255(a)	• 170.36(c)(4)(i)(A) • 170.36(c)(4)(ii)(A)	9a, 9b, and 9c	You must include a list of all of the data and information that you discuss in part 6 of your GRAS notice to provide a basis for your view that the notified substance is safe under the conditions of its intended use.	Clarifies that the list includes all data and information, not just generally available data and information.
170.255(b)	• 170.36(c)(4)(i)(A) • 170.36(c)(4)(ii)(A)	9a, 9b, and 9c	The data and information that you list must specify which data and information are generally available, and which data and information are not generally available.	Requires that you characterize each item in your list as to whether it is generally available.

In the requirements for Parts 6 and 7 of the final rule, we made changes to require that the narrative in Part 6 of your GRAS notice, and the accompanying list of supporting data and information in Part 7 of your GRAS notice, clarify the status of all data and information that you rely on to establish safety as to whether it is generally available (see §§ 170.250(a)(2) and 170.255, table 15, and table 16). We made these changes relative to the proposed requirements for a detailed summary and comprehensive discussion for consistency with: (1) The criteria for eligibility for classification as GRAS through scientific procedures (which provide that a conclusion of GRAS status may be corroborated by the application of unpublished scientific data, information, or methods (see § 170.30(b), Response 8, and Response 12)); and (2) the provisions of the rule that allow you to include data and information that are not generally available (see § 170.230(b) (which no longer stipulates that the method of manufacture must exclude trade secret), § 170.225(c)(8), Response 57 and Response 69).

In the requirements for Part 6 of a GRAS notice, we also made a change to require that your narrative either: (1) Identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with your

conclusion of GRAS status, regardless of whether those data and information are generally available; or (2) state that you have reviewed the available data and information and are not aware of any data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status. See § 170.250(c) and table 15. We made this change relative to the proposed requirement for a comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with a conclusion of GRAS status to emphasize your responsibility to seek out such reports and information, as we do during our evaluation of a GRAS notice. See also § 170.225(c)(9) and Response 58, in which we discuss the requirements for a statement certifying that the GRAS notice is ''complete'' in addition to ''representative'' and ''balanced,'' to emphasize your responsibility to identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with a conclusion of GRAS status. Under §§ 170.225(c)(9) and 170.250(c), we expect you to describe unpublished reports of investigations or other information that may appear to be inconsistent with a conclusion of GRAS status, not just published reports. If we identify relevant information that was not discussed in the GRAS notice, we may question the credibility of the certification statements in the GRAS notice and respond with an ''insufficient basis letter.'' As noted in Response 58, the use of certification statements has become routine in other submissions to FDA for food programs, and the certification statements in Form FDA 3480 (for a food contact notification submission) (Ref. 39) and in Form FDA 3537 (for registration of a food facility) (Ref. 40) remind the submitter of criminal penalties under 18 U.S.C. 1001 for a materially false, fictitious, or fraudulent statement to the U.S. Government. Now that certification statements will be required in a GRAS notice, we intend to modify the form that we make available for the submission of a GRAS notice (*i.e.,* Form FDA 3667 (Ref. 38)) to likewise remind any person who submits a GRAS notice of the applicability of criminal penalties for a materially false, fictitious, or fraudulent statement to the U.S. Government.

See also Response 78. We also expect you to describe unpublished data and information that you consider to be corroborative of safety (*e.g.,* if you consider that the unpublished data and information warrant sharing with any ''GRAS panel'' that you convene).

(Comment 77) One comment asserts that the proposed requirement for a GRAS notice to include the basis for concluding that there is consensus among qualified experts about the safety of the substance misstates the statutory standard for general recognition in section 201(s) of the FD&C Act. This comment asserts that the term ''consensus'' denotes complete or near unanimity, whereas the standard of general recognition requires that qualified experts predominantly, but not unanimously, accept the safety of the substance. Although the comment acknowledges that the proposed rule stated that the term ''consensus'' does not imply unanimity (62 FR 18938 at 18941), the comment argues that the example used in our explanation, about whether a single published report questioning the safety of use of a substance in food would preclude general recognition, wrongly implied that general recognition requires near unanimity (62 FR 18938 at 18941). The comment asks us to revise the rule by replacing the term ''consensus,'' which does not appear in the statute, with the phrase ''general recognition,'' which derives from the statute itself.

(Response 77) As discussed in the proposed rule (62 FR 18938 at 18939), our interpretation that general recognition requires consensus is consistent with the case law on the general recognition standard. See *United States* v. *Western Serum Co., Inc.,* 666 F.2d 335, 338 (9th Cir. 1982); *United States* v. *Articles of Drug...Promise Toothpaste,* 624 F.Supp. 776, 778 (N.D. Ill. 1985), aff'd 826 F.2d 564 (7th Cir. 1987); *United States* v. *Articles of Drug...Hormonin,* 498 F.Supp.2d 424, 435 (D.N.J. 1980). See also the discussion of the consensus standard in Response 20.

We proposed to provide our interpretation of section 201(s) of the FD&C Act in the requirement for Part 6 of a GRAS notice to provide more context to notifiers than merely repeating the statutory language. We disagree with the comment's assertion that the example we described in the proposed rule requires ''near unanimity''; CFSAN's experience during the Interim Pilot program demonstrates that CFSAN's ''insufficient basis letters'' did not apply a standard of ''near unanimity'' when evaluating the notifier's basis for a conclusion of GRAS status (see section III.A.3 of CFSAN's 2010 experience document (Ref. 18)).

However, we have decided to use the statutory language (*i.e.,* ''generally recognized'') rather than the proposed term ''consensus'' because the revised GRAS criteria that we are establishing in § 170.30 continue to use the statutory language rather than the consensus standard applied by the courts in applying the statutory language to specific situations. Using the statutory language in both the GRAS criteria and the requirement for the submission of a narrative in a GRAS notice will emphasize your burden to explain how the data and information in the notice regarding the safety of the notified substance under the conditions of its intended use satisfy the GRAS criteria.

See also Response 128, in which we respond to comments recommending that we clarify that the same standards apply to a conclusion of GRAS status regardless of whether the conclusion is submitted to us as a GRAS notice or is not submitted to us. As noted in Response 128, 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. In developing any recommendations (*e.g.,* in guidance) that would broadly apply to any conclusion of GRAS status, it is simpler to consistently use the same regulatory text in both the GRAS criteria and the submission requirements for a GRAS notice.

(Comment 78) One comment notes that industry has various options for handling confidential information. For example, confidential agreements are commonly used instruments to help maintain the confidentiality of proprietary trade secret information, and therefore qualified experts on GRAS panels can have access to such information if it is necessary for a conclusion of GRAS status. The comment asks us to require that notifiers indicate whether qualified experts (such as on the notifier's GRAS panel) had access to trade secrets when they concluded that the substance is safe under the conditions of its intended use.

(Response 78) The rule establishes no requirements specific to a GRAS panel. However, we agree that it is appropriate for a notifier to indicate whether qualified experts (such as on the notifier's GRAS panel) who reviewed the data and information supporting safety had access to safety-related trade secrets in reaching a conclusion that the notified substance is safe under the conditions of its intended use. Therefore, we are requiring that a notifier explain how there could be a basis for a conclusion of GRAS status if

qualified experts generally do not have access to non-public safety-related data and information (see § 170.250(e)). This requirement applies to all non-public safety-related data and information, not just trade secret information, and is not limited to non-public safety-related data and information that are included in the notice. As requested by the comment, this requirement would apply if the notifier provided non-public safety-related information to outside experts (such as on a GRAS panel). As already discussed, if a GRAS panel considers non-public safety-related information that a notifier does not include in a GRAS notice, we also expect the notifier to inform us that the GRAS panel had access to such information, consistent with the notifier's signed statement that the GRAS notice is a complete, representative, and balanced submission (see § 170.225(c)(9)) (see Response 58 and Response 69).

See also table 11 and table 15. The rule also requires that a notifier state his view as to whether any of the data and information in Parts 2 through 7 of a GRAS notice are exempt from disclosure under the FOIA (see § 170.225(c)(8)) and identify what specific data and information in the notice are generally available, and what specific data and information in the notice are not generally available (see § 170.250(a)(2) and (d)). Collectively, the requirements in §§ 170.225(c)(8) and (9) and 170.250(a)(2), (d), and (e) address the underlying issue in the comment's request, *i.e.,* that there must be a basis for a conclusion of GRAS status if some safety-related data and information that a notifier assesses in his deliberations are non-public (*e.g.,* trade secret information or otherwise are confidential information), regardless of whether the notifier shares such information with a GRAS panel. If a GRAS notice does not provide a basis for a conclusion that the notified substance is safe under the conditions of its intended use without access to such information, we would respond to the notice with an ''insufficient basis letter.'' If we respond with a ''no questions letter,'' and later determine that the GRAS notice was not ''complete'' (*e.g.,* because it did not describe unpublished reports of investigations that are, or may appear to be, inconsistent with the conclusion of GRAS status), we may send the notifier a subsequent letter regarding the omission; such a letter would be readily accessible to the public (§§ 170.265(c) and 170.275(b)(2)).

(Comment 79) One comment suggests that if the qualified experts are FDA reviewers, an option might be for the notifier to submit a ''sanitized'' version of the GRAS notice, excluding non-public information, together with a separate appendix to the GRAS notice where the notifier would include relevant trade secrets or confidential information needed to support the conclusion of GRAS status. Alternatively, we could require that a notifier submit two versions of the submission: (1) A sanitized version that excludes non-public information; and (2) a more detailed version including the confidential information. The comment states that these options would both allow our reviewers access to the information and facilitate the process of promptly making GRAS notices available for public disclosure.

(Response 79) In enacting the GRAS provision, Congress clearly contemplated a process of concluding that a food substance is GRAS under the conditions of its intended use as an alternative to submission of a food additive petition to FDA and establishment of a regulation prescribing the conditions under which the substance may be safely used. It follows that the qualified experts who evaluate the basis for a conclusion that the notified substance is safe under the conditions of its intended use must not exclusively be ''FDA's experts'' (such as our scientific staff who evaluate GRAS notices). The suggestion of this comment that a notifier could rely exclusively on evaluation by FDA experts to support his view that there is a basis for concluding that there is consensus among ''qualified experts'' is inconsistent with the GRAS provision in section 201(s) of the FD&C Act, which requires general recognition among qualified experts. See also the discussion in Response 70, in which we explain our reasons for why we may decide to decline to file a GRAS notice that is accompanied by a separate file containing data and information that you view as non-public.

XVIII. Comments on Steps a Notifier May Take Before We Respond to a GRAS Notice

In the 2010 notice, we described comments regarding steps you may take before we respond to your GRAS notice (see table 17). As noted in section VIII.A, we are establishing a definition for ''amendment'' in the rule (see § 170.203). In the following paragraphs, we discuss additional comments regarding the issues in table 17. Some of these comments agree that the rule should have such a provision. Other comments ask us to clarify how such a provision would operate in practice (see, *e.g.,* Comment 82) or suggest one or more changes to the provision as we described it in the 2010 notice (see, *e.g.,* Comment 80, Comment 81, and Comment 83). After considering these comments, we are establishing two provisions regarding steps you may take before we complete our evaluation of a GRAS notice. The first provision specifies that you may submit a timely amendment to your filed GRAS notice, to update your GRAS notice or in response to a question from us, before we respond to your notice by letter (see the regulatory text of § 170.260(a)). The second provision specifies that you may ask us to cease to evaluate your GRAS notice as described in the 2010 notice, with clarifications as a result of comments (see the regulatory text of § 170.260(b)). One clarification is that such a request does not preclude you from submitting a future GRAS notice with respect to the notified substance. A second clarification is that we will send you a letter informing you of our decision regarding your request (see the regulatory text of § 170.265(b)(3)).

TABLE 17—ISSUES IN THE 2010 NOTICE REGARDING STEPS YOU MAY TAKE BEFORE WE RESPOND TO YOUR GRAS NOTICE

Issue No.	Description of our request for comment	Reference
3a	Whether to define ''amendment'' to mean any data or other information that you submit regarding a filed GRAS notice before we respond to the notice.	75 FR 81536 at 81538.
5	Whether the final rule should explicitly provide that you may request in writing that we cease to evaluate your GRAS notice at any time during our evaluation of that GRAS notice.	75 FR 81536 at 81538–81539.

See section XXV.I for a discussion of comments regarding steps you may take before we respond to your GRAS notice for a substance used in animal food, and for our response to those comments.

A. Communicating With a Notifier Before We Respond to a GRAS Notice

(Comment 80) Several comments note that the proposed rule did not say that we would contact a notifier, before we issue our publicly available response, to provide preliminary feedback regarding our evaluation of a GRAS notice. One of these comments asks us to include a provision specifying that we may communicate with the notifier about any aspect of a notice while the notice is pending. Some comments express concern that a letter listing answerable and nonsubstantive questions about a GRAS notice could cause confusion and misunderstanding in the marketplace, particularly if additional information, clarification, or amendment would address our concerns.

(Response 80) We decline the request to include a provision specifying that we may communicate with you about any aspect of a notice while your notice is pending. As discussed in section III.C.1 of CFSAN's 2010 experience document (Ref. 18), during the Interim Pilot program CFSAN contacted several notifiers to request clarification about data and information in the notice under the framework of existing regulations governing meetings and correspondence (§ 10.65(g)). It is not necessary to duplicate the existing procedures in § 10.65(g) in the requirements for the GRAS notification procedure.

We infer that this comment is specifically asking us to require that we contact you to provide preliminary feedback before we respond to your GRAS notice with an ''insufficient basis letter.'' As discussed in section III.C.1 of CFSAN's 2010 experience document (Ref. 18), our experience during the Interim Pilot program demonstrates that we are willing to engage in a dialog with a notifier to clarify particular aspects of a GRAS notice. As discussed in section IV.H.4 of CFSAN's 2010 experience document (Ref. 18), our experience during the Interim Pilot program also demonstrates that we do not issue an ''insufficient basis letter'' with ''nonsubstantive questions.'' Although we have issued ''insufficient basis letters'' due to an overall poor quality of a submission, to conserve resources our practices have evolved so that we generally do not file such submissions as GRAS notices (see section XIX.A regarding filing decisions and section III.K of CFSAN's 2010 experience document (Ref. 18)). Although we expect to contact you when we have questions, whether we intend to provide you with an opportunity to submit an amendment to a GRAS notice before responding to the notice has been, and will continue to be, a matter committed to our discretion.

In the following paragraphs, we discuss some key factors we intend to consider regarding the purpose of our contact with you regarding your GRAS notice, particularly with respect to whether we intend to provide you with an opportunity to submit an amendment to a GRAS notice. These factors are: (1) Whether our questions can be addressed by a timely, clarifying amendment; (2) whether our evaluation identifies a safety concern; and (3) whether we question whether GRAS criteria are satisfied, even if our evaluation does not identify a safety concern. See also the discussion in Response 85 regarding factors that could lead us to decline to file a submission as a GRAS notice, rather than to file it for our evaluation of your view that the notified substance is GRAS under the conditions of its intended use and issue an ''insufficient basis letter.''

We agree that an ''insufficient basis letter'' listing answerable questions about a GRAS notice could cause confusion and misunderstanding in the marketplace, particularly if additional information, clarification, or amendment would address our concerns. Section III.C.1 of CFSAN's 2010 experience document provides examples of circumstances where CFSAN contacted a notifier and expected that the information exchanged between CFSAN and the notifier would clarify, rather than substantively amend, the original notice. We intend to continue contacting notifiers in such circumstances. By ''clarify, rather than substantively amend,'' we mean that the amendment would add or modify specific sections in the notice, not that the clarifying information would necessarily be nonsubstantive in nature. For example, as discussed in Response 96 during the Interim Pilot program we contacted notifiers when the notice contained insufficient information about dietary exposure and when the notice contained insufficient information to adequately identify the substance. We did so because it is efficient, for us as well as the notifier, to bring a GRAS notice to closure with a ''no questions letter'' when it is likely that a timely, clarifying amendment would resolve our questions. For example, it is more efficient for us to bring a GRAS notice to closure while our reviewers are already immersed in the substantive evaluation of the notice, rather than to issue an ''insufficient basis letter'' and begin the evaluation process anew when the notifier addresses the questions in a new GRAS notice. See section XVIII.B for a discussion of what we mean by a ''timely'' amendment.

If we file your submission as a GRAS notice and our evaluation of the available data and information identifies a safety concern, the purpose of our contact with you would depend on whether the safety concern could be addressed by a timely, clarifying amendment. For example, in some cases the available data and information may support safety only under modified conditions of use relative to the conditions of use described in your GRAS notice, and our contact with you would focus on your opportunity to address the safety concern through a timely amendment specifying modified conditions of use. However, if we believe that the safety concern could not be addressed through a timely, clarifying amendment or by re-submission of a new GRAS notice (*e.g.,* after studies are conducted to address the safety concern), we likely would contact you to make you aware of our concerns and then issue an ''insufficient basis letter'' that clearly and fully articulates our reasons for that safety concern, including the full context of the risk to human or animal health.

If we file your submission as a GRAS notice and find that your narrative does not support a conclusion of GRAS status, even if the available data and information support your view that the notified substance is safe under the conditions of its intended use (*e.g.,* because data and information that are necessary to establish safety are not generally available), the purpose of our contact with you would focus on your opportunity to address the regulatory status of the notified substance. For example, it may be possible for you to submit a new GRAS notice after publishing applicable data and information and allowing sufficient time to allow the expert scientific community to access the published information. Alternatively, it may be more appropriate for you to consider the notified substance as a food additive under the conditions of its intended use, and to make a premarket submission such as a food additive petition. For examples of circumstances leading to the options for addressing questions about the regulatory status of the substance when we have not identified a safety concern, see section III.A.4 of CFSAN's 2010 experience document (Ref. 18). Any letter we issue would

include our view of the regulatory status of the substance at the time that we issued the letter, based on the generally available data and information at that time.

B. Submitting an Amendment

Comments support adding a provision to clarify that you may submit an amendment to your GRAS notice and, thus, we are establishing a provision specifying that you may submit a timely amendment to your filed GRAS notice (§ 170.260(a)). In some cases, you would submit such an amendment after we contact you to discuss our questions about your GRAS notice. (See the discussion in Response 80 regarding contacting a notifier.) In other cases, you may conclude that it is appropriate to submit an amendment to update your GRAS notice on your own initiative, *e.g.,* if new data and information about the notified substance under the conditions of its intended use become available after we file your submission as a GRAS notice. Depending on the circumstances, you could then decide to explain your view that the new data and information do not alter the basis for your conclusion of GRAS status; alternatively, you could decide to ask us to cease to evaluate your GRAS notice while you evaluate the impact of the new data and information on the GRAS status of the notified substance under the conditions of its intended use (see § 170.260(b)).

By timely, we mean that you submit your amendment in a timeframe that provides us with sufficient time to evaluate it before we respond to your GRAS notice. Given that the rule requires us to end our evaluation and respond to your GRAS notice within 180 days, with an extension of up to an additional 90 days on an as needed basis § 170.265(b)(1)), we reserve the right to not consider your amendment if you submit it so late in our evaluation that it would impact our ability to respond within our established timeframes. Therefore, as a companion provision, the rule also provides that we will consider any timely amendment that you submit to a filed GRAS notice, to update your GRAS notice or in response to a question from us, before we respond to you by letter based on our evaluation of your notice if we deem that doing so is feasible within the established timeframes (see § 170.265(a)(4)). If we deem that considering your amendment is not feasible within the established timeframes, we will inform you that we are not considering your amendment.

See also the discussion in Response 101, which emphasizes that the role of an amendment is to clarify questions that we have about your conclusion of GRAS status rather than to substantively amend the GRAS notice.

C. Notifier's Request That We Cease To Evaluate a GRAS Notice

(Comment 81) Some comments ask us to make public the reason for a notifier's request that we cease to evaluate a notice. One comment asks that any new information, or questions about the scientific consensus about whether a substance is safe, be made clear to the public as well as FDA. Another comment expresses concern that companies ask FDA to cease evaluations of their GRAS notices with ''alarming frequency.''

(Response 81) We are establishing a provision specifying that a notifier may ask us to cease to evaluate his GRAS notice (see § 170.260(b)). As a companion provision, we are specifying that if a notifier asks us to cease to evaluate a GRAS notice, we will send the notifier a letter informing the notifier of our decision regarding that request (see § 170.265(b)(3)). As discussed in section III.E of CFSAN's 2010 experience document (Ref. 18), during the Interim Pilot program CFSAN's ''cease to evaluate letters'' generally repeated any reason specified in a request letter, but may not have otherwise described the reasons underlying the request. If a notified substance is marketed even though we issue a ''cease to evaluate letter,'' there could be confusion about the GRAS status of the notified substance even when the conditions of use in the marketplace differ from the notified use that was the subject of the ''cease to evaluate letter.'' For example, a notifier could ask us to cease to evaluate a GRAS notice because we identified a safety concern about the specified use level of the notified substance in food products, and then decide to market the substance at a lower use level than the level specified in the GRAS notice, where we would no longer have that concern. In addition, as discussed in the proposed rule we proposed to make all response letters readily accessible to the public because such a system will properly underscore a notifier's acceptance of responsibility for the conclusion of GRAS status, and a GRAS notice that is submitted to us is a public notice (62 FR 18938 at 18953). A ''cease to evaluate letter'' signals that a submitted GRAS notice does not provide an adequate basis for a conclusion that the notified substance is GRAS under the conditions of its intended use, even though we do not issue an ''insufficient basis letter.'' Given the public nature of a GRAS notice, it is appropriate for the reasons leading to a ''cease to evaluate letter'' to also be public. Therefore, as of October 17, 2016, we intend to change this practice and increase transparency by describing the reasons leading to any ''cease to evaluate letter.''

Table 1 in CFSAN's 2010 experience document (Ref. 18) shows that approximately 16 percent of GRAS notices that CFSAN responded to during the 12-year period spanning 1998 through 2009 came to closure when the notifier asked us to cease to evaluate a GRAS notice. Table 1 in CFSAN's 2010 experience document also shows that CFSAN issued equal numbers of ''cease to evaluate letters'' and ''insufficient basis letters'' during the years 1998 through 2002 (*i.e.,* 16 ''cease to evaluate letters'' and 16 ''insufficient basis letters''). However, during the years 2003 through 2009 CFSAN issued 31 ''cease to evaluate letters,'' but no ''insufficient basis letters.'' In addition, table 1 in CFSAN's 2016 experience document (Ref. 19) shows that during the years 2010 through 2015 CFSAN issued 48 ''cease to evaluate letters'' but only one ''insufficient basis letter.'' We acknowledge that there has been a distinct shift between the ratio of the number of ''cease to evaluate letters'' compared to the number of ''insufficient basis letters'' issued during the years 1998 through 2002 and the corresponding ratio for letters issued during the years 2003 through 2015. We consider that the data in the experience document demonstrate an evolving practice in which CFSAN has declined to file some submissions as GRAS notices when the notice lacks much of the required data and information necessary for us to evaluate a notifier's view that the notified substance is GRAS under the conditions of its intended use (see Response 85). In addition, such a frequency demonstrates that CFSAN has been willing to contact notifiers with questions about a conclusion that the notified substance is GRAS under the conditions of its intended use. As discussed in Response 80, when our questions cannot be addressed by a timely amendment, contacting the notifier provides the notifier an opportunity to re-submit a new GRAS notice or other regulatory submission (such as a food additive petition) that addresses our questions.

As discussed in section III.E of CFSAN's 2010 experience document (Ref. 18), in many cases a notifier who received a ''cease to evaluate letter'' resubmitted a new GRAS notice, and CFSAN responded with a ''no questions letter.'' For many GRAS notices, the

questions we raised and discussed with the notifier clearly addressed issues other than a fundamental safety concern. For example, some of the letters that CFSAN lists in section III.E of its 2010 experience document provide reasons such as preparing a new notice that will not contain any confidential business information and that will clarify that the statutory basis for the conclusion of GRAS status is through scientific procedures; needing to revise an estimate of dietary exposure; and clarifying and providing additional information for a new notice. However, CFSAN only made these reasons transparent to the public because the notifier chose to provide these reasons in his request that we cease to evaluate the GRAS notice. In other circumstances, the public had no way to know what the issue was until we responded to the resubmitted notice. We intend to continue to contact a notifier to discuss our questions, and provide an opportunity for the notifier to ask us to cease to evaluate the GRAS notice (*e.g.,* so that the notifier can submit a new GRAS notice that addresses the issues). However, we also intend to briefly describe these issues in a ''cease to evaluate letter'' that follows that contact. As CFSAN did during the Interim Pilot program, we intend to consider any reasons a notifier provides for the request, and to include those reasons in our ''cease to evaluate letter.'' If, however, we conclude that a notifier's explanation does not adequately describe the reasons leading to a ''cease to evaluate'' request, we intend to explain the reasons for ceasing to evaluate the notice from our point of view. Doing so will both ensure clear communication about the reasons and make the reasons transparent to the public.

As discussed in Response 80, if we identify a safety concern and believe that the safety concern could not be addressed through a timely, clarifying amendment, by re-submitting a new GRAS notice, or by submitting another premarket submission (such as a food additive petition), we likely would issue an ''insufficient basis letter'' even though we would have contacted the notifier to discuss our concerns.

Asking us to cease to evaluate a GRAS notice does not guarantee that we will honor that request. Depending on the circumstances, we may decide to decline the request and instead respond with an ''insufficient basis letter''; depending on the time remaining between when we receive the request and the timeframes by which we must respond to the GRAS notice, we may either send the notifier a separate letter declining the request, or note in the ''insufficient basis letter'' that we had declined the request. See the discussion in section III.C.1 of CFSAN's 2010 experience document (Ref. 18) for an example of a situation in which CFSAN responded with an ''insufficient basis letter'' after a notifier asked CFSAN to cease to evaluate its GRAS notice, submitted a new GRAS notice, and asked CFSAN to cease to evaluate the second submitted GRAS notice.

(Comment 82) One comment asks us to clarify that a notifier's request that we cease to evaluate a GRAS notice would be without prejudice for future submissions.

(Response 82) The final provision specifies that your request that we cease to evaluate a GRAS notice does not preclude you from submitting a future GRAS notice with respect to the notified substance.

(Comment 83) One comment asks us to specify that, if feasible, the files could be returned to the notifier at the notifier's expense.

(Response 83) We decline this request. As discussed in the 2010 notice (75 FR 81536 at 81538–81539), our current regulations regarding public information stipulate that no person may withdraw records submitted to FDA (see § 20.29), and those regulations will apply to any GRAS notice that we receive. To make this clear, the provision we are establishing in the final rule provides an opportunity for you to ask us to ''cease to evaluate'' a GRAS notice rather than ''withdraw'' a GRAS notice.

(Comment 84) Some comments ask us to specify that if a notifier requests that we cease to evaluate a submitted GRAS notice, such notices will remain in our files and will be available for public disclosure.

(Response 84) See § 20.29 and the discussion of Issue 5 in the 2010 notice (75 FR 81536 at 81538–81539). If a notifier asks us to cease to evaluate a submitted GRAS notice, the notice will remain in our files and will be available for public disclosure in accordance with part 20. It is not necessary to repeat the provisions of § 20.29 in the GRAS notification procedure.

XIX. Comments on What We Will Do With a GRAS Notice

We proposed that: (1) We would acknowledge receipt of a notice, within 30 days of receipt, by informing the notifier in writing of the date on which the notice was received (proposed § 170.36(d)); (2) we would respond to the notifier in writing within 90 days of receipt of the notice (proposed § 170.36(e)); and (3) a copy of any subsequent letter that we issued regarding a GRAS notice would be readily accessible for public review and copying (proposed § 170.36(f)(2)(iii)). In the 2010 notice, we asked for comment on issues relating to what we will do with a GRAS notice as shown in table 18.

TABLE 18—ISSUES IN THE 2010 NOTICE REGARDING WHAT WE WILL DO WITH A GRAS NOTICE

Issue No.	Description of our request for comment	Reference
12	Whether we should make explicit the process by which we make a filing decision, including the factors we would use to determine whether to file a submission as a GRAS notice.	75 FR 81536 at 81541.
14	Whether we should retain a set timeframe for us to respond to a GRAS notice, and, if so, whether it should be 90 days or another timeframe.	75 FR 81536 at 81542.

In the following sections, we discuss comments on what we will do when we receive a GRAS notice. After considering these comments, we are establishing requirements in § 170.265 for what we will do when we receive a GRAS notice as shown in table 19, with editorial, clarifying, and conforming changes as shown in table 29. Table 19 identifies changes we made relative to the proposed rule or the description in the 2010 notice other than the editorial, clarifying, and conforming changes shown in table 29 and the additional editorial changes associated with the redesignation of proposed § 170.36(d), (e), and (f)(2)(iii) as § 170.265. See section XXV.I for a discussion of comments specific to a filing decision for a substance used in animal food.

TABLE 19—FINAL REQUIREMENTS FOR WHAT FDA WILL DO WITH A GRAS NOTICE

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.265(a)(1)	N/A	12	We will conduct an initial evaluation of your submission to determine whether to file it as a GRAS notice for evaluation of your view that the notified substance is GRAS under the conditions of its intended use.	N/A.
170.265(a)(2)	170.36(d)	12	If we file your submission as a GRAS notice, we will send you a letter that informs you of the date of filing.	N/A.
170.265(a)(3)	N/A	12	If we do not file your submission as a GRAS notice, we will send you a letter that informs you of that fact and provides our reasons.	Clarifies that we would inform you by letter if we do not file your submission as a GRAS notice.
170.265(a)(4)	N/A	3a	We will consider any timely amendment that you submit to a filed GRAS notice, to update your GRAS notice or in response to a question from us, before we respond to you by letter based on our evaluation of your notice if we deem that doing so is feasible within the established timeframes. If we deem that considering your amendment is not feasible within the established timeframes, or if we have granted your request to cease to evaluate your notice, we will inform you that we are not considering your amendment.	Clarifies that we will only consider an amendment if we deem that doing so is feasible within the established timeframes.
170.265(b)(1)	170.36(e)	14	Within 180 days of filing, we will respond to you by letter based on our evaluation of your notice. We may extend the 180 day timeframe by 90 days on an as needed basis.	• Specifies that the timeframe for our response is 180 days, rather than 90 days. • Provides for an extension of our evaluation by 90 days on an as needed basis.
170.265(b)(2)	N/A	14	If we extend the timeframe, we will inform you of the change in writing as soon as practicable but no later than within 180 days of filing.	Provides that we will inform you if we extend the timeframe for our response.
170.265(b)(3)	N/A	5	If you ask us to cease to evaluate your GRAS notice, we will send you a letter informing you of our decision regarding your request.	Companion change in light of new regulatory text (in § 170.260(b)) expressly providing that you may ask us to cease to evaluate your GRAS notice.
170.265(c)	170.36(f)(2)(iii)	N/A	If circumstances warrant, we will send you a subsequent letter about the notice.	Clarifies that we may send a subsequent letter, in addition to specifying under the public disclosure provisions of the rule that such a letter would be readily available to the public (see § 170.275(b)(2)).

A. Filing Decision

(Comment 85) One comment asks for greater refinement, clarity, and transparency when we decline to file a GRAS notice. Some comments ask us to communicate any questions or concerns that could be quickly addressed upon submission of a GRAS notice. Another comment asks us to use specific criteria for a ''decline to file'' determination when format and general categories are adequate. Another comment states that an explicit process for how we will make a filing decision need not be detailed ''in the public domain'' even though it would be beneficial to the notifier.

Another comment asks us to specify the criteria that we use to decide to provide verbal feedback to a notifier (*e.g.,* by telephone) rather than send the notifier a letter informing the notifier that we have declined to file a submission as a GRAS notice. This comment expresses concern that our refusal to explain the problem in a letter could be interpreted to mean that we have safety concerns. This comment asserts that a process in which we neither provide specific guidance, nor provide written feedback, when we decline to file a submission as a GRAS notice would both discourage voluntary submissions of GRAS conclusions from industry and conflict with GAO's recommendations (in their 2010 report) that we should take steps to increase our awareness of independent conclusions of GRAS status.

(Response 85) These comments raise a number of issues regarding the importance of a written communication from us to a notifier when we decline to file a submission as a GRAS notice, including transparency and the potential that lack of a written explanation for why we declined to file

a submission as a GRAS notice could lead to suppositions, such as whether we have safety concerns. To address these issues, the final rule provides that if we do not file a submission as a GRAS notice, we will send the notifier a letter that informs the notifier of that fact and provides our reasons for not filing the submission as a GRAS notice (see § 170.265(a)(3)). We would not place that letter ''in the public domain'' by including it in our publicly available Inventory of GRAS Notices, because the submission had not been filed as a GRAS notice and, thus, there would be no entry where we would place the letter. However, whether the letter would be releasable in response to a FOIA request would be a case-by-case determination based on the contents of the letter and the provisions of part 20.

We are not specifying in the regulatory text the factors that could lead us to decline to file a submission as a GRAS notice, because the factors that apply to a particular GRAS notice may be very specific to that notice. Importantly, a GRAS notice presents an opportunity for a notifier to inform us about a conclusion of GRAS status rather than an opportunity for a notifier to test a hypothesis that there is a sufficient basis to reach a conclusion of GRAS status. If our initial evaluation of a submission demonstrates that it lacks much of the required data and information necessary for us to evaluate the notifier's view that the notified substance is GRAS under the conditions of its intended use, our current practice is to decline to file it as a GRAS notice (see § 170.265(a)(3)). By declining to file a submission as a GRAS notice, we would both conserve our own resources and provide the notifier an opportunity to submit a new GRAS notice, that contains appropriate data and information and an adequate narrative, rather than move forward knowing that an amendment necessary for us to evaluate the notifier's view that the notified substance is GRAS under the conditions of its intended use would be so substantive as to make the original submission largely irrelevant. For additional examples of factors we have considered in determining whether to file a submission as a GRAS notice, see the examples we provided in the 2010 notice (75 FR 81536 at 81541), the discussion of filing decisions in section III.K of CFSAN's 2010 experience document (Ref. 18), Response 48, and Response 70. As discussed in Response 152, CVM intends to consider the same factors that CFSAN considers regarding whether to file a submission as a GRAS notice.

(Comment 86) In the 2010 notice, we explained that we may decide to respond to a submission as general correspondence, rather than file it as a GRAS notice, if the subject of the submission is: (1) Already authorized for use under our regulations; or (2) a mixture of substances that are already authorized for use under our regulations. One comment asks us to clarify how we would determine that the use of a substance is authorized for use under our regulations, with respect to the similarity of factors such as: (1) The substance; (2) the intended conditions of use of the substance, including food categories and use levels; and (3) the manufacturing process.

(Response 86) We decline this request because it is overly broad. We do not have a ''formula'' that would apply in all circumstances. Just as the factors that apply to a particular GRAS notice may be very specific to that notice, the factors that would apply in determining whether the intended conditions of use of a notified substance are already authorized by our regulations may be very specific to that substance. However, with regard to similarities in the manufacturing process, we likely would apply the same factors that we have advised industry to apply when assessing the effects of significant manufacturing process changes on the safety and regulatory status of food ingredients (Ref. 6).

We note that we also may decide to respond to a submission as general correspondence, after communicating with the submitter as appropriate, rather than file it for evaluation as a GRAS notice, if the subject of the submission is: (1) Already the subject of a GRAS notice, and we have responded to that GRAS notice with a ''no questions letter''; or (2) a mixture of substances that already are the subject of GRAS notices, and we have responded to those GRAS notices with ''no questions letters.'' In contrast to the statutory provisions for the FCN program (section 409(h) of the FD&C Act), there is no provision in the FD&C Act providing exclusivity for a notifier for the use of a substance on the basis that it is GRAS under the conditions of its intended use.

(Comment 87) One comment asks us to conduct a preliminary evaluation of a GRAS notice to determine whether the notice appears to be inadequate because the intended conditions of use of the notified substance raise ''general policy'' issues.

(Response 87) It is not clear what the comment means by ''general policy'' issues. However, we note that we would not file a submission as a GRAS notice if the intended conditions of use of the notified substance are not eligible for classification as GRAS because, for example, the intended conditions of use are excepted from the definition of ''food additive'' in section 201(s) of the FD&C Act (and thus, from the GRAS provision included in that definition of ''food additive''). See, for example, the exception for a color additive in section 201(s)(3) of the FD&C Act, for a dietary ingredient intended for use in a dietary supplement in section 201(s)(6) of the FD&C Act, and for a new animal drug in section 201(s)(5) of the FD&C Act.

(Comment 88) Some comments ask us to contact the notifier when our initial evaluation of a GRAS notice raises questions, and provide the notifier with an opportunity to withdraw the notice without prejudice before we begin a substantive evaluation of the notice.

(Response 88) We agree that our decision to not file a submission as a GRAS notice would be without prejudice to a future submission of a GRAS notice for the notified substance. However, see Response 70, Response 112, and the discussion in the 2010 notice at 75 FR 81536 at 81539. Just as a filed GRAS notice is available for public disclosure subject to the procedures established in part 20, a submission that you send to us is a record that is available for public disclosure subject to the procedures established in part 20, regardless of whether we file that submission as a GRAS notice. Thus, you cannot ''withdraw'' a submission from our files after you send it to us.

(Comment 89) One comment asks whether ''substantial equivalence'' considerations are linked to ''decline to file'' decisions or play a dominant role in ''decline to file'' decisions. This comment also asks us to issue a letter to the notifier explaining the basis for a ''decline to file'' decision if ''substantial equivalence'' is the reason.

(Response 89) As discussed in section IV.N of CFSAN's 2010 experience document (Ref. 18), several GRAS notices filed during the Interim Pilot program relied, in part, on the concept of ''substantial equivalence''; in each of the listed examples CFSAN had no questions about the notifier's conclusion of GRAS status. As discussed in Response 21, whether, and to what extent, similarity between two substances could support a conclusion of GRAS status depends on many situation-specific variables. Thus, it would be the complete evaluation process, rather than the initial evaluation that we conduct as part of a filing decision, that would determine whether a GRAS notice that relies on the concept of ''substantial equivalence''

provides a basis for a conclusion of GRAS status. As discussed in Response 85, the final rule provides that if we do not file a submission as a GRAS notice, we will send the notifier a letter that informs the notifier of that fact and provide our reasons for not filing the submission as a GRAS notice (see § 170.265(a)(3)); if problems with a notifier's use of the concept of ''substantial equivalence'' play a role in our decision to not file a submission as a GRAS notice, we intend to say so.

B. Our Response to a GRAS Notice

1. Administrative Content of Our Response to a GRAS Notice

(Comment 90) Several comments address the administrative content of a letter that responds to a GRAS notice. In general, these comments ask us to include the following items in the response letter: (1) Name and address of the notifier; (2) the date of our receipt of the notice; (3) the common or usual name of the notified substance; and (4) the applicable conditions of use of the notified substance. One comment states that use of a standard format and language in our letters would be administratively efficient.

(Response 90) We agree that a standard format and language in our letters would be administratively efficient and that the administrative features suggested by these comments are appropriate to include in our response letter. During the Interim Pilot program, we both developed a standard format and language for our response letters and included the administrative features suggested by these comments (see section III.H.1 of CFSAN's 2010 experience document (Ref. 18)). We intend to continue incorporating these features in letters issued under the final rule. However, as discussed in Response 51, the final rule requires that you provide the name of the notified substance, using an appropriately descriptive term, rather than the ''common or usual name'' of the notified substance (see § 170.225(c)(3)). Therefore, CFSAN's response letters will include an appropriately descriptive term for the notified substance provided in a GRAS notice submitted to CFSAN. See section XXV.C regarding the name of the notified substance provided in a GRAS notice submitted to CVM.

2. Substantive Content of Our Response to a GRAS Notice

(Comment 91) Several comments note that the proposed rule did not specify what we would say in a letter responding to a GRAS notice and ask us to include in the final rule the specific language for the response letter, particularly when we do not raise any questions about the notifier's conclusion of GRAS status. Some comments assert that a notifier who invests resources in a GRAS notice deserves a response that is standardized and predictable and will not change as personnel changes occur.

(Response 91) See table 1. During the Interim Pilot program we developed three categories of response letter: (1) ''No questions letter''; (2) ''insufficient basis letter''; and (3) ''cease to evaluate letter.'' As discussed in sections IV.H.1 through IV.H.7 of CFSAN's 2010 experience document (Ref. 18), these letters include some standard information that is consistent across those letters, such as opening and closing paragraphs using a standard format, and administrative information (*e.g.,* the date of our receipt of the GRAS notice). They also include unique features that depend upon the circumstances, such as labeling issues and whether the use of the substance could require a color additive listing. The content of the three categories of response letter has evolved over time, and may continue to evolve. In addition, it is possible that in the future a response to a GRAS notice may not fit squarely within one of the current categories of response letter. Therefore, the final rule continues to specify that we will respond to a GRAS notice but does not specify any detail about the nature of the response.

(Comment 92) Several comments address the content of a ''no questions letter.'' These comments ask that a ''no questions letter'' be clear and definitive, provide clear assurance that we recognize the GRAS status of the substance under the conditions of its intended use, have some regulatory significance, and be as affirmative as possible. Some of these comments note that our statements in the proposed rule (62 FR 18938 at 18950) indicated that we would evaluate a GRAS notice to determine whether there is a sufficient basis for the notifier's conclusion of GRAS status and suggest that our response to a GRAS notice could reflect those statements. Comments also suggest the following specific statements that could be included in a ''no questions letter'':

- ''FDA at this time does not question your determination that the notified use(s) of this substance is (are) Generally Recognized as Safe.''
- ''The Agency finds that there is substantial evidence supporting both the safety of the intended uses of the substance and the fact that this safety is generally known and accepted by qualified experts.''
- ''The notice provides a sufficient basis for the notifier's determination that the substance is GRAS for its intended use.''

(Response 92) See table 1 for the typical text of a ''no questions letter'' that we issued during the Interim Pilot program. At this time, we intend to continue including such text in our ''no questions letters.'' We agree that the regulatory significance of a ''no questions letter'' should be clear. As shown in table 1, during the Interim Pilot program a typical ''no questions letter'' made clear that: (1) It is the information that is provided by the notifier that forms the basis for our response, and that the notifier (rather than FDA) is responsible for the conclusion of GRAS status; and (2) our response must be considered in context based on the knowledge and information available to us at a point in time, because scientific knowledge and information about a particular ingredient can evolve and sometimes change over time.

The typical text of a ''no questions letter'' issued during the Interim Pilot program is similar to the specific suggestion of one comment (*i.e.,* FDA at this time does not question your determination that the notified use of this substance is GRAS), except that under the final rule we will use the term ''conclusion'' rather than ''determination.'' We disagree that a ''no questions letter'' should state that we ''find'' that there is substantial evidence supporting both the safety of the intended conditions of use of the notified substance and the fact that this safety is generally known and accepted by qualified experts; a GRAS notice reflects the conclusion of the notifier, not a finding by FDA. Likewise, we disagree that a ''no questions letter'' should state that a notice ''provides a sufficient basis'' for the notifier's conclusion that the notified substance is GRAS under the conditions of its intended use; the phrase ''providing a sufficient basis'' would imply that we are taking responsibility for the notifier's conclusion of GRAS status.

As discussed in Response 41, we are replacing the term ''determination'' with ''conclusion,'' and referring to a ''conclusion of GRAS status'' rather than to a ''GRAS determination,'' throughout the regulatory text for the GRAS notification procedure. We intend to modify the typical text of our response letters to refer to the ''notifier's conclusion'' (rather than the ''notifier's determination'') in letters issued under the final rule (see table 20). We also

intend to specify that we have not affirmed the GRAS status of the notified substance under the conditions of its intended use, rather than to specify that we have not made our own determination. However, as noted in section II.B, we intend to adapt our practices, consistent with the provisions of this rule, as circumstances warrant and as necessary to administer the GRAS notification program consistent with appropriate public health policy, current scientific information, our available resources, and the scientific and regulatory issues raised by specific GRAS notices. Thus, the text shown in table 20 is for illustrative purposes only and could evolve over time.

TABLE 20—CATEGORIES OF LETTERS RESPONDING TO A GRAS NOTICE UNDER THE FINAL RULE

Category of response letter	Typical text of for a response as modified to incorporate terms used in the rule
''No questions letter''	Based on the information provided by the notifier, as well as other information available to FDA, the Agency has no questions at this time regarding the notifier's conclusion that the notified substance is GRAS under the conditions of its intended use. By this letter, however, the Agency has not affirmed the GRAS status of the notified substance under the conditions of its intended use in accordance with 21 CFR 170.35. As always, it is the continuing responsibility of the notifier to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.
''Insufficient basis letter''	FDA has evaluated the data and information in the GRAS notice as well as other available information. The notice does not provide a sufficient basis for a conclusion that the notified substance is GRAS under the conditions of its intended use.
''Cease to evaluate letter''	In correspondence dated [month, day, year], you asked that we cease to evaluate your GRAS notice. We ceased to evaluate your GRAS notice, effective the date we received your correspondence.

(Comment 93) One comment suggests that a written response need not assess the quality of the submission but rather could acknowledge whether the notice was complete in addressing all key issues.

(Response 93) We disagree that we could acknowledge whether a notice is ''complete'' without assessing the quality of the submission. Providing a basis for whether the data and information regarding the safety of a substance under the conditions of its intended use satisfy GRAS criteria is not a matter of whether there is ''something behind each tab.'' It would not be appropriate, for example, for us to acknowledge that a GRAS notice is ''complete'' because it included the narrative required by Part 6 of a GRAS notice without assessing the adequacy of the narrative. Whether a notice is ''complete'' in addressing all key issues depends on the nature and quality of the submitted data and information.

(Comment 94) Some comments ask that a ''no questions letter'' qualify that we have not affirmed that the intended conditions of use of the notified substance are GRAS. Other comments ask that a ''no questions letter'' qualify that we have not conducted a substantive review.

(Response 94) We agree that a ''no questions letter'' should be clear that we have not affirmed that the substance is GRAS under the conditions of its intended use. See table 20.

However, we disagree that a ''no questions letter'' should state that we did not conduct a substantive review of the GRAS notice. See Response 25. Our evaluation of a GRAS notice is a substantive evaluation of the notifier's basis for concluding that the intended conditions of use of the notified substance are safe and the criteria for GRAS status are satisfied. In addition, as circumstances warrant, we evaluate information that is not included in the notice but is otherwise available to us (see section IV.G of CFSAN's 2010 experience document (Ref. 18)).

(Comment 95) Some comments ask that a ''no questions letter'' include a positive statement that we have not identified a problem with the notice because finished food producers have been reluctant to use a substance without such documentation. These comments both assert that the only alternative available to manufacturers whose customers require such a positive statement would be to seek food additive approval for an ingredient and maintain that such approval is unnecessary from a legal perspective.

(Response 95) Consistent with the request of these comments, we intend to continue including a statement that we ''have no questions at this time'' (see table 1 and table 20). Whether a manufacturer's customer requires a regulation prescribing the conditions under which a substance may be safely used in food, when there is a basis for concluding that the substance is GRAS under the conditions of its intended use, is a business matter between the manufacturer and the customer. If the manufacturer submits a food additive petition and we find, based on the data and information submitted in the petition, that the intended conditions of use of the substance are safe, we would issue a regulation prescribing the conditions under which the food additive may be safely used.

(Comment 96) Several comments address the specific content of an ''insufficient basis letter'' and ask us to be specific about any deficiencies that we identify in the notice. Some comments assert that an ''insufficient basis letter'' must clearly distinguish between deficiencies that relate to safety and those that relate to a technical matter, such as the level of the substance that is needed to accomplish the intended technical effect. One comment asks us to include in the final rule guidelines that articulate clear standards for issues that are of sufficient magnitude to result in an ''insufficient basis letter.''

(Response 96) We agree that we should be specific about identified problems and distinguish between circumstances that lead to an insufficient basis letter. Our experience during the Interim Pilot program demonstrates that we have done so, and we intend to continue this practice under the final rule. For example, as discussed in sections IV.H.4 and IV.H.7 of CFSAN's 2010 experience document (Ref. 18), we have issued an insufficient basis letter in cases where health effects seen in toxicological or clinical studies were not adequately explained or because the notice did not describe adequate toxicological studies; when the notice contained insufficient information about dietary exposure; when the notice contained insufficient information to adequately identify the substance; when the notice contained insufficient information to satisfy the standard for demonstration of GRAS status through experience based on common use in food; and as a result of the regulatory framework associated with the substance. To date, we have not issued an insufficient basis letter solely as a result of insufficient

evidence regarding the level of the substance that is needed to accomplish the intended technical effect. However, CVM's experience document demonstrates that CVM has included lack of information regarding the intended technical effect as one of several reasons leading to an insufficient basis letter (Ref. 20). Some ''no questions letters'' issued by CFSAN have discussed the level of the substance that is needed to accomplish the intended technical effect, *e.g.,* when CFSAN informed a notifier who received a ''no questions letter'' that FSIS needed information regarding the lowest level necessary for the substance to achieve its intended effect in meat, meat food product, or poultry product (see section III.L of CFSAN's 2010 experience document (Ref. 18)).

Our experience during the Interim Pilot program demonstrates that whether a notice provides a sufficient basis for a conclusion of GRAS status is a case-by-case evaluation and that the circumstances vary. Therefore, we decline the request to specify standards for issues that are of sufficient magnitude to result in an ''insufficient basis letter.'' See sections IV.H.4 and IV.H.7 of CFSAN's 2010 experience document (Ref. 18) for information on specific GRAS notices that received an ''insufficient basis letter'' from CFSAN, and table 1 in CVM's experience document (Ref. 20) for information on GRAS notices that received an ''insufficient basis letter'' from CVM. Our letters responding to each of these GRAS notices describe the problems in more detail and are available on CFSAN's Web site (Ref. 46) and CVM's Web site (Ref. 47).

(Comment 97) Some comments ask that an ''insufficient basis letter'' include a qualifying statement that we have not conducted a substantive review and have not concluded that the intended conditions of use of the notified substance are not GRAS. These comments assert that a response that does not include such a statement could have the practical effect of challenging the use of a substance in the absence of a threshold determination that the notified use is not GRAS.

(Response 97) We disagree that an ''insufficient basis letter'' should state that we did not conduct a substantive review of the GRAS notice. See Response 25 and Response 94. Our evaluation of a GRAS notice is a substantive evaluation.

The typical text of an ''insufficient basis letter'' specified that ''the notice does not provide a sufficient basis'' for a determination that the notified substance is GRAS under the conditions of its intended use (see table 1), and we intend to continue including such text in letters issued under the final rule, modified to refer to a ''conclusion'' of GRAS status rather than a ''determination'' of GRAS status (see table 20). This typical text addresses the adequacy of the notice rather than the regulatory status of the substance; consistent with the request of these comments, this text does not specify that we have concluded that the intended conditions of use of the notified substance are ''not GRAS.'' In several cases during the Interim Pilot program, a notifier who received an ''insufficient basis letter'' submitted a second GRAS notice and received a ''no questions letter'' in response to the second GRAS notice (see sections III.D and IV.K of the experience document (Ref. 18)). In these examples, CFSAN's response to the notifier's first GRAS notice made clear that the submitted notice did not provide a basis for a conclusion of GRAS status, but CFSAN had no questions about the basis for GRAS status provided by the second notice.

3. Our Consideration of a Timely Amendment

As discussed in section XVIII.B, the rule provides that you may submit a timely amendment to your filed GRAS notice to update your GRAS notice or in response to a question from us (§ 170.260(a)). As a companion provision, the rule also provides that we will consider any timely amendment that you submit to a filed GRAS notice, to update your GRAS notice or in response to a question from us, before we respond to your notice based on our evaluation of your notice if we deem that doing so is feasible within the established timeframes (see § 170.265(a)(4)). If we deem that considering your amendment is not feasible within the established timeframes, we will inform you that we are not considering your amendment (see § 170.265(a)(4)). We also will inform you that we are not considering your amendment if we have granted your request to cease to evaluate your notice (*i.e.,* if we send you a ''cease to evaluate letter''). See § 170.265(b)) and Response 98 for the timeframe established in this rule for our response to your GRAS notice.

4. Timeframe for Our Response to a GRAS Notice

(Comment 98) Several comments support retaining the proposed 90-day timeframe. According to these comments, a 90-day timeframe would provide an incentive for a manufacturer to submit a GRAS notice. One comment asserts that we should be held accountable to the proposed 90-day timeframe, whereas another comment suggests that the proposed 90-day timeframe provide a benchmark at which we should make the notifier aware of the current status of our evaluation of the notice even if we have not had sufficient time to completely review the safety of the notified substance.

One comment that asks us to retain the proposed 90-day timeframe stresses that we should have flexibility to take additional time as needed. Another comment agrees that it would be appropriate for us to extend the evaluation period, provided we do so only in limited instances.

One comment asserts that the requirements of the GRAS notification procedure are similar to the requirements of the GRAS affirmation petition process and questions whether we could respond to a GRAS notice within 90 days because we did not respond to a GRAS petition in such a short timeframe. One comment that stresses the importance of retaining a set evaluation timeframe suggests that the timeframe be 90–180 days based on CFSAN's experience during the Interim Pilot program, and opposes a timeframe greater than 180 days. Other comments support a 180-day timeframe because it would be realistic and reasonable, would be sufficient to resolve all of the issues raised by a GRAS notice with procedural fairness, and could be consistent and fair across both CFSAN and CVM.

(Response 98) We are establishing a timeframe of 180 days from the date of filing for our response to a GRAS notice. We also are providing that we may extend the 180-day response timeframe by 90 days on an as needed basis; if we do so, we will inform you of the extension in writing as soon as practicable but no later than within 180 days of filing. (See the regulatory text of § 170.265(b)(1) and (2)). We agree that the 180-day timeframe is realistic and reasonable, would be sufficient to resolve all of the issues raised by a GRAS notice with procedural fairness in most cases, and could be consistent and fair across both CFSAN and CVM.

We disagree that we should establish a 90-day timeframe merely because we had proposed this timeframe before we gained experience with evaluating GRAS notices. As shown in section III.M of CFSAN's 2010 experience document, less than 12 percent of the response letters CFSAN issued as of December 31, 2009, were sent within the proposed 90-day timeframe (Ref.

18). Importantly, section III.M of CFSAN's 2010 experience document also shows that in many cases a dialog between FDA and a notifier about scientific issues associated with a GRAS notice, with an ensuing amendment from the notifier, played a role in the timeframe for CFSAN's response to a GRAS notice. As discussed in the 2010 notice, several comments ask us to allow a notifier to address questions we have about a GRAS notice by submitting an amendment to the notice (see Issue 3a, 75 FR 81536 at 81538), and the final rule expressly provides that you may submit an amendment to a filed GRAS notice before we respond to the notice (see § 170.260(a)). Although we are including flexibility to take additional time as needed, our goal is to do so in only limited instances, such as when the intended conditions of use of the notified substance raise complex scientific issues.

We have no basis to judge whether a 90-day timeframe, but not a 180-day timeframe, would provide an incentive to a manufacturer to submit a GRAS notice. However, as noted in Response 24 CFSAN filed more than 600 GRAS notices during the time period 1998 through 2015, including 69 GRAS notices filed during 2014 and 51 GRAS notices filed during 2015, even though CFSAN rarely responded to a GRAS notice within 90 days. We believe that the ongoing submission of GRAS notices is evidence that the 180-day timeframe that is consistent with our experience during the Interim Pilot program is not a disincentive to a manufacturer.

We note that the procedural requirements of the GRAS notification procedure are very different from the procedural requirements of the GRAS affirmation petition process in that we respond to a GRAS notice by letter whereas we respond to a GRAS affirmation petition through rulemaking. As previously discussed (62 FR 18938 at 18941), the resource-intensive rulemaking process includes: (1) Publishing a filing notice in the **Federal Register**; (2) requesting comment on the petitioned request; (3) conducting a comprehensive review of the petition's data and information and comments received to the filing notice to determine whether the evidence establishes that the petitioned use of the substance is GRAS; (4) drafting a detailed explanation of why the use is GRAS (as opposed to simply being safe); and (5) publishing that explanation in the **Federal Register**. Therefore, we disagree with the perspective of one comment that our experience in responding to a GRAS affirmation petition should have any bearing on the determination of an appropriate timeframe for our response to a GRAS notice.

(Comment 99) One comment expresses concern that a 90-day timeframe would be unrealistic unless we allocate additional resources to the program. This comment asks us to consider a process similar to the process for the FCN program, where there is a fixed review period during which we can ''object to'' a submitted notification. If we do not object within the review period or do not request an extension to the review period, a notification submitted to the FCN program is considered effective.

(Response 99) We decline this request. We disagree that the GRAS notification procedure should be modeled after the FCN program. Unlike the GRAS notification procedure, the FCN program is a mandatory process for food contact substances under section 409(h) of the FD&C Act. Furthermore, the statute provides that the FCN program shall not operate unless it has certain appropriated funds. See section 409(h)(5)(A)(i) of the FD&C Act and § 170.104(c)(3). There are no similar statutory requirements applicable to our evaluation of the basis for a conclusion of GRAS status.

(Comment 100) One comment asserts that we should respond to a GRAS notice within 90 days unless we identify a problem that warrants dialog with the notifier and an ensuing amendment.

(Response 100) We disagree. The suggestion of this comment could lead to the unintended consequence of seeking unnecessary amendments merely to stay within an established timeframe. We believe it is more appropriate to establish a single timeframe that would broadly apply to all GRAS notices, with the potential to extend the timeframe on an as needed basis.

(Comment 101) One comment asks us to stop the ''review clock'' when we inform a notifier that we have questions about a notice and then restart the ''review clock'' upon receipt of an amendment that answers our questions.

(Response 101) We decline this request. We acknowledge that there could be an advantage to such a process, because stopping the review clock would reduce the time pressures on our staff. However, the role of an amendment is to clarify questions that we have about your conclusion of GRAS status rather than to substantively amend the GRAS notice. A process in which we stop and start a review clock implies that the timeframe for you to submit an amendment could be so long as to significantly impact our ability to respond within an established timeframe. Rather than a process in which we stop and start a review clock on a particular GRAS notice, we have provided that you may ask us to cease to evaluate a GRAS notice when your preparation of an amendment would impact our ability to respond within 180 days.

5. Responding to a GRAS Notice in All Circumstances

In the proposed rule, we noted that the GRAS notification procedure could be structured so that we respond only when we question the GRAS status of the intended use of the substance and requested comment on whether we should, in all cases, provide a notifier with a letter at the conclusion of our evaluation of a notice (62 FR 18938 at 18951).

(Comment 102) Several comments agree with our discussion in the proposed rule that a written response from us would give manufacturers an incentive to notify us of their conclusions of GRAS status; these comments recommend that we respond in writing in all circumstances. Other comments suggest that we limit our response to circumstances in which we identify a problem with a notice because such a limitation would make it easier for us to respond within the proposed 90-day timeframe. One comment expresses concern that a written response could create a misperception that we had undertaken an independent review of the data described in the GRAS notice; to prevent this misperception, this comment suggests that we respond in writing only if we find a problem with the notice.

(Response 102) We acknowledge that limiting our response to circumstances in which we identify a problem with a notice would reduce the number of letters that we write. However, we believe that it is important to publicly document our evaluation of the GRAS notice in light of all the comments submitted to this rulemaking. (See, *e.g.,* Comment 25 and the comments we discuss in section VII.C). In addition, in our experience it is the process of evaluating a submission and reaching a decision about whether the notice provides a basis for a conclusion of GRAS status, rather than the process of drafting and issuing a letter, that requires the most time.

We acknowledge the potential that a ''no questions letter'' could be misinterpreted, *e.g.,* to mean that FDA, rather than the notifier, had reached a conclusion of GRAS status. To mitigate the potential for such misinterpretation, the typical text of our response letters

issued during the Interim Pilot program referred to the notifier's determination and stated that we have not made our own determination regarding the GRAS status of the subject use of the notified substance (see table 1). We intend to continue including such typical text in letters issued under the final rule, modified as shown in table 20.

(Comment 103) One comment suggests that we respond in writing only at the notifier's request.

(Response 103) We decline this suggestion, which is contrary to emphasis that the rule places on the notifier's acceptance of responsibility for a conclusion of GRAS status (see the discussion at 62 FR 18938 at 18953).

(Comment 104) One comment asserts that a letter acknowledging receipt of a GRAS notice would constitute a form of response. Another comment suggests that a letter acknowledging receipt of a GRAS notice state whether the notice meets the listed requirements for a GRAS notice, eliminating the need for a second letter responding to the notice when we complete our evaluation. This comment asserts that a second letter would be unnecessary for two reasons. First, the notifier has accepted full responsibility for the conclusion of GRAS status and does not require premarket approval from us. Second, under the terms of the rule a notifier must agree to make all data and information available to us.

(Response 104) The final rule provides that we will inform you of the date on which we filed your notice rather than the date on which we received it, as we had proposed. We disagree that a letter informing you of the date of filing in any way responds to a GRAS notice or should state whether the notice meets the listed requirements for a GRAS notice. As discussed in Response 93, we cannot acknowledge whether a notice ''meets the listed requirements'' without assessing the quality of the submission, which we do during the evaluation that follows filing the submission as a GRAS notice.

We acknowledge that submitting a GRAS notice means that a notifier has accepted full responsibility for the conclusion of GRAS status. We also acknowledge that the use of a GRAS substance is not subject to our premarket review. However, we disagree that a relevant factor in determining whether we should respond to a notifier is the notifier's agreement to make all data and information available to us if we question whether the notice provides an adequate basis for a conclusion of GRAS status. A GRAS notice presents an opportunity for you to inform us about your conclusion of GRAS status rather than an opportunity for you to test a hypothesis that there is a sufficient basis to reach a conclusion of GRAS status.

(Comment 105) One comment suggests that we issue a written response only when we have reached a conclusion regarding safety.

(Response 105) This comment may have misunderstood the proposed notification procedure. Under the notification procedure, you analyze the available data and information and reach a conclusion about whether the notified substance is safe under the conditions of its intended use and whether there is a basis to conclude that the criteria for GRAS status are satisfied. We evaluate your conclusions regarding the available data and information. During the Interim Pilot program, the typical text of a ''no questions letter'' stated that we had not reached our own determination regarding the GRAS status of the notified substance under the conditions of its intended use (see table 1).

To the extent that the comment is suggesting that we issue an ''insufficient basis letter'' when the problem with the notice relates to safety, but not to general recognition, we disagree. It would be inconsistent with the legal basis of the GRAS standard for us to only focus on safety, and we did not do so during the Interim Pilot program. (See section III.A.3 of CFSAN's 2010 experience document (Ref. 18), where CFSAN identifies ''insufficient basis letters'' in which CFSAN had questions about whether there was general recognition of safety.)

C. Additional Correspondence as Circumstances Warrant

(Comment 106) One comment expresses the view that a ''no questions letter'' should not affect our ability to change our position if additional information indicates that the use of the substance raises any safety concerns.

(Response 106) We agree, and the final rule expressly provides that we will send the notifier a subsequent letter about the notice if circumstances warrant (see § 170.265(c)). The circumstances may not relate to safety. As discussed in section IV.J of CFSAN's 2010 experience document (Ref. 18), as of December 31, 2009, none of the subsequent letters CFSAN issued during the Interim Pilot program reflected a change in CFSAN's position and several addressed issues other than the safety of the use of the substance. For example, CFSAN issued subsequent letters that: (1) Clarified the intended conditions of use; (2) clarified that the term CFSAN used to refer to the notified substance for the purpose of the letter should not be considered an endorsement of that term for the purpose of declaring the substance in the ingredient statement of food products; (3) clarified FSIS' position regarding the use of the notified substance in meat, meat food product or poultry product; and (4) corrected a mistake in the original response. CFSAN also sent a subsequent letter as an administratively efficient mechanism of responding to a notifier who provided CFSAN with information supporting a conclusion that an additional use of the notified substance satisfied GRAS criteria.

In addition, CFSAN has issued a subsequent letter when CFSAN's first letter was an ''insufficient basis letter'' rather than a ''no questions letter.'' For example, CFSAN did so when a notifier who received an ''insufficient basis letter'' submitted a new GRAS notice that did not address the questions CFSAN raised in the ''insufficient basis letter.'' CFSAN also did so when a notifier who received an ''insufficient basis letter'' submitted a supplement to its original GRAS notice rather than submit a new GRAS notice. See section IV.J of CFSAN's 2010 experience document (Ref. 18).

D. Procedures if a Notifier Disagrees With Our Response

In the proposed rule, we explained that there are existing processes that we considered would be appropriate for a notifier to use to engage us if the notifier disagreed with our response (see 62 FR 18938 at 18952 and table 21). We also noted that any person with concerns about our response to a GRAS notice may contact our Office of the Chief Mediator and Ombudsman; that office works on resolving issues and conflicts that arise in any FDA component.

TABLE 21—EXISTING PROCEDURES IN OUR REGULATIONS THAT CAN APPLY IF A NOTIFIER DISAGREES WITH OUR RESPONSE TO A GRAS NOTICE

Regulatory section (§)	Description
10.25	Initiation of administrative proceedings.
10.33	Administrative reconsideration of action.
10.65	Meetings and correspondence.
10.75	Internal agency review of decisions.

(Comment 107) Several comments express concern that the processes discussed in the proposed rule would be

available only after we sent, and made readily accessible to the public, an ''insufficient basis letter.'' Other comments express concern about the practical effect of an ''insufficient basis letter'' on the notifier's ability to market a notified substance while the notifier is seeking review of our evaluation. Some comments ask that our letter be ''stayed'' until any problems that we identified in our response to the notice are resolved under such a process.

(Response 107) We acknowledge the concerns expressed in these comments but are making no changes to the rule to address these concerns. One of the underpinnings of the GRAS notification procedure is that making our response readily accessible to the public will properly underscore your responsibility for the conclusion of GRAS status (62 FR 18938 at 18953). As discussed in Response 104, a GRAS notice presents an opportunity for you to inform us about your conclusion of GRAS status rather than for you to test a hypothesis that there is a sufficient basis to reach a conclusion of GRAS status. If we send you an ''insufficient basis letter,'' we advise you to carefully consider whether marketing the notified substance would be lawful. ''Staying'' an ''insufficient basis letter'' informing you that there may not be a legal basis to market the notified substance, *e.g.,* so that you could market the substance while you are working to resolve the issues that led us to send you an ''insufficient basis letter'', would not change the legal status of the notified substance.

(Comment 108) Several comments assert that the processes we had identified in the proposed rule are cumbersome and do not provide manufacturers with a clear framework or timeline for responding to our questions or concerns. In general, these comments ask us to include in the final rule a prompt, fair, and effective process that would be specific to the GRAS notification procedure. A few comments suggest that such an appeal mechanism also apply to subsequent correspondence from us about a GRAS notice.

Some comments provide specific suggestions for how an appeals mechanism specific to the GRAS notification procedure could work, *e.g.,* by specifying that a notifier may submit additional data and information for our evaluation, or by providing for an independent advisory committee or an FDA-certified third-party review organization to review the matter and issue an opinion. Some comments suggest that an appeals mechanism specify appeal steps and stressed the importance of timeframes for decisions by our officials.

(Response 108) We decline the request to include in the final rule an appeals process that would be specific to the GRAS notification procedure. We agree that the process to contact us about a response to a GRAS notice should be clear. However, we disagree that the existing procedures are unclear, because our regulations fully describe these procedures (§§ 10.25, 10.33, 10.65, and 10.75). We acknowledge that the listed procedures do not provide a clear timeline and that some of the listed procedures (*e.g.,* §§ 10.25 and 10.33) are more cumbersome than others (such as requesting a meeting under § 10.65 or requesting internal Agency review of a decision under § 10.75). In practice during the Interim Pilot program, several notifiers who received an ''insufficient basis letter'' took steps to resolve our questions and subsequently submitted a new GRAS notice or a food additive petition (see the discussion in section III.K of CFSAN's 2010 experience document (Ref. 18)). Given the variety of circumstances that could lead to an ''insufficient basis letter,'' we believe that taking steps to resolve our questions, and submitting a new GRAS notice or a food additive petition, can be an efficient mechanism for you to use in lieu of the procedures we discussed in the proposed rule. Doing so would be consistent with the suggestion of some comments that an appeals mechanism specific to the GRAS notification procedure could include submission of additional data and information for our evaluation, except that the data and information would be submitted in a new GRAS notice rather than be an ''appeal'' to the GRAS notice that received an ''insufficient basis letter.''

We do not have an FDA-certified third-party review organization that could review the matter and issue an opinion. We disagree that convening an independent advisory committee would be appropriate as an additional, routine mechanism to appeal an ''insufficient basis letter.'' Under our regulations in part 14 governing advisory committees, it would be FDA—not a notifier—who decided to convene a meeting of our Food Advisory Committee about the use of a substance in food. We would have little basis to convene a meeting of our Food Advisory Committee as part of an appeal to an ''insufficient basis letter'' unless the notifier had first used one or more of the procedures listed in table 21.

XX. Coordinating Our Evaluation of a GRAS Notice With FSIS

In the 2010 notice, we described some of the terms of a MOU, between FDA and USDA's FSIS, that provides for a coordinated evaluation process with FSIS when the intended conditions of use of a notified substance include use in a product or products subject to regulation by USDA under statutes that it administers (75 FR 81536 at 81541–81542). We also asked for comment on whether to make our coordinated evaluation process with FSIS explicit in the final rule (see Issue 13, 75 FR 81536 at 81541–81542). In 2015, we amended that MOU to include more details about the procedures FDA and FSIS will follow to do so (Ref. 36).

(Comment 109) Comments support coordinating our evaluation of GRAS notices with FSIS and including the procedure for this coordination in the final rule. Comments also support requiring the notifier to provide an additional paper copy that we would send to FSIS as part of this procedure.

(Response 109) The final rule includes procedures for coordinating our evaluation of a GRAS notice with FSIS when the use of the notified substance includes use in a product or products subject to regulation by FSIS under statutes that it administers. (See § 170.270). If you send your GRAS notice on paper, a single paper copy is sufficient; we would send FSIS an electronic copy. (See § 170.210(b) and Response 46). Under § 170.270(d), we will inform you of the advice we receive from FSIS in the letter we send you in accordance with § 170.265(b)(1), as appropriate. By ''as appropriate,'' we mean that in most circumstances we do not intend to provide advice from FSIS about the use of the notified substance when we respond with an ''insufficient basis letter,'' because doing so has the potential to create confusion about the regulatory status of a use of the notified substance in products subject to regulation by FSIS. Likewise, we do not intend to provide advice from FSIS about the use of the notified substance when we respond with a ''cease to evaluate letter'' and, thus, the procedure described in § 170.270(d) does not specify that we will inform you of the advice we receive from FSIS in a letter we send you in accordance with § 170.265(b)(3).

As we noted in section XII.I, this rule does not specify the data and information that FSIS will need to evaluate whether the intended use of the notified substance complies with applicable statutes and regulations, or, if not, whether the use of the substance

would be permitted in products under FSIS jurisdiction under specified conditions or restrictions. We recommend that you contact the appropriate staff at FSIS regarding the data and information that FSIS will need you to provide. FSIS provides contact information for its programs on its Web site (Ref. 41).

(Comment 110) One comment agrees that the evaluation of a GRAS notice should be coordinated between FDA and FSIS when ''animal products'' are involved. This comment notes that FSIS does not currently review the use of a substance intended for use in animal food and recommends that CVM be involved in the safety review process of the notice if the notice involves a substance to be used in animal food.

(Response 110) This comment appears to have misunderstood the purpose of the coordinated evaluation process that we discussed in the 2010 notice. That process applies to the use of a substance in human food products, such as meat and poultry products, that are subject to regulation by USDA and would be evaluated by CFSAN; it does not apply to the use of a substance in animal food. FSIS, under the statutes it administers, does not evaluate a substance intended for use in animal food and, thus, the process would not apply to a GRAS notice received by CVM. See also Response 45.

XXI. Comments on Public Disclosure of a GRAS Notice

We proposed that a ''GRAS exemption claim'' would be immediately available for public disclosure on the date the notice is received. All remaining data and information in the notice would be available for public disclosure, in accordance with part 20, on the date the notice is received (proposed § 170.36(f)(1)). We also proposed that the following information would be readily accessible for public review and copying: (1) A copy of the ''GRAS exemption claim'' (proposed § 170.36(f)(2)(i)); (2) a copy of our response letter (proposed § 170.36(f)(2)(ii)); and (3) a copy of any subsequent letter we issued regarding the notice (proposed § 170.36(f)(2)(iii)). In the 2010 notice, we noted that although the decision to submit a GRAS notice would be voluntary, the provisions governing the GRAS notification procedure, including the information to be submitted, would be mandatory (75 FR 81536 at 81540).

In the final rule, you include the signed statements that we proposed be in a ''GRAS exemption claim'' in Part 1 of your GRAS notice, and we no longer use the term ''GRAS exemption claim'' (see Response 42). As discussed in Response 50, the final rule stipulates that you must not include any information that is trade secret or confidential commercial information in Part 1 of your GRAS notice (see § 170.225(b)).

In the following sections, we discuss comments on the proposed requirements for public disclosure of a GRAS notice. After considering these comments, we are establishing requirements applicable to the public disclosure of a GRAS notice as shown in table 22, with editorial, clarifying, and conforming changes as shown in table 29. (See § 170.275.) Table 22 identifies changes we made relative to the proposed rule or the description in the 2010 notice other than the editorial, clarifying, and conforming changes shown in table 29 and the additional editorial changes associated with the redesignation of proposed § 170.36(f) as § 170.275.

TABLE 22—FINAL REQUIREMENTS APPLICABLE TO PUBLIC DISCLOSURE OF A GRAS NOTICE

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.275(a)(1)	N/A	N/A	The data and information in a GRAS notice (including data and information submitted in any amendment or supplement to your GRAS notice or incorporated into your GRAS notice) are considered a mandatory, rather than voluntary, submission for purposes of its status under the FOIA and part 20.	Clarify that a notice is considered a mandatory, rather than voluntary, submission for purposes of their status under the FOIA and part 20.
170.275(a)(2)	170.36(f)(1)	N/A	The data and information in a GRAS notice (including data and information submitted in any amendment or supplement to your GRAS notice or incorporated into your GRAS notice) are available for public disclosure in accordance with part 20 as of the date that we receive your GRAS notice.	Clarify that part 20 applies to amendments and supplements as well as to the GRAS notice as originally submitted.
170.275(b)(1)	170.36(f)(2)(i)	N/A	We will make readily accessible to the public a list of filed GRAS notices, including the information described in the signed statements you include in § 170.225(c)(2) through (c)(5).	Clarifies that the list of submissions that we make publicly available are those that we have ''filed'' as GRAS notices.
170.275(b)(2)	170.36(f)(2)(ii)	N/A	We will make readily accessible to the public the text of any letter that we issue under § 170.265(b)(1) or (3) (*e.g.,* a ''no questions letter'' or an ''insufficient basis letter''); or under § 170.265(c) (a ''subsequent letter'').	N/A.
170.275(b)(3)	170.36(f)(2)(ii)	N/A	We will make readily accessible to the public the text of any letter that we issue under § 170.265(b)(3) (*e.g.,* a ''cease to evaluate letter'').	Clarify that the provisions in which we make certain letters readily accessible to the public apply to a ''cease to evaluate letter''.

TABLE 22—FINAL REQUIREMENTS APPLICABLE TO PUBLIC DISCLOSURE OF A GRAS NOTICE—Continued

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.275(c)	170.36(f)(2)(iii)	N/A	We will disclose public information in accordance with part 20.	N/A.

A. Data and Information in a GRAS Notice Are Available for Public Disclosure on the Date That We Receive It

(Comment 111) One comment asserts that the releasability of the contents of a GRAS notice should be governed by § 20.111 (data and information submitted voluntarily to us) because the FD&C Act does not require submission of a GRAS notice. The comment asserts that § 20.111 would affect the releasability of the content of a GRAS notice in three ways. First, while a GRAS notice is pending, § 20.111 would protect from disclosure safety data or information about an ingredient under development. Second, § 20.111 would permanently protect from disclosure any data or information relating to manufacturing, production or sales, or formulas. Third, § 20.111 would establish that a notifier has the right to request that we evaluate the notifier's position that specific data or information in a GRAS notice are protected from disclosure because these data or information fall within the exemption in § 20.61 for trade secrets and commercial or financial information, which is privileged or confidential.

(Response 111) We disagree that the provisions of § 20.111 apply to a GRAS notice. Although your decision to submit a GRAS notice is voluntary, the information included in your GRAS notice is required. To make that clear, the final rule stipulates that the data and information in a GRAS notice (including data and information submitted in any amendment or supplement to your GRAS notice or incorporated into your GRAS notice) are considered a mandatory, rather than voluntary, submission for purposes of its status under the FOIA and part 20 (see § 170.275(a)(1)).

We agree that a notifier has a right to request that we evaluate the notifier's position that specific data or information in a GRAS notice are protected from disclosure because these data or information fall within the exemption in § 20.61 for trade secrets and confidential commercial information. See § 170.225(c)(8), which requires that you state your view as to whether any of the data and information in Parts 2 through 7 of your GRAS notice are exempt from disclosure under the FOIA.

(Comment 112) Several comments assert that a GRAS notice should not be publicly available until after we have completed our evaluation. These comments also assert that a delay in disclosure, coupled with an opportunity for a notifier to amend the notice, would: (1) Avoid the release of information that we deemed to be inadequate or incomplete; and (2) avoid release of a notice that was withdrawn if coupled with an opportunity for a notifier to withdraw a notice.

(Response 112) We disagree that we should refrain from disclosing the existence of a GRAS notice, or the contents of a GRAS notice, until after we have completed our evaluation. As previously discussed, immediate disclosure of a GRAS notice underscores a notifier's responsibility for a conclusion of GRAS status (62 FR 18938 at 18953). As discussed in Response 2, immediate disclosure of a GRAS notice also provides an opportunity for outside parties to make us aware of dissenting views about whether the available data and information support a conclusion that the notified substance is safe under the conditions of its intended use, and we did receive information from outside parties during the Interim Pilot program. Continuing to provide an opportunity for public participation is consistent with our substitution of the GRAS notification procedure for the former GRAS affirmation petition process, in which there was a public comment period.

As discussed in Response 83, our current regulations regarding public information stipulate that no person may withdraw records submitted to FDA (see § 20.29), and those regulations will apply to a GRAS notice that you to ask us to ''cease to evaluate.''

(Comment 113) One comment asks us to make a GRAS notice available for public disclosure only after we accept the submission for review. Some comments contrast our proposal for immediate disclosure of a GRAS notice with the provisions of: (1) The GRAS affirmation petition process, in which a GRAS affirmation petition is disclosed only after the petition has been accepted for filing (former § 170.35(c)(2)); and (2) the health claim petition process, in which a health claim petition becomes available for public disclosure only after it is filed and a health claim petition that is denied without filing is not available for disclosure (21 CFR 101.70(j)).

(Response 113) The final rule continues to specify that the data and information in a GRAS notice are available for public disclosure as of the date of receipt (see § 170.275(a)(2)). The former GRAS affirmation petition process did not specify when a submitted GRAS affirmation petition would be available for public disclosure. Instead, the former GRAS affirmation petition process merely specified that we would place the petition on public file in the office of the Division of Dockets Management and publish a notice of filing in the **Federal Register** within 30 days after the date of filing. In addition, we disagree that the public disclosure provisions in § 101.70(j) applicable to the health claim petition process should apply to the GRAS notification procedure. Those provisions derive directly from the statutory provisions that direct the health claim program (section 403(r)(4)(A)(i) of the FD&C Act (21 U.S.C. 343(r)(4)(A)(i))).

Under § 20.103, with few exceptions all correspondence from members of the public, organization or company officials, or other persons, is available for public disclosure at the time that we receive it unless a different time for such disclosure is specified in other rules established or cross-referenced in part 20. As noted in Comment 86 and Response 86, we may decide to file and respond to a submission as general correspondence, rather than as a GRAS notice, in certain circumstances; if we do so, the data and information in the submission would be available as of the date of receipt. Retaining date of receipt as the timeframe for when a submission you transmit as a GRAS notice is available for public disclosure is both consistent with § 20.103 and a practical approach to a situation in which we receive a FOIA request for a GRAS

submission before we have determined whether to file the submission as a GRAS notice. As a practical matter, we believe that such situations will be rare, and that in most cases a GRAS submission will be disclosed after we have determined whether to file it and evaluate it as a GRAS notice, or to file it and respond to it as general correspondence.

(Comment 114) Some comments disagree with the assumption we stated in the proposed rule (62 FR 18938 at 18952) that submission of a GRAS notice would not reflect the notifier's plans about the timing or the use of the substance in a marketed product, because a GRAS substance may be marketed without prior approval.

(Response 114) We acknowledge that immediate disclosure of a GRAS notice could, in certain circumstances, provide information about the timing of market entry. However, when the data and information regarding the safety of the substance under the conditions of its intended use satisfy GRAS criteria, neither the law nor this rulemaking would prevent you from marketing a substance before submitting a GRAS notice or during our evaluation of that notice.

B. We Will Make a List of Filed GRAS Notices and Our Responses to GRAS Notices Readily Accessible

(Comment 115) Several comments address our stated intention to maintain an inventory of GRAS notices that we receive, our response, and any subsequent relevant correspondence. (See the discussion at 68 FR 18938 at 18953.) Some of these comments agree with the discussion in the proposed rule that an inventory of GRAS notices should be an adjunct to the proposed rule rather than be included in the regulatory text. Other comments disagree and ask us to include the creation and availability of the inventory in the regulatory text. These comments assert that a provision that merely states that the inventory exists and is available for public review would address the concern that we identified in the proposed rule about the need to maintain flexibility regarding our administration of the inventory.

(Response 115) The final rule specifies that we will make the following readily accessible to the public: (1) A list of filed GRAS notices, including the information described in certain of the signed statements that are included in Part 1 of a GRAS notice (*i.e.,* § 170.225(c)(2) through (c)(5)); and (2) The text of any letter that we issue under § 170.265(b)(1) (our response to a GRAS notice based on our evaluation of the notice), § 170.265(b)(3) (a letter if we grant a request that we cease to evaluate a GRAS notice), or § 170.265(c) (a subsequent letter that we send about a GRAS notice). (See § 170.275(b).) We are not specifying that the mechanism for us to do so is through an ''Inventory'' because the procedure we used to make this information readily accessible to the public evolved over time during the Interim Pilot program, and may continue to evolve (see section III.I.1 in CFSAN's 2010 experience document (Ref. 18)).

(Comment 116) In the proposed rule, we stated our intention to initially maintain a paper version of an inventory at our Dockets Management Branch (now Division of Dockets Management) and asked for comment on making an inventory available through electronic means such as the Internet (62 FR 18938 at 18953). Comments support maintaining an inventory in paper format, electronic format, or both formats so that all members of the public could have ready access to such information regarding GRAS notices. Some comments point out that electronic access would be particularly important to the international food industry. Some comments support the Division of Dockets Management as the best location for an inventory maintained in paper format.

(Response 116) As discussed in section III.I.1 in CFSAN's 2010 experience document (Ref. 18), the procedure we used to make this information readily accessible to the public evolved over time during the Interim Pilot program. It began as a paper file (first maintained at the Division of Dockets Management, and then maintained in the public reading room of our Freedom of Information Staff), and evolved into its current electronic format on our Internet site (Ref. 46). We intend to continue using the Internet as the principal means to make the inventory readily accessible because doing so is an efficient and effective mechanism to disseminate information to anyone who has access to the Internet. The inventory on the Internet can be accessed and printed from computers in the public reading room at Division of Dockets Management, as well as from computers located at businesses, at homes, and at public locations such as libraries and Internet cafes. If a person either does not have access to the Internet or chooses not to access the inventory through the Internet, that person can request each GRAS notice, and each letter listed in § 170.265(b)(1) or (3) or (c), under the FOIA. It is no longer practical for us to maintain a paper file at the Division of Dockets Management, because all new information sent to the Division of Dockets Management is maintained electronically; paper submissions are scanned to electronic form.

(Comment 117) One comment that addresses the discussion in the 2010 notice about the reasons that may lead us to decline to file a submission as a GRAS notice, such as when the use is covered by an existing regulation, asks us to include those submissions in the GRAS inventory so there will be no confusion as to the status of the ingredient.

(Response 117) We decline this request. The purpose of the inventory of GRAS notices is to provide a list of all the GRAS notices that we have filed and evaluated, not to interpret the uses listed in our regulations or, as discussed in Response 86, covered by an existing GRAS notice.

(Comment 118) A few comments suggest that a publicly available inventory of GRAS notices could suffice to document that certain notices raised no significant issues.

(Response 118) We agree that a publicly available inventory of GRAS notices can document which notices result in a ''no questions letter, *e.g.,* by prominently listing the category of our response. The Inventory of GRAS Notices developed during the Interim Pilot program prominently classifies each response letter as ''no questions,'' ''insufficient basis,'' and ''cease to evaluate'' (Ref. 46). However, we disagree that merely displaying the category of our response, without providing the full text of a letter that places that category of response in context, is appropriate, regardless of whether the response to the GRAS notice is ''no questions,'' ''insufficient basis,'' or ''cease to evaluate.'' For example, even when we answer ''FDA has no questions,'' our response letter highlights key safety considerations, such as the importance of ensuring that the method of manufacture removes potential contaminants.

(Comment 119) One comment asks us to provide ''public notice'' of all GRAS notices and the information provided therein. Another comment asks us to make the ''GRAS exemption claim'' readily accessible to the public by publishing information that would be in the publicly accessible file in the **Federal Register** in addition to placing the ''GRAS exemption claim'' in a readily accessible file. This comment states that doing so would provide the public with access to as much information as possible about what substances would be used in food on the basis of the GRAS provision if FDA is

going to ''forgo its role'' in the evaluation of the safety of GRAS substances. This comment also asks us to publish the receipt of the notice and all of our subsequent responses to the notice in the **Federal Register**.

Another comment asks us to publish semi-annually, either in a **Federal Register** notice or by regulation, a list of GRAS notices that receive a ''no questions letter'' in addition to posting the Inventory of GRAS notices on our Web site. This comment explains that questions are sometimes raised—especially from outside the United States—about the regulatory status of a substance used in food on the basis of the GRAS provision unless that use of the substance is either incorporated into the CFR or otherwise officially published. This comment asserts that periodic publications in the **Federal Register** would assist in addressing this concern.

(Response 119) By specifying that we will make a list of filed GRAS notices readily accessible (currently, through the inventory on the Internet), the rule requires us to actively disclose those GRAS notices. There is a gap between the date on which we receive a GRAS notice and the date on which we add it to the inventory, *e.g.,* CFSAN currently updates its inventory on an approximately monthly basis. However, in practice during the Interim Pilot program there was ample public notice of the receipt of the GRAS notice before CFSAN responded to it (see the discussion of the timeframe for CFSAN's response in section III.M of CFSAN's 2010 experience document (Ref. 18)). In addition, the rule provides that we may send a subsequent letter about the GRAS notice if circumstances warrant; such circumstances could include data and information, received from a member of the public, after we responded to the GRAS notice.

We decline the requests to provide public notice through an announcement in the **Federal Register**. Publishing an announcement in the **Federal Register** requires an expenditure of our resources (including time and cost of publication) that would be inconsistent with our goal of using our resources efficiently and effectively. Even if we conserved resources by publishing such a notice only on a semi-annual basis, we disagree that ''officially publishing'' a list of GRAS notices that receive a ''no questions letter'' in the **Federal Register** would address concerns, in the domestic or international community, about the regulatory status of the use of a substance when that use is not listed in our regulations. It is the Code of Federal Regulations, not the **Federal Register**, that is the official repository of our regulations listing authorized uses of food substances.

We disagree that we are forgoing our role in the evaluation of the safety of substances used in food on the basis of the GRAS provision. See Response 25.

(Comment 120) One comment asks us to place the entire GRAS notice, rather than only the proposed ''GRAS exemption claim,'' in a readily accessible paper file, *e.g.,* at the Division of Dockets Management. In the comment's view, a simple provision that a notifier submit one additional paper copy would mitigate our concerns about the administrative inefficiency of maintaining duplicate files at both the center and Agency levels. Another comment asks us to make the entire notice readily accessible in electronic form.

(Response 120) We currently make a hyperlink to an electronic copy of each GRAS notice accessible from within the entry for that GRAS notice in the inventory, after appropriate redaction (*e.g.,* of privacy information, copyrighted material, and any data and information that are exempt from public disclosure) (Ref. 18, footnote 3). As a practical matter, placing paper files on public display requires space, which is finite, and our Division of Dockets Management scans paper submissions into electronic format.

C. Public Disclosure of a GRAS Notice Is in Accordance With Our Public Information Regulations in Part 20

(Comment 121) One comment agrees that information submitted under the proposed ''GRAS exemption claim'' should exclude from public disclosure the non-public confidential information with the exception of safety data.

(Response 121) This comment appears to have misinterpreted the proposed provisions regarding submission of non-public information and how the public disclosure provisions of this rule apply to non-public information. The proposed ''GRAS exemption claim'' is the precursor of Part 1 of a GRAS notice (which we are establishing in § 170.225). The rule specifies that you must not include any information that is trade secret or confidential commercial information in Part 1 of your GRAS notice, except in the statement of your view as to whether any of the data and information in Parts 2 through 7 of your GRAS notice are exempt from disclosure under the FOIA. Part 1 of a GRAS notice includes signed statements and a certification, not ''safety data.'' The ''safety data'' would be included in Parts 2 through 7 of the GRAS notice. Consistent with the view of this comment, the rule provides that those data and information are available for public disclosure upon receipt (see § 170.275(a)(2)). See also Response 50.

(Comment 122) Some comments ask us to alert the notifier, and grant the notifier an option to withdraw the notice, in order to protect information designated as confidential from disclosure.

(Response 122) We decline this request. A person who submits a record to us may not withdraw that record from our files (§ 20.29). Rather, the procedures that govern the release of information that a notifier identifies as confidential in a GRAS notice are established in §§ 20.61 and 20.27. Under § 20.61(d), a person who submits records to us may designate part or all of the information in such records as exempt from disclosure under exemption 4 of FOIA. However, under § 20.27 marking records submitted to us as confidential, or with any other similar term, raises no obligation by FDA to regard such records as confidential, to return them to the person who has submitted them, to withhold them from disclosure to the public, or to advise the person submitting them when a request for their public disclosure is received or when they are in fact disclosed.

XXII. Submission of a Supplement

The rule provides that you may submit a supplement to a GRAS notice after we respond to your notice based on our evaluation of your notice or cease to evaluate your notice (§ 170.280). However, if our response to your GRAS notice raises questions about your conclusion that the notified substance is GRAS under the conditions of its intended use, the appropriate mechanism for you to address those questions would be to submit a new GRAS notice or other regulatory submission (such as a food additive petition) rather than to submit a supplement. See section III.C.2 of CFSAN's 2010 experience document for examples of supplements that CFSAN received during the Interim Pilot program (Ref. 18).

XXIII. Comments on the Administrative Process for Pending GRAS Affirmation Petitions

We proposed that any pending petitions would be presumptively converted to a GRAS notice on the date the final rule becomes effective (proposed § 170.36(g)(1)). An affected petitioner would have an opportunity to amend the converted petition to meet the requirements of the GRAS notification procedure by submitting a

''GRAS exemption claim'' (proposed § 170.36(g)(2)). A GRAS affirmation petition that is converted to a notice and that the affected petitioner amends would be reviewed and administered according to the provisions of the GRAS notification procedure; the date of receipt of the amendment would be the date of receipt of the notice (proposed § 170.36(g)(3)(i)). After 90 days from the date of publication of the final rule, we would inform any affected petitioner who had not amended an applicable petition that the converted petition is inadequate as a GRAS notice.

In the 2010 notice, we requested comments on three issues related to the pending petitions as shown in table 23. Although the 2010 notice classified all of these issues as ''Issue 17,'' for presentation purposes in this document we classify the three issues as 17a, 17b, and 17c.

TABLE 23—ISSUES IN THE 2010 NOTICE REGARDING PENDING GRAS AFFIRMATION PETITIONS

Issue No.	Description of our request for comment	Reference
17a	How to reduce the impact on affected petitioners while retaining the principle that we will not devote resources to pending petitions.	75 FR 81536 at 81542–81543.
17b	Whether an outcome of ''withdrawal without prejudice'' instead of ''insufficient basis'' would be more appropriate when an affected petitioner simply chooses not to have the pending petition considered under the GRAS notification procedure.	75 FR 81536 at 81542–81543.
17c	Whether an affected petitioner could request that we incorporate into a GRAS notice a withdrawn GRAS affirmation petition into a GRAS notice, and if so, if any requirements of the GRAS notification procedure should be waived.	75 FR 81536 at 81542–81543.

In the following paragraphs, we discuss comments regarding the disposition of pending petitions in light of the deletion of the GRAS affirmation petition process. After considering these comments, we are establishing provisions for the pending petitions as shown in table 24, with editorial, clarifying, and conforming changes as shown in table 29. (See § 170.285.) Table 24 identifies changes we made relative to the proposed rule or the description in the 2010 notice other than the editorial, clarifying, and conforming changes shown in table 29 and the additional editorial changes associated with the redesignation of proposed § 170.36(g) as § 170.285.

TABLE 24—FINAL REQUIREMENTS FOR DISPOSITION OF PENDING GRAS AFFIRMATION PETITIONS

Final designation in the regulatory text (§)	Proposed designation in the regulatory text (§)	Issue No. in the 2010 notice	Description	Revisions (other than editorial, clarifying, and conforming changes) relative to the proposed rule or the 2010 notice
170.285(a)	170.36(g)(1)	17a and 17b	On the effective date of the rule, we will close the docket for any GRAS affirmation petition that is still pending as of that date.	We administratively close the docket for the GRAS affirmation petition rulemaking rather than convert the pending petition to a GRAS notice.
170.285(b)	170.36(g)(2)	17c	Any person who submitted a GRAS affirmation petition that is pending as of the date of the final rule may submit a GRAS notice and request that we incorporate the GRAS affirmation petition.	The affected petitioner submits a GRAS notice rather than an amendment to a ''converted petition''.
N/A	170.36(g)(3)(i)	N/A	N/A	No longer specifies the procedures for FDA's evaluation of a former pending petition.
N/A	170.36(g)(3)(ii)	17a and 17b	N/A	No longer treats a pending petition that is not evaluated as a GRAS notice as having an insufficient basis to support GRAS status.

(Comment 123) Some comments to the proposed rule support our proposal to convert pending GRAS affirmation petitions to GRAS notices on the effective date of the rule. However, as discussed in the 2010 notice, many comments to the proposed rule object to our proposal for administering the pending petitions as being fundamentally unfair, because an affected petitioner had invested considerable time and resources in the petition process and should not be penalized by our adoption of a new GRAS notification procedure. Some of these comments state that, in most cases, FDA also had dedicated significant resources to the review of these petitions and, in some cases, had even arranged for an additional third party to review the substance that was the subject of the petition. These comments suggest options such as ''grandfathering'' pending petitions, *i.e.,* completing the rulemaking process for them, particularly if we had completed our scientific review with no outstanding questions. Some comments ask us to provide an affected petitioner 180 days, rather than 90 days, to amend the converted petition to satisfy the requirements of the GRAS notification procedure. One of these comments argues that there need not be any urgency in closing the applicable files because many of these petitions had been pending for years, and the subjects of the petitions had been marketed during those years.

Some comments to the proposed rule assert that more resources would be needed to review a petition that is converted to a GRAS notice than would be needed to complete the review of each pending petition and issue a

regulation. One comment suggests that it would be simpler and more efficient administratively to allow an affected petitioner an option to update a GRAS affirmation petition to include additional conditions of use or new specifications than to require separate GRAS notices for such changes.

Other comments ask us to clarify the procedures we would use to convert a GRAS affirmation petition to a GRAS notice as well as procedures for amending a petition that was converted to a GRAS notice through an additional submission. Some comments assert that we should not require an affected petitioner to submit such an amendment because all of the pertinent information would already be included in the petition and argue that technical adherence to the format of a GRAS notice should not take precedence over administrative efficiency and common sense. Other comments express concern that it was not clear that the proposed additional submission (proposed § 170.36(g)(2)) was in fact a skeleton notice that primarily would cross-reference the original GRAS affirmation petition.

Some comments to the 2010 notice suggest that a pending petition could be ''withdrawn without prejudice'' or ''suspended'' so that it would no longer require FDA resources to review it. Other comments to the 2010 notice express the view that a simple letter of conversion should be adequate, but that if an affected petitioner chose not do so then the outcome of the converted petition would more appropriately be described as ''withdrawn without prejudice'' rather than ''insufficient'' as a GRAS notice. Other comments to the 2010 notice continue to express the view that we should ''grandfather'' a pending petition. One of these comments asserts that failure to grandfather those affirmation petitions where FDA had completed its review and no outstanding scientific issues exist would be unfair because the GRAS notification procedure results in a lower level of authoritativeness than the GRAS affirmation petition process, and the affected petitioners had invested considerable time and resources in the petition process. This comment also notes that after we published the proposed rule we continued to review GRAS affirmation petitions and completed the process for six GRAS affirmation petitions before discontinuing further activity in 1999. Comments that address Issue 17c recommend that an affected petitioner be allowed to incorporate information from a ''withdrawn'' GRAS affirmation petition into a GRAS notice.

We received no comments asking us to waive any of the requirements of the notification procedure.

(Response 123) We have revised the proposed provisions regarding the disposition of pending petitions in light of the concern of the comments that the proposed process was unfair to affected petitioners. The final rule provides that on the effective date of the rule, we will close the docket for any GRAS affirmation petition that is still pending as of that date (§ 170.285(a)). Any person who submitted a GRAS affirmation petition that is pending as of the date of the final rule may submit a GRAS notice and request that we incorporate the GRAS affirmation petition (§ 170.285(b)). We are closing the docket for the petition by operation of law because the process that would be necessary to bring a petition to closure (*i.e.,* § 170.35(c)) no longer exists. We decided to close the docket for the petition, rather than classify the petition as withdrawn without prejudice, for two reasons. First, closing the docket is an administrative option that is open to us, whereas in our petition processes withdrawing a petition is an option that falls to the petitioner (see, *e.g.,* § 171.1(j) for withdrawal of a food additive petition without prejudice). Second, ''withdrawal without prejudice'' generally means ''without prejudice to a future filing,'' and ''future filing'' refers to the same type of filing; however, we have eliminated the GRAS affirmation petition process and, thus, an affected petitioner could not submit another GRAS affirmation petition.

Closing the docket is neutral with respect to a conclusion by an affected petitioner that the petitioned substance is GRAS under the conditions of its intended use, because closing the docket does not result in a publicly available ''insufficient basis letter.'' To clarify that closing the petition is without prejudice to eligibility for classification of the use of the substance as GRAS, the final rule specifically provides that an affected petitioner may incorporate the former GRAS affirmation petition into a GRAS notice. Given the passage of time since the pending petitions were submitted, it is likely that some of the data and information in the petition would need to be updated. In addition, the affected petitioner would need to follow all format requirements for a GRAS notice, including the narrative required in Part 6 of a GRAS notice.

We acknowledge that our response to a GRAS notice does not have the same level of ''authoritativeness'' as a listing in our regulations. However, some of the comments that objected to the proposal to convert a pending petition to a GRAS notice assert that the substances that are the subject of the pending petitions have been marketed for years; clearly, these affected petitioners are able to market the substance without a listing in our regulations.

We agree that it is appropriate to extend the timeframe for an affected petitioner to take action with respect to a pending petition. Under final § 170.285(b), there is no limit on the timeframe for an affected petitioner to submit a GRAS notice that incorporates a GRAS affirmation petition.

We decline the request to ''grandfather'' any pending petitions. We simply do not have sufficient resources to devote to the rulemaking process that is required for GRAS affirmation, regardless of whether we already have completed our scientific review. For example, even if we have completed our scientific review, the Administrative Procedures Act (5 U.S.C. 553) requires that we consider relevant data, views, or arguments submitted to us by interested persons and that we publish a concise general statement of the basis and purpose of the regulation. In addition, Executive Order 12866 requires that we assess the costs and benefits of available regulatory alternatives when we conduct rulemaking, and the Regulatory Flexibility Act (5 U.S.C. 601–612) requires that we consider alternatives that would minimize the economic impact of our regulations on small entities. Thus, to complete the rulemaking associated with the GRAS affirmation petition process, we require significant resources beyond those associated with scientific review. Even if we did ''grandfather'' a pending petition, it is highly unlikely that we would be able to devote resources to this voluntary process in light of competing programs that are required by statute. For example, the resources that could be directed to the GRAS affirmation petition process must be considered together with the resources that are required to administer the food and color additive petition processes and the premarket notification process for food contact substances, which are required programs under sections 409 and 721 of the FD&C Act.

For the reasons discussed in the previous paragraph, we disagree that we would have needed more resources to review a petition that is converted to a GRAS notice than to complete the review of each pending petition and issue a regulation. We also disagree that it would be simpler and more efficient administratively to allow an affected

petitioner an option to update a GRAS affirmation petition. As discussed in CFSAN's 2016 experience document (Ref. 19), during the 10-year period extending from 1990 through 1999, CFSAN completed the rulemaking process for 24 GRAS affirmation petitions, with an average elapsed time of approximately 7.9 years (median elapsed time approximately 6.9 years). In contrast, under the final rule we will respond to a GRAS notice in 180 days, with an option to extend the timeframe by an additional 90 days (see Response 98).

As of August 17, 2016 there are 45 pending GRAS affirmation petitions. We intend to contact each affected petitioner to inform the petitioner that: (1) We are closing the affected docket as of October 17, 2016; and (2) the petitioner may submit a GRAS notice that incorporates the former GRAS affirmation petition.

(Comment 124) One comment asks us to issue a regulation, to be included in part 184, that lists the pending petitions. The comment also asks us to include a statement that the lack of an affirmation regulation does not indicate that FDA disagrees with the affected petitioner's GRAS determination.

(Response 124) We decline this request. Our regulations in part 184 represent our own conclusions regarding the GRAS status of a listed substance under the conditions of its intended use. It is inappropriate for our regulations to become a catalog of circumstances where we have not reached our own conclusion regarding GRAS status.

However, under final § 170.275(b), we will make a list of filed GRAS notices readily accessible to the public. The inventory of GRAS notices that currently makes this list available includes a link to information about each listed GRAS notice. When the GRAS notice was originally submitted as a GRAS affirmation petition, we have included the petition number. We intend to continue this practice under the final rule.

We also have placed a list of the pending petitions that we are closing in the docket for this rule (Ref. 48).

XXIV. Other Comments

A. GRAS Panels and Conflict of Interest

In the 2010 notice, we explained that the GAO report noted that we have not issued any conflict of interest guidance that companies can use to help ensure that the members of their expert panels are independent (75 FR 81536 at 81542). The GAO report recommended that we develop a strategy to minimize the potential for conflicts of interest, including taking steps such as issuing guidance for companies on conflict of interest and requiring information in GRAS notices regarding expert panelists' independence. In the 2010 notice, we requested comments on three issues related to GAO's recommendation regarding conflict of interest as shown in table 25. Although the 2010 notice classified all of these issues as ''Issue 15,'' for presentation purposes in this document we classify the three issues as 15a, 15b, and 15c.

TABLE 25—ISSUES IN THE 2010 NOTICE REGARDING GUIDANCE ON CONFLICT OF INTEREST

Issue No.	Description of our request for comment	Reference
15a	Whether companies would find it useful to have guidance on potential conflicts of interest of GRAS expert panelists.	75 FR 81536 at 81542.
15b	If guidance on potential conflicts of interest of GRAS expert panelists would be useful, what companies currently do to mitigate such a conflict.	75 FR 81536 at 81542.
15c	Whether to require that GRAS notices include information regarding expert panelists' independence	75 FR 81536 at 81542.

(Comment 125) Most of the comments that addressed Issues 15a and 15b ask us to provide guidance regarding potential conflicts of interest of GRAS panel members. One of these comments provided an example of a draft guidance for our consideration. Other comments provide criteria that they ask us to consider in the guidance. One comment asks us to provide an opportunity for industry, academia, and the public to comment on our proposed course of action for the topic of conflict of interest.

One comment asserts that there is no need for guidance regarding potential conflicts of interest of GRAS panel members because industry is aware of the importance of disclosing and addressing potential conflicts of interest and often has Standard Operating Procedures delineating rules for disclosure.

(Response 125) We have decided to issue guidance regarding conflict of interest. We will do so as Level 1 guidance within the framework of our good guidance practices regulation (see § 10.115(c) and (g)). Under that framework, we prepare a draft of Level 1 guidance and then: (1) Publish a notice in the **Federal Register** announcing that the draft guidance document is available; (2) post the draft guidance document on the Internet and make it available in hard copy; and (3) invite public comment on the draft guidance document. After providing an opportunity for public comment on a Level 1 guidance document, FDA will: (1) Review any comments received and prepare the final version of the guidance document that incorporates suggested changes, when appropriate; (2) publish a notice in the **Federal Register** announcing that the guidance document is available; (3) post the guidance document on the Internet and make it available in hard copy; and (4) implement the guidance document. We will consider the recommendations and draft guidance submitted in the comments to this rule in developing our draft guidance for public comment.

We acknowledge that some members of industry are aware of the importance of disclosing and addressing potential conflicts of interest. However, we disagree that this awareness means that we should not issue a guidance regarding conflict of interest. A guidance from us on conflict of interest could promote consistency in addressing conflict of interest by different companies.

(Comment 126) One comment notes that an external GRAS panel is not required for a conclusion of GRAS status when the conclusion is supported by peer-reviewed literature or a ''long history of safe use.'' (By ''long history of safe use,'' we assume that the comment is referring to the provision that GRAS criteria may be satisfied through experience based on common use in food prior to January 1, 1958. See § 170.30(a) and (c)).

(Response 126) We agree that an external GRAS panel is not required for a conclusion of GRAS status. As we previously noted, convening 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 (62 FR 18938 at 18943).

(Comment 127) Some comments address Issue 15c and recommend that a notifier include information on independence of the panel members in a submitted GRAS notice.

(Response 127) The rule neither requires that a notifier convene a GRAS panel nor establishes any other requirements applicable to a GRAS panel. Therefore, we are addressing issues regarding a GRAS panel in guidance rather than in the regulation. See also Comment 14 and Response 14.

B. Guidance on Documenting Conclusions of GRAS Status

In the 2010 notice, we explained that the GAO report recommended that we issue guidance on how to document a conclusion of GRAS status (75 FR 81536 at 81542). We noted that there is guidance in the preamble to the proposed rule and in our guidance for industry entitled ''Frequently Asked Questions About GRAS'' (Ref. 49). We requested comments on two issues related to guidance on documenting a conclusion of GRAS status as shown in table 26. Although the 2010 notice classified both of these issues as ''Issue 16,'' for presentation purposes in this document we classify the two issues as 16a and 16b.

TABLE 26—ISSUES IN THE 2010 NOTICE REGARDING GUIDANCE ON DOCUMENTING GRAS CONCLUSIONS

Issue No.	Description of our request for comment	Reference
16a	Whether there is a need to clarify that our guidance applying to GRAS submissions also applies to a GRAS conclusion that is not submitted to us in the form of a GRAS notice.	75 FR 81536 at 81542.
16b	Whether there is a need for us to develop further guidance on documenting a GRAS conclusion when the GRAS conclusion is not submitted to us as a GRAS notice.	75 FR 81536 at 81542.

(Comment 128) Most of the comments that addressed Issue 16a recommend that we clarify that the same standards apply to a conclusion of GRAS status regardless of whether the conclusion is submitted to us as a GRAS notice or is not submitted to us.

(Response 128) To reach a conclusion of GRAS status, the proponent of GRAS status must: (1) Establish that the substance is safe under the conditions of its intended use within the meaning of section 409(c)(5) of the FD&C Act and our implementing regulation in § 170.3(i); and (2) establish that the safety of the substance under the conditions of its intended use is generally recognized within the meaning of section 201(s) of the FD&C Act and our regulations in § 170.30 governing the eligibility for classification as GRAS. See the discussion in section I.C of the proposed rule of the elements of the GRAS standard, where we described the evaluation of safety as the ''technical element'' of the GRAS standard and the evaluation of general recognition as the ''common knowledge element'' of the GRAS standard. In considering whether GRAS criteria are satisfied because the available data and information demonstrate that the use of a substance is safe and the safety is generally recognized, we do not distinguish between a conclusion of GRAS status submitted to us as a GRAS notice and an independent conclusion of GRAS status that remains with the proponent. As discussed in Response 41, in this rulemaking we made conforming changes to current regulations regarding the use of GRAS substances in food, and our affirmation of GRAS status on our own initiative, to emphasize that point (see the changes to §§ 170.3(i) and (k), 170.30(c), 170.30(e), and 170.35(a) and (b) in table 29). As already noted in section I.E of this document, we advise any company that intends to market a food substance on the basis of an independent conclusion of GRAS status to carefully consider whether this use fully satisfies the criteria for eligibility for classification as GRAS and to carefully review the discussions in this document relevant to those criteria, such as the discussion in Response 9 regarding the role of corroborative data and information, the discussions in Response 10 and Response 11 regarding the limitations of a published report of a GRAS panel, and the discussion in Response 69 regarding the ramifications of providing trade secret information (or other non-public information) to a GRAS panel.

Our 2004 guidance entitled ''Frequently Asked Questions About GRAS'' generally applies to a conclusion of GRAS status regardless of whether that conclusion of GRAS status is submitted to us as a GRAS notice. Exceptions include current questions specific to the notification procedure as it operated during the Interim Pilot program, such as ''Where do I send my GRAS notice?'' We are modifying that guidance to update it in light of the publication of this rule.

We believe that the provisions of the GRAS notification procedure in part 170, subpart E 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 or is an independent GRAS conclusion that is not submitted to us. For example, the requirements in Part 3 of a GRAS notice make clear that a conclusion of GRAS status requires consideration of dietary exposure. Likewise, the requirements in Part 6 of a GRAS notice demonstrate the importance of a complete and balanced evaluation of all applicable data and information, including data and information that are, or may appear to be, inconsistent with a conclusion of GRAS status. Therefore, we recommend that any person who intends to use a substance in food based on a conclusion of GRAS status, but does not intend to submit a GRAS notice to us, use the provisions of part 170, subpart E as guidance. We also recommend that such persons organize the data and information that support an independent conclusion of GRAS status according to the organization presented by Parts 1 through 7 of a GRAS notice. Doing so would facilitate our evaluation of that independent conclusion of GRAS status if circumstances warrant, *e.g.,* if we have cause to question the independent conclusion of GRAS status. Because we make information about GRAS notices readily accessible to the public, we also recommend that you make the basis for your independent GRAS conclusion publicly available (*e.g.,* by making publicly available a document analogous to the narrative of a GRAS notice, a report of a GRAS panel (if you convene a GRAS panel), or both a narrative and a report of a GRAS panel).

General recognition of safety based upon scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain

approval of a food additive regulation for the ingredient (§ 170.30(b)). We address scientific issues associated with demonstrating the safety of a food substance in a series of guidance documents on our Internet (Ref. 6, Ref. 25, and Ref. 32 through Ref. 35). Currently, some of these scientific guidance documents are expressly directed to evaluation of the safety of food additives. For example, in Response 66 we noted that our guidance entitled ''Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions'' (Ref. 31) currently is structured to address the specific requirements of a food additive petition, even though many of the recommendations in that guidance could nonetheless be useful to any person who evaluates whether a substance is GRAS under the conditions of its intended use. As resources allow, we intend to re-visit these scientific guidance documents to determine whether and how to modify them to clarify that our guidance on evaluating the safety of a food substance generally applies regardless of whether the substance would be used in food as a food additive or as a GRAS substance. Regardless of any implication, in the title or text of these guidance documents, that the subject of the document applies to a food additive, we recommend that you consider that the scientific recommendations in these guidance documents may also apply to substances that would be used in food on the basis of a GRAS conclusion.

Some scientific guidance documents already do make clear that they apply regardless of the regulatory status of a substance (*e.g.,* as a food additive, color additive, food contact substance, or GRAS substance) (Ref. 6). In addition, as discussed in Response 37, we recently issued a notice announcing a public meeting, and requesting comments, on our intent to update our guidance entitled ''Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients'' (79 FR 64603), and reiterated that general recognition of safety based upon scientific procedures requires the same quantity and quality of evidence as is required to approve a food additive.

(Comment 129) Some comments support issuing additional guidance on documenting a conclusion of GRAS status, particularly for a GRAS conclusion that is not submitted to us. One comment asserts that there is no need for us to develop additional guidance on documenting a conclusion of GRAS status that is not submitted to us. One comment agrees with the recommendation in the GAO report that we take steps to ensure that companies maintain proper documentation to support a conclusion of GRAS status.

(Response 129) We agree that companies should maintain proper documentation to support a conclusion of GRAS status. As we discussed in the proposed rule (62 FR 18938 at 18947), any person who concludes that a substance is GRAS under the conditions of its intended use should have assembled and evaluated the evidence that forms the basis of that conclusion, regardless of whether the person subsequently notifies us. Preserving the applicable data and information represents prudent practice for those who assert that the statutory premarket review requirements do not apply to the use of a substance in food.

To emphasize the importance of maintaining the data and information that support an independent conclusion of GRAS status, we are issuing a guidance directed to any person who evaluates whether the available data and information regarding the safety of a substance under the conditions of its intended use satisfy GRAS criteria. The purpose of the guidance is to: (1) Remind such persons of their responsibilities under the FD&C Act regarding a conclusion of GRAS status, regardless of whether the conclusion of GRAS status is submitted to us as a GRAS notice; and (2) refer such persons to key resources, such as those discussed in Response 128, for evaluating the safety of the substance under the conditions of its intended use and for evaluating whether the available data and information regarding safety satisfy the criteria for eligibility for classification as GRAS in § 170.30. We believe that such guidance is appropriate in light of the recommendations of the GAO report.

C. Compliance With Other FDA Regulations

We proposed that a GRAS notice would not constitute compliance with the requirements for a health claim petition in § 101.14(b)(3)(ii) or for a new infant formula submission in § 106.120(b)(6)(ii). We specified that any person who submits a health claim petition, or who submits a new infant formula submission, must comply in full with the requirements of the applicable program (proposed § 170.36(a)(2)).

(Comment 130) Several comments object to the perceived implication that a GRAS notice could never be used to support a health claim petition or a new infant formula submission. In general, the comments maintain we should consider, on a case-by-case basis, whether a particular GRAS notice is sufficient to comply with the requirements of the applicable program rather than categorically disallow a GRAS notice as a means for satisfying the requirements of the applicable program.

(Response 130) We are not including this proposed provision in the final rule because it is not necessary to do so. Any person who submits a health claim petition, or who submits a new infant formula submission, must comply in full with the requirements of the applicable program whether this rule says so or not. An FDA office that evaluates a health claim petition or a new infant formula submission will take into account our response to a GRAS notice when evaluating the health claim petition or new infant formula submission. In practice during the Interim Pilot program, an FDA office evaluated a health claim petition or a new infant formula submission for several substances that were the subject of a previously submitted GRAS notice. In each case, FDA's evaluation of the health claim petition or new infant formula submission had an outcome that was consistent with our response to that GRAS notice (see section IV.A of CFSAN's 2010 experience document (Ref. 18)).

D. Impact on Other Federal Agencies

In our discussion in the proposed rule of the proposed procedures for making information about GRAS notices readily accessible to the public, we stated our belief that there would be considerable interest, from a broad segment of the public, including other Federal agencies, in notices received under the proposed notification procedure (62 FR 18938 at 18952). We also stated our expectation that such groups will likely want to know whether we are aware that a substance is being used in food on the basis of the GRAS provision and whether we have advised a notifier that we have identified a problem with the notice.

(Comment 131) The Bureau of Alcohol, Tobacco and Firearms (BATF) (in the U.S. Department of the Treasury (now TTB) submitted a comment stating that it has no major problem with our proposal to replace the GRAS affirmation petition process with a notification procedure, but that there are two ways in which the proposed rule would impact TTB. First, TTB's wine regulations in 27 CFR 24.250 (Application for use of new treating material or process) require that a proprietor who wishes to use a new

wine treating material submit to TTB an application that includes documentary evidence of FDA's approval of the material under the conditions of its intended use. If we issue a final rule to establish a GRAS notification procedure, TTB would need to amend this requirement to state that TTB needs either evidence of FDA approval or evidence that FDA has been notified of a conclusion of GRAS status and has no questions about that conclusion.

Second, certain alcoholic beverage products require formula approval by TTB due to the ingredients (such as colors, flavors, herbs, and spices) in the products. Currently, TTB requires that these ingredients be approved by FDA before TTB approves the formula. If we issue a final rule to establish a GRAS notification procedure, TTB would still check the ingredients in these formulas before approving the formula, but could accept evidence that FDA has been notified of a conclusion of GRAS status and has no questions about that conclusion.

TTB asks us to include the conditions of use in our response to a GRAS notice so that TTB would know the parameters that FDA evaluated in considering the GRAS notice (*i.e.,* the foods and beverages and the amounts in those foods and beverages). TTB also asks us to publish and update a list of GRAS notices on a frequent basis, and to include the conditions of use that FDA evaluated in this list.

(Response 131) The provisions of this rule are consistent with TTB's requests. The rule specifies that we will make a list of filed GRAS notices, including the information described in § 170.225(c)(2) through (c)(5), readily accessible to the public (see § 170.275(b)(1)). The information the rule specifies will be readily accessible includes the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purpose(s) for which the substance will be used (see § 170.225(c)(4)). The response letters that we issued during the Interim Pilot program described the conditions of use of the notified substance, and we intend to continue describing the conditions of use of the notified substance in letters issued under the final rule.

(Comment 132) Some comments assert that our affirmation of GRAS status established a clear standard that was needed by other Federal agencies to carry out their own regulatory responsibilities. The comments cite BATF (now TTB), FSIS (in USDA), and EPA as examples of such Federal agencies. In general, these comments maintain that the applicable Federal agency must be able to accept our response to a GRAS notice in lieu of a regulation affirming GRAS status. One comment notes that the proposed rule did not explicitly address the impact of the proposed rule on other Federal agencies and urges us to consult with the cited Federal agencies prior to issuing the final rule.

(Response 132) None of the Federal agencies cited by these comments have advised us that the absence of a regulation affirming GRAS status for the use of a food substance would preclude the applicable Agency from carrying out its statutory responsibilities. As discussed in the following paragraphs, we have interacted with each of these agencies as requested.

TTB. As discussed in section IV.B of CFSAN's 2010 experience document (Ref. 18), during the Interim Pilot program CFSAN received and filed several GRAS notices for substances intended for use in alcoholic beverage products. These notices demonstrate that manufacturers of alcoholic beverage products are aware of the GRAS notification procedure and are using GRAS notices as a means to satisfy TTB's regulations. As also discussed in section IV.B of CFSAN's 2010 experience document (Ref. 18), on September 29, 2005, representatives of TTB met with representatives of CFSAN in the offices of CFSAN's Office of Food Additive Safety. At that meeting, representatives of CFSAN described the GRAS notification procedure that was operating under the framework of the proposed rule. CFSAN provided a copy of TTB's comments to these representatives, and none of TTB's representatives expressed any concern about the operation of the program.

FSIS. As discussed in section III.L of CFSAN's 2010 experience document (Ref. 18), during the period 1998 through 2009 more than 25 percent of GRAS notices filed by CFSAN described use of the notified substance in meat, meat food products, or poultry products. During CFSAN's review of these GRAS notices, CFSAN consulted with FSIS regarding the use of the applicable substance. FSIS provided feedback to CFSAN about the use of the notified substance in products regulated by FSIS and requested that CFSAN provide this feedback to the notifier. In 2000, FDA and FSIS formalized this process of inter-agency consultation in a MOU (65 FR 33330, May 23, 2000). Subsequently, FDA and FSIS have amended the MOU to include simultaneous evaluation of substances subject to regulation by USDA under the Egg Products Inspection Act (21 U.S.C. 1033(a)(2)) (Ref. 36). The final rule includes the procedures CFSAN will use when coordinating its evaluation of a GRAS notice with FSIS (see § 170.270).

EPA. CFSAN has discussed the concerns raised by these comments with representatives from EPA (Ref. 50). The representatives from EPA deferred to CFSAN regarding the appropriate process for voluntary interaction between us and the regulated industry with respect to GRAS substances.

E. Impact on International Trade

In the proposed rule, we requested comment on whether the proposed substitution of a GRAS notification procedure for the GRAS affirmation petition process would have any impact on international trade (62 FR 18938 at 18955).

(Comment 133) Comments that responded to this request for comment express the view that whether the proposed substitution of a GRAS notification procedure for the GRAS affirmation petition process would have a positive, neutral, or negative impact on international trade would depend on the nature of our response to a GRAS notice, particularly when we do not question the notifier's basis for a conclusion of GRAS status. The comments explain that the proposed rule could have a positive or neutral impact on international trade if our response is clear and definitive, provides regulatory significance, and is as affirmative as possible, but could have a negative impact on international trade if our response is neutral or vague. One comment expresses the opinion that any impact on international trade would be minimal because JECFA frequently assesses uses of a food ingredient, and foreign regulatory agencies frequently reach a decision to allow uses of a food ingredient, before we complete our rulemaking under the GRAS affirmation petition process.

(Response 133) The ''no questions letters'' we issued during the Interim Pilot program make clear that the notifier (rather than FDA) is responsible for the conclusion of GRAS status, and place our statement that we have no questions about the notifier's conclusion of GRAS status in the contexts of both time and the available data and information (see table 1). These features of the ''no questions letters'' make the letters clear and definitive and provide regulatory significance (*i.e.,* regulatory status), and we intend to retain these features in letters we issue under the final rule. Moreover, the fact that many GRAS notices were submitted by foreign firms demonstrates that foreign firms see value in submitting GRAS notices to us (Ref. 51).

Under the final rule, we will respond to a GRAS notice within 180 days after we file a submission as a GRAS notice, with an option to extend the timeframe by an additional 90 days as needed (see § 170.265(b)(1)). As discussed in Response 123, during the ten year period extending from 1990 through 1999, we completed the rulemaking process for 24 GRAS affirmation petitions, with an average elapsed time of approximately 7.9 years (median elapsed time approximately 6.9 years). Thus, we believe that the GRAS notification procedure will come to closure more quickly than the GRAS affirmation petition process.

F. Audits

In the proposed rule, we stated that it would be prudent for us monitor compliance with the essence of the statutory requirements for GRAS status (*i.e.,* that there is common knowledge among qualified experts that there is reasonable certainty that the substance is not harmful under the conditions of its intended use) and announced that we intended to conduct random audits of data and information maintained by the notifier (62 FR 18938 at 18947). In addition, because the proposed substitution of a GRAS notification procedure for the GRAS affirmation petition process would allow us to direct our resources to priority questions about GRAS status, we might conduct an audit on a broad issue or class of products if the issue or use of a class of products raises important public health issues.

(Comment 134) One comment asks us to renew our commitment to random auditing to ensure that companies maintain proper recordkeeping practices.

(Response 134) As discussed in section IV.C of CFSAN's 2010 experience document (Ref. 18), during the Interim Pilot program, CFSAN did not conduct any random audits of data and information maintained by the notifier. However, CFSAN did not hesitate to ask a notifier to provide certain data or information as an amendment to a GRAS notice. (See also the discussion in section III.C.1 of CFSAN's 2010 experience document regarding amendments to GRAS notices.) In essence, CFSAN used its resources to seek access to data and information on a priority, rather than a random, basis. At this time, we intend to continue directing our resources on a priority basis under the final rule.

(Comment 135) One comment asks us to provide a notifier with the option of converting a GRAS notice to a GRAS affirmation petition if we audit the data supporting a GRAS notice.

(Response 135) As discussed in Response 24 and Response 123, we have eliminated the former GRAS affirmation petition process. Therefore, the administrative process requested by these comments is no longer operative.

(Comment 136) One comment asks us to incorporate two procedures to avoid any uncertainty regarding the results of the audit. First, the comment asks us to provide the notifier with a letter confirming that the audit is completed and we have no basis to question the conclusion of GRAS status if that is the outcome of our audit. Second, the comment asks us to apply any appeal mechanism specified by the rule to circumstances in which we question a conclusion of GRAS status based on an audit.

(Response 136) We decline these requests. If we have no questions about the notifier's conclusion of GRAS status, we would respond with a ''no questions letter'' based on our evaluation of the entire GRAS notice, not based solely on the results of an audit of the data and information maintained by the notifier to support the notifier's GRAS notice. As discussed in Response 108, the rule does not include an appeals process that would be specific to the GRAS notification procedure.

(Comment 137) One comment suggests that our audit examine the same ''quantum of evidence'' as we would review to affirm GRAS status, and asserts that a strong statement of confidence, if not outright affirmation, would be appropriate after successful completion of this type of an indepth review.

(Response 137) The purpose of the audit would be to verify that a notifier maintains the data and information specified in the notice, not to conduct a full scientific evaluation of those data and information (62 FR 18938 at 18947). Therefore, we decline the request to examine the same ''quantum of evidence'' as we would review to affirm GRAS status. Because the purpose of an audit would be to verify compliance with the statutory requirements for GRAS criteria, we disagree our response to a GRAS notice following a favorable audit should result in a ''strong statement of confidence'' rather than a ''no questions letter.'' However, we intend that our response letter would mention any audit that we conduct before responding to a GRAS notice.

G. Lack of an Environmental Assessment

(Comment 138) One comment suggests that a GRAS notice is ideal in circumstances where our evaluation of an environmental assessment, which is required for a food additive petition, precludes timely action by us on a petition.

(Response 138) We advise potential notifiers that the lack of a requirement to submit an environmental component (*e.g.,* an environmental assessment) with a GRAS notice does not eliminate a notifier's responsibility to comply with applicable Federal, State, tribal, and local law or requirements regarding protection of the environment.

H. Substances Affirmed as GRAS With Specific Limitations

(Comment 139) One comment asks us to ''modernize the standard'' in § 184.1(b)(2) to allow expedited review under the notification program of new uses of substances affirmed as GRAS under § 184.1(b)(2). (Section 184.1(b)(2) specifies that if an ingredient is affirmed as GRAS with specific limitation(s), it shall be used in food only within such limitation(s), including the category of food(s), the functional use(s) of the ingredient, and the level(s) of use, and any use of such an ingredient not in full compliance with each such established limitation shall require a food additive regulation.)

(Response 139) We decline the request to amend § 184.1(b) beyond the editorial, clarifying, and conforming changes listed in table 29. The comment provides no basis for us to do so. As discussed during the rulemaking to establish § 184.1(b)(2) (41 CFR 53600 at 53601, December 7, 1976), that regulation does not require that a subsequent use be covered by a food additive regulation even though it may be GRAS. As an alternative to a food additive regulation, the regulation affirming a substance as GRAS with specific limitations on the conditions of use may be amended to cover additional uses that have become GRAS. Importantly, both mechanisms (*i.e.,* food additive regulation and GRAS affirmation regulation) require rulemaking, and the appropriate mechanism for a manufacturer to lawfully use a substance outside the limitations established in a regulation affirming specific uses of the substance as GRAS with specific limitations is to submit a petition to us. A manufacturer may submit a food additive petition asking us to conduct rulemaking that results in a food additive regulation; alternatively, now that the GRAS affirmation petition process is no longer operative, the manufacturer may submit a citizen petition in accordance with § 10.30 asking us to conduct rulemaking that amends the regulation affirming a

substance as GRAS with specific limitations on the conditions of use. (See also Ref. 4.58 to CFSAN's 2010 experience document).

See section III.N.2 of CFSAN's 2010 experience document (Ref. 18) for a discussion of a GRAS affirmation petition to amend a specific regulation that affirmed a substance as GRAS with specific limitations on the conditions of use; we converted that GRAS affirmation petition to a food additive petition and authorized the additional conditions of use in a food additive regulation. We advise persons who wish to petition us to provide for additional uses of substances that have been affirmed as GRAS with specific limitations that under § 10.30(e) we may advise that we are denying the request to initiate rulemaking to amend the GRAS affirmation regulation, but note that we could accommodate the request to conduct rulemaking through the food additive petition process.

XXV. Comments on Substances Intended for Use in Animal Food

A. Issues in the 2010 Notice Specific to Animal Food

In the 2010 notice, we discussed several issues associated with the requirements for a GRAS notice for an intended use in animal food to consider dietary exposure (see table 27). Although we discussed these issues in a section entitled ''Dietary exposure,'' these issues broadly applied to several provisions of the rule (see, *e.g.,* §§ 570.30, 570.225(c)(4), 570.235, 570.245, and 570.250). In the following sections, we discuss how comments on these issues, and associated conforming changes, lead to specific revisions to the regulatory text. See table 28 for the principal changes specific to the proposed animal food rule other than the editorial, clarifying, and conforming changes shown in table 29 and the additional editorial changes associated with the redesignation of the proposed notification procedure (proposed § 570.36) as part 570, subpart E. Table 28 does not include those changes that we made to the proposed requirements when we made an analogous change to the human food regulations in part 170.

TABLE 27—ISSUES IN THE 2010 NOTICE SPECIFIC TO ANIMAL FOOD

Issue No.	Description of our request for comment	Reference
11c	Whether it is necessary to clarify that the GRAS notification procedure is applicable to substances used in both food and drinking water of animals and, if so, whether it would be necessary to clarify this in the provisions of the proposed notification procedure.	75 FR 81536 at 81541.
11d	Whether it is necessary to clarify proposed § 570.36(c)(1)(iii) to explicitly require submission of information about the animal species expected to consume the substance.	75 FR 81536 at 81541.
11e	Whether it is necessary to clarify applicable sections of the proposed rule to explicitly require, for substances intended for use in the food of an animal used to produce human food, the submission of information about both target animal and human safety.	75 FR 81536 at 81541.

TABLE 28—SUMMARY OF PRINCIPAL CHANGES SPECIFIC TO THE PROPOSED ANIMAL FOOD RULE

Regulatory section in the final rule	Change
§ 570.30(a), (b), and (c)	Specify that general recognition of safety is based on data and information that addresses safety for both the target animal and for humans consuming human food derived from food-producing animals.
§ 570.225(c)(4)	Requires you to describe the intended conditions of use of a notified substance in animal food by specifying the levels of use in foods or drinking water.
§ 570.235	In part 3 of your GRAS notice, you must provide data and information about exposure to the target animal and to humans consuming human food derived from food-producing animals.
§ 570.250(a) and (b)	You must explain how the generally available data and information in your notice provide a basis for your view that the notified substance is generally recognized as safe, among qualified experts, under the conditions of its intended use for both the target animal and for humans consuming human food derived from food-producing animals.

B. Criteria for Eligibility for Classification as GRAS for a Substance Intended for Use in Animal Food (§ 570.30)

(Comment 140) Comments that address Issue 11e agree that data and information in a GRAS notice must be sufficient to address safety for both the target animal and for humans consuming human food derived from food-producing animals (see Comment 150 and Comment 151).

(Response 140) We have modified several provisions of the GRAS notification procedure to specify how the notifier must provide data and information to address the safety of the notified substance under the conditions of its intended use for both the target animal and for humans consuming human food derived from food-producing animals (see §§ 570.225(c)(4), 570.235, 570.245, and 570.250). To clarify that the submission requirements reflect the GRAS criteria for the use of a substance in animal food, we also have modified § 570.30(a), (b), and (c) to specify that general recognition of safety is based on data and information that addresses safety for both the target animal and for humans consuming human food derived from food-producing animals. See the regulatory text of § 570.30. See also Response 141 regarding the definition of common use in food in § 570.3(f).

(Comment 141) One comment notes that the proposed human food regulations, but not the proposed animal food regulations, include specific criteria for eligibility for classification as GRAS through experience based on common use in food prior to 1958 when that use occurred exclusively or primarily outside the United States (see § 170.30(c)(2)). This comment asks us to maintain parallel criteria for eligibility for classification as GRAS through experience based on common use in food in the human food regulations and the animal food regulations by amending § 570.30(c) of the animal food regulations to include a provision analogous to § 170.30(c)(2).

(Response 141) We are amending § 570.30(c) to include a provision analogous to § 170.30(c)(2). See the regulatory text of § 570.30(c)(1) and (2). For consistency with the clarifying

amendment to the general criteria in § 570.30(a), we also are revising § 570.30(c) to clarify that general recognition of safety through experience based on common use in food shall address safety for both the target animal and for humans consuming human food derived from food-producing animals. For consistency with the clarifying amendment to the general criteria in § 570.30(a), we also are revising the definition of common use in food to mean a substantial history of consumption of a substance by a significant number of animals of the species to which the substance is intended to be fed (and, for food-producing animals fed with such substance, also means a substantial history of consumption by humans consuming human foods derived from those food-producing animals), prior to January 1, 1958 (see § 570.3(f) and table 29).

C. Part 1 of a GRAS Notice for a Substance Intended for Use in Animal Food: Name of the Notified Substance (§ 570.225(c)(3))

As shown in table 6, in the 2010 notice we asked for comment on whether to require that the GRAS notice include the name of the notified substance, using an appropriately descriptive term, instead of the ''common or usual name'' of the notified substance (Issue 7). The final rule requires that Part 1 of a GRAS notice for an intended use of a notified substance in animal food include the name of the notified substance, using an appropriately descriptive term (§ 570.225(c)(3)). The appropriately descriptive term may be the same as the common or usual name of the substance. You may consult with CVM's staff in operating divisions that address the labeling requirements of the FD&C Act, currently CVM's Division of Animal Feeds, regarding any common or usual name for a substance used in animal food. In addition, for substances used in animal food, the Association of American Feed Control Officials (AAFCO) annually publishes its Official Publication, a handbook which contains, among other things, Official Feed Terms, which define many of the terms commonly used in the animal food manufacturing industry. It also contains Official and Tentative Definitions of Feed Ingredients, a set of definitions for ingredients commonly used in animal food. Under CVM's Compliance Policy Guide CPG 665.100 (Common or Usual Names for Animal Feed Ingredients), the definitions, as they appear in the AAFCO Official Publication, are generally regarded as constituting the common or usual name for animal food ingredients, including pet food (Ref. 52).

D. Part 1 of a GRAS Notice for a Substance Intended for Use in Animal Food: Intended Conditions of Use (§ 570.225(c)(4))

(Comment 142) One comment asks us to require that a notifier specify whether the intended use of the notified substance is in food or in drinking water. Another comment asks CVM to accept the anticipated consumption levels by animals that are based upon general formulation principles that consider the availability of contemporary feedstuffs.

(Response 142) The final requirements for Part 1 of a GRAS notice require you to describe the intended conditions of use of a notified substance in animal food by stating whether the substance will be added to food (including drinking water) for animals in which the substance will be used, and by identifying the foods to which it will be added and the levels of use in such foods (see § 570.225(c)(4)). In describing the levels of use of the notified substance, you may base the levels of use upon general formulation principles that consider the availability of contemporary feedstuffs. See also Response 148 regarding the calculation of target animal exposure.

(Comment 143) Some comments ask us to specifically require submission of information about the animal species expected to consume the substance. One comment states that specifying the target animal is as important as specifying whether the substance would be consumed by humans in human food derived from the animal. Another comment suggests that requiring submission of information about the animal that would consume the substance would avoid the unnecessary delays associated with CVM's questions that result in an amendment to the notice with information about the animal species expected to consume the substance.

(Response 143) The final requirements for Part 1 of a GRAS notice require you to describe the intended conditions of use of a notified substance in animal food, including the animal species for which the foods are intended. In addition, the final requirements for Part 1 of a GRAS notice specify that in describing the intended conditions of use of a notified substance in animal food, you must, when appropriate, describe any ''subpopulation'' expected to consume the notified substance; the life stage of an animal is an example of what we mean by ''subpopulation.'' The physical, physiologic, and absorption/distribution/metabolism/elimination characteristics of a given animal species may vary based on life stages within the same animal species. A substance that is safe for use in an animal species at one stage of life may not be safe for use in the same animal species at a different stage of life. See also Response 51.

E. Part 2 of a GRAS Notice for a Substance Intended for Use in Animal Food: Data and Information Bearing on the Physical or Other Technical Effect of the Notified Substance (§ 570.230(d))

(Comment 144) Several comments discuss CVM's practice, during the Interim Pilot program, of asking a notifier to provide data or information demonstrating the effectiveness, or utility, of the substance. Some comments ask us to limit the notification procedure to the information necessary to conduct an appropriate safety assessment, without submission of additional data and information to demonstrate the technical effect of the substance within animal food in cases where the technical effect has no impact on safety. Some comments agree that the intended conditions of use of the notified substance in animal food must be described and supported in the notice, but assert that the need for utility data generated from target animal feeding studies is inappropriate and unnecessary because the pivotal issue is whether the ingredient is safe to feed to animals.

(Response 144) We have added a requirement for Part 2 of a GRAS notice to include relevant data and information bearing on the physical or other technical effect the notified substance is intended to produce, including the quantity of the notified substance required to produce such effect, when necessary to demonstrate safety (see § 570.230(d)). We agree that data and information bearing on the physical or other technical effect the notified substance is intended to produce are only necessary when they bear on safety. This relationship to safety is consistent with the requirements of the FD&C Act for a petition to establish the safety of a food additive (see section 409(b)(2)(C) of the FD&C Act).

The physical or other technical effects of substances added to animal food fall into two main categories: (1) Substances fed for a nutritive effect in the animal (*e.g.,* providing one or more nutrients or other nutritive effect); and (2) substances that have technical effects in the food (*e.g.,* anti-caking agents, binders, emulsifiers, enzymes, mixing

aids, preservatives, processing aids, stabilizers, and substances added for aroma, flavor, or other technical effects) rather than nutritive effects in the animal. As discussed in the following paragraphs, a substance added for either a nutritive effect or for a technical effect in animal food can have an impact on safety for the target animal.

Nutritive effect in the animal. Data and information bearing on the nutritive effect of a substance may be necessary to demonstrate safety because animals (*e.g.,* food-producing animals, companion animals) typically are fed the same diet formula for long periods of their life. These diets are formulated to supply all of the animal's daily nutrient needs for a specific life stage (*e.g.,* growth, reproduction, adult maintenance). The diet must provide appropriate amounts of all nutrients the animal requires in a form that the animal can use and consume daily; otherwise, a nutrient deficiency or toxicity can result, causing adverse effects to animal health, including poor growth, excessive weight loss, organ system failures, and death. Under these constraints of how animals are fed, a substance intended to provide one or more nutrients becomes unsafe if the nutrients are, in fact, not provided in a form usable by the animals consuming the diet.

The typical approach to support the nutritive effect of a substance intended for use in animal food is to combine generally available and accepted data and information about the general function of the substance with animal feeding studies demonstrating that the substance acts as intended. When an appropriate animal feeding study (*i.e.,* an animal feeding study that is relevant, properly designed, and well-controlled) is already generally available (*e.g.,* in the peer-reviewed scientific literature), it can be possible to support the nutritive effect of a substance without conducting a new study. If an appropriate animal feeding study is not already generally available, an animal feeding study specifically conducted to support the nutritive effect would ordinarily be published and, as discussed in Response 19, there would be a time gap between the publication of the study and the use of the published study to support a conclusion of GRAS status. (As discussed in Response 9, unpublished studies can be used to corroboratively support the intended nutritive effect of the substance under the conditions of its intended use.) In addition, for any animal feeding study a factor to be considered is whether data and information obtained from a feeding study conducted in one animal species (or in one stage of life of an animal species) can be used to support safety in another animal species (or in a different stage of life in the same animal species). See Response 145 for a discussion of when data and information that are obtained from an animal study and bear on the nutritive effect of a substance could be extrapolated from one animal species to another animal species, or to a different stage of life of the same animal species. In the following paragraphs, we provide examples of when data and information bearing on the nutritive effect of a substance intended for use in animal food could be established through the use of generally available and accepted data and information, or likely would need to be established through an animal feeding study that specifically supports the nutritive effect of the substance under the conditions of its intended use.

For some types of substances, generally available and accepted data and information about the function of a substance may be adequate to support the nutritive effect of the substance without also relying on an animal feeding study. For example, generally available and accepted data and information about the function of fat and carbohydrates as sources of dietary energy often can be used for substances providing fat intended as a source of dietary energy (rather than as a source of essential fatty acids) and for substances providing carbohydrates intended as a source of dietary energy. Likewise, generally available and accepted data and information about the nutritive content of human food can provide support for the nutritive effect of unsalable human food products (such as bruised produce) being collected for animal food use for their nutritional content rather than entering landfills or being incinerated.

For other types of substances, an animal feeding study (whether previously published or newly conducted) is the norm to support the nutritive effect of the substance. For example, for an ingredient that is intended to supply an essential mineral (such as phosphorus or zinc), generally available data and information can provide support that the mineral is an essential nutrient for the animal, but the bioavailability of the mineral in the ingredient that would be added to animal food generally needs to be determined in an animal feeding study conducted with that specific ingredient, because data regarding the amount of the mineral that is added to the feed in the ingredient (or that can be detected analytically in the feed or in the ingredient) would not provide evidence that the mineral is in a form that is available to the animal. However, for an ingredient that is intended to provide an essential amino acid, the need for an animal feeding study can depend on the form and composition of the ingredient. For example, it can be possible to rely on published literature to establish that a crystalline amino acid will be bioavailable to an animal (and, thus, functional). However, if a complex matrix, such as a biomass composed of microbial cells or a processed oilseed meal, is intended to be a source of amino acids, an animal feeding study generally would be needed to provide evidence that the bioavailability of the amino acids has not been adversely impacted by the other substances present in the complex matrix.

Technical effect in the food (rather than nutritive effect in the animal). As with a substance intended to provide a nutritive effect in the animal, data and information bearing on a substance's technical effect in the food (*e.g.,* substances such as anti-caking agents, binders, emulsifiers, enzymes, mixing aids, preservatives, processing aids, stabilizers, and substances added for aroma, flavor or other technical effects) may be necessary to demonstrate safety because of the physical form and properties of animal diets. Although generally available and accepted data and information can provide evidence of a technical effect in the food, it is common for studies to be conducted with the animal food to demonstrate the intended technical effect. Depending on the intended technical effect, an animal feeding study (whether previously published or newly conducted) may be also needed to demonstrate the intended technical effect of the substance. In the following paragraphs, we provide examples of when animal feeding studies may be needed to support the intended technical effect of the substance. We also provide examples of when an intended technical effect in animal food could be established through the use of generally available and accepted data and information about the technical effect and the studies conducted with the intended animal food matrix. As with a substance intended to provide a nutritive effect in the animal, when an appropriate study, which may be an animal feeding study, is already generally available (*e.g.,* in the peer-reviewed scientific literature), it can be possible to support the technical effect of a substance in the food without conducting a new study. If an appropriate study is not already generally available, a study conducted

to support the technical effect in the food would ordinarily be published and, as discussed in Response 19, there would be a time gap between the publication of the study and the use of the published study to support a conclusion of GRAS status.

Enzymes are often added to animal food to alter the bioavailability of nutrients already in the food. For example, it is well known that the enzyme phytase increases the bioavailability to animals of the phosphorus present in grain (Ref. 53), and substances that provide phytase activity are often added to diets for poultry and swine. Poultry and swine diets are typically formulated with the minimal amount of phosphorus. If the phytase enzyme does not carry out the effect of improving phosphorus availability to the animal as intended, the consequence will be a diet that is deficient in phosphorus and therefore results in adverse impacts on animal health in the form of decreased growth, increased orthopedic disease (*e.g.,* rickets), and suffering animals (Ref. 54). As another example, protease enzymes can be added to an animal food to affect the digestibility of proteins in the food (Ref. 55). Both animal feeding studies and stability studies (to assess the stability of the enzyme in the food and, thus, its ability to perform its intended technical effect) are the norm when enzymes are added to animal food. However, when the function of an enzyme in animal food is well known, it is also common to use generally available and accepted data and information about the function of the enzyme in combination with animal feeding studies and stability studies to support the function of the enzyme (see section IV in CVM's experience document (Ref. 20)).

Substances such as binders, lubricants, and pelleting agents are added to animal food that will be fed as pellets. In some cases, such substances are added to ensure that the pellet retains its desired form and that the individual ingredients remain agglomerated, making it more difficult for an animal to select only those ingredients it prefers. In aquaculture foods, such substances are added to prevent the pellet from dissolving or prevent the nutrients from leaching out of the pellet. Depending on the circumstances, either technical effect studies conducted with the animal food, or generally available and accepted data and information about the function of the substance, can be used to support the intended technical effect, such as that of a binder, lubricant, or pelleting agent, etc., when added to animal food.

Flavors are added to animal food for certain species, generally for specific life stages of that species. For example, flavors can be added to animal food intended for consumption by piglets being transitioned from a milk-based diet to a commercial growth diet to increase consumption of the commercial growth diet. Flavors also are added to commercial animal food intended for aquaculture to attract newly hatched fish (fish fry) to the commercial food when the commercial food does not resemble the food that fish fry would consume in nature. If the fish fry are not attracted to the commercial food, the fish fry can starve to death. Animal feeding studies are the norm to support the function of the substance as a flavor when added to animal food.

Substances such as emulsifiers and stabilizers are added to animal food to ensure that an animal consumes all of the ingredients in the correct proportions in order to meet its nutritional needs. Inconsistent nutrient content and delivery of a diet to the animal can cause either nutrient deficiency diseases, or toxicities. For example, liquid cattle foods are often available to the animal at all times and cattle simply lick the feeding device to obtain the food. If the minerals present in the liquid fall out of suspension and settle to the bottom, the first animals to access the feeder will consume lower nutrient levels than expected, while those animals that access the feeder later and consume the bottommost material may be at risk of toxicity due to higher nutrient levels. For dry ingredients, the ingredients in the formulated diet must be uniformly dispersed and mixed, remain mixed during handling, and be physically stable as a formulated animal diet is moved through augers and conveyors, and transported in bulk in trucks, which can result in the loss of nutrients through sifting or ''unmixing.'' These effects are assessed on the diet itself through appropriate studies.

(Comment 145) One comment asks us to accept reasonable arguments as to the worst-case exposures (inclusion levels) if the substance or class of substances has well-established use patterns rather than require utility data to support the intended nutritional effect. This comment also asks us to be flexible when utility data are warranted to support an entirely new use in animal feeds when utility data from one representative species would be sufficient to address utility in the target animal.

(Response 145) When animal feeding studies are necessary to provide data and information bearing on the nutritive effects of a substance intended for use in animal food, the potential to extrapolate from the conclusions of a feeding study conducted in one animal species to another animal species depends on the similarities of their digestive systems, physiology, and diets. For example, when a bioavailability study for selenium present in selenium yeast is conducted in cattle (which have a fermentative digestive tract), it can be possible to extrapolate the conclusions of that bioavailability study to other animal species that have fermentative digestive tracts. However, when a bioavailability study for copper is conducted in a ruminant animal species, it may not be appropriate to extrapolate the conclusions of that bioavailability study to sheep, even though sheep are ruminants, because sheep physiology is such that sheep are much more sensitive to copper toxicity than other ruminant species. In addition, when a bioavailability study for a nutrient is conducted in animals other than fish, it may not be possible to extrapolate the conclusions of that bioavailability study to aquaculture-fed fish, because aquaculture diets that are consumed in the water present special challenges, particularly for slow-feeding or bottom-feeding aquaculture species, where the diet pellet must retain its form and nutrient content until the pellet is consumed. For example, it is possible for nutrients that are soluble in water to dissolve out of the pellet before consumption, preventing the aquaculture animal from accessing all the required nutrients.

See Response 144 for a discussion of circumstances where generally available and accepted data and information can be used to provide evidence bearing on the nutritive effects of a substance intended for use in animal food (*e.g.,* for substances providing fat intended as a source of dietary energy, for substances providing carbohydrates intended as a source of dietary energy, for unsalable human food products, and when a crystalline amino acid is added to animal food). See also Response 150 for additional discussion of limitations on the use of generally available and accepted data and information, such as a weight of evidence approach, for the extrapolation of available data and information from an animal species other than the target animal.

Regardless of whether the intended use of the notified substance is to provide nutritive value or technical effect, any person who concludes that the available data and information regarding the safety of a notified substance under the conditions of its intended use satisfy GRAS criteria must

have a basis for the conclusion of GRAS status, irrespective of whether that person notifies us of that conclusion in a GRAS notice. If you submit your conclusion of GRAS status to FDA, you must explain how the data and information in your GRAS notice provide the basis for your conclusion, *e.g.,* in Part 2 of the GRAS notice (where you would describe the applicable data and information), in the narrative in Part 6 of your GRAS notice, or in both Parts 2 and 6 of your GRAS notice. We would then evaluate whether the data, information, and narrative in your GRAS notice support your conclusion. When data and information bearing on the physical or other technical effect of the notified substance are necessary to support safety, we could conclude that a GRAS notice that does not discuss such data and information is incomplete, and either contact a notifier to request an amendment discussing such data and information, or issue an insufficient basis letter.

(Comment 146) One comment asserts that a requirement for proof of utility, with subsequent publication of utility data, is unnecessary, and that a requirement for utility data to be documented by means of a peer-reviewed publication would burden the industry with additional cost, not only to conduct the studies but also to prepare the manuscript and have it accepted for publication. This comment also asserts that finding a journal willing to publish such germane studies may be challenging because the manuscript may be viewed as serving the manufacturer's interest rather than providing any new scientific information. As alternatives to publication of a target animal feeding study, this comment suggests means such as documenting the chemical nature of the substance in relation to same (or similar) substance with ample public information, and placing unpublished studies conducted by the notifier in the context of published literature about the use of the substance or related substances. This comment also asserts that CVM and industry resources could be better utilized to demonstrate the safety of the intended use of the substance with a focus on establishing the worst-case exposure and relating it to available safety information to establish a margin of safety.

(Response 146) See Response 15, in which we respond to comments asserting it can be difficult to publish data and information that do not raise an issue of concern. Consistent with CFSAN's experience during the Interim Pilot program, we believe that some journals directed to food safety would be willing to publish data and information bearing on the physical or other technical effect the notified substance is intended to produce when those data and information are necessary to demonstrate safety (see section III.A.1 of CFSAN's 2010 experience document (Ref. 18)).

See also Response 144 for a discussion of circumstances where generally available and accepted data and information can be used to provide evidence bearing on the nutritive effects of a substance intended for use in animal food. There may be situations where sufficient generally available and accepted data and information on exposure to the substance or class of substances can satisfy GRAS criteria without publication of specific data and information bearing on the physical or other technical effect the notified substance is intended to produce. For example, as discussed in section IV of CVM's experience document during the Interim Pilot program CVM responded with a ''no questions letter'' when the use of published information for technical effects such as nutrient, enzyme, and component of a defoamer was used, in whole or in part, to support such technical effects (Ref. 20). As discussed in Response 12, GRAS status may be corroborated by unpublished scientific data, information, or methods, and there may be some unpublished scientific data, information, or methods regarding the safety of a use of a food substance. As discussed in Response 8, the criteria for GRAS status through scientific procedures provide for the application of ''generally available and accepted'' scientific data, information, or methods, which ''ordinarily'' are published and, thus, provide flexibility for supporting a conclusion of GRAS status through the application of scientific data, information, or methods that are generally available through a mechanism other than publication in a peer-reviewed scientific journal.

See the discussion in Response 150 regarding the evaluation of safety studies, including the applicability of worst-case exposure on a case-by-case basis.

F. Part 3 of a GRAS Notice for a Substance Intended for Use in Animal Food: Target Animal and Human Exposures (§ 570.235)

1. Substances Intended for Use in Food or Drinking Water for Animals

(Comment 147) Comments that address Issue 11c support clarifying that the GRAS notification procedure is applicable to substances used in both food and drinking water of animals.

(Response 147) The final requirements for Part 3 of a GRAS notice specify that ''animal food'' includes ''drinking water.'' See also Response 142.

2. Data and Information About the Dietary Exposure for the Target Animal

(Comment 148) One comment states that exposure information can usually be obtained from published data sources and that if a worst-case exposure cannot be established without new data, then data for one representative animal species are sufficient, especially if the selected species represents a worst-case scenario. As an example, the comment suggests that data from one representative poultry species would be sufficient to address the conditions of use of a notified substance intended for poultry. As noted in Comment 142, another comment asks CVM to accept the anticipated consumption levels by animals that are based upon general formulation principles that consider the availability of contemporary feedstuffs.

(Response 148) See the regulatory text of § 570.235(a) for the requirements for what you must provide in Part 3 of a GRAS notice regarding exposure to the target animal. The regulatory text addressing the types of exposure to the target animal parallels the regulatory text for dietary exposure to a notified substance in the human food regulations (see § 170.235). As noted in Response 142, you may base the levels of use upon general formulation principles that consider the availability of contemporary feedstuffs. We agree that exposure information may be available from published data sources. If exposure cannot be established without new data, then data for one representative animal species may be sufficient if the selected species represents a worst-case scenario.

(Comment 149) One comment asks that any restatement of the regulatory text regarding dietary exposure consider how to use the word ''consumer,'' because ''consumers'' are humans for the purpose of part 170 but are ''animals'' for the purpose of part 570.

(Response 149) To reduce the potential for confusion, the final requirements for part 3 of a GRAS notice for a substance intended for use in animal food do not use the term ''consumer.''

G. Data and Information in a GRAS Notice About Safety for the Target Animal (§ 570.250)

(Comment 150) Comments that address Issue 11e agree that data and information in a GRAS notice must be

sufficient to address safety for the target animal. However, most of these comments express concern about the standard for demonstrating safety to the target animal, specifically whether safety must be established through feeding studies specific to the target animal or could be extrapolated from data and information regarding species other than the target animal. Although one comment asserts that a notifier must submit evidence that the substance is safe for all the species in question if a substance is expected to be consumed by different animal species, other comments emphasize that safety could be established through either feeding studies in the target animal or through extrapolation of data obtained from species other than the target animal. Some comments suggest that the rule require a clear and concise written explanation of how studies in non-target species relate to the target animal rather than require safety data in the target animal species.

One comment disagrees that the GRAS notification procedure should establish any absolute requirement for data addressing safety for the target species. This comment asserts that CVM should not require species-specific data for all substances and species covered by the intended use of the notified substance because recognized scientific procedures, such as a weight of evidence approach, allow for the extrapolation of data and that these types of scientific procedures can be applied to notified substances. This comment also asserts that a CVM requirement for safety data in the target animal, rather than a written explanation of how studies in non-target species relate to the target animal, cannot be scientifically justified and will put the animal feed industry at a disadvantage for obtaining recognition of new GRAS substances, and that the additional cost and time will stifle innovation and reduce growth in the U.S. feed industry and animal agriculture.

(Response 150) Whether species-specific data and information (such as feeding studies) are necessary to satisfy GRAS criteria depends on the intended use of the notified substance. We recognize that there may be situations where scientific procedures, such as a weight of evidence approach, allow for the extrapolation of available data and information from an animal species other than the target animal. For example, CVM had no questions regarding an enzyme preparation intended for use in food for turkeys, broiler chickens, and laying hens, when the feeding studies used to support target animal safety were conducted only on broiler chickens (Ref. 20). In such cases, you would explain the relevance of the available data to the target species in the narrative required in Part 6 of a GRAS notice rather than describe species-specific data and information.

However, extrapolating data from one animal species to another is not always appropriate because a substance that is safe for use in one animal species may not be safe for use in another species or in the same species at a different stage of life. For example, a substance that is safe for use in a species that is a ruminant animal (*e.g.,* cattle) may not be safe for use in a species considered a monogastric animal (*e.g.,* swine) because of the difference in their digestive systems and different nutrient requirements. For example, in ruminant animals, non-protein nitrogen compounds (*e.g.,* urea and biuret) release ammonia, which is then metabolized by rumen microorganisms into microbial proteins. These microbial proteins are a useful source of protein to ruminant animals. However, in monogastric animals, the liberated ammonia from non-protein nitrogen compounds is absorbed directly by the animal, resulting in adverse toxicological events, and possibly death. Even within the same species of animal, or for different species in the same class of animals (*e.g.,* chicken, duck, turkey), extrapolating safety data may not be appropriate. For example, a substance that is safe for laying hens may not be safe for use in broilers because of the different nutrient requirements, such as the higher calcium level in a laying hen diet (which is intended to meet the nutrient demand for egg production). If that high level of calcium is consumed by broiler chickens, the potential calcification of soft tissue such as that of kidneys could become detrimental to the broiler chickens. Likewise, a substance that is safe for chickens may not be safe for ducks or turkeys because the nutrient requirements for different species of poultry vary widely. Feeding a diet intended for one species of poultry to another species could cause nutrient imbalances, deficiencies, or excesses, which could have adverse consequences ranging from loss of production to damages to tissues and organs and even to death. When extrapolating data and information from another animal species is not appropriate, in Part 6 of your GRAS notice you would discuss data and information developed specifically for the target animal, or for the stage of life in the same animal species, rather than explain how you extrapolated available data and information from an animal species other than the target animal, or how you extrapolated available data and information from the same animal species to a different life stage of that animal species.

Any person who concludes that the available data and information regarding the safety of a notified substance under the conditions of its intended use satisfy GRAS criteria must have a basis for the conclusion of GRAS status, regardless of whether that person notifies us of that conclusion in a GRAS notice. A resource that may help determine when it could be appropriate to extrapolate species-specific data and information from one animal species to another animal species is our guidance entitled ''Guidance for Industry: Recommendations for Preparation and Submission of Animal Food Additive Petitions'' (# 221) (June 2015) (Ref. 56). Section G.2 of that guidance (on target animal safety) recommends that target animal safety studies be conducted using the life stage and animal species for which the food additive will be marketed. In cases where the food additive is intended for multiple animal species or life stages, the food additive should be tested in the most sensitive life stage and/or species. The guidance recommends using current scientific literature to identify the most sensitive life stage and/or species. As with guidance documents prepared by CFSAN, CVM's scientific recommendations in a guidance directed to food additives can be applied to the evaluation of whether a substance is GRAS under the conditions of its intended use (see Response 66).

Another resource is a book entitled ''Safety of Dietary Supplements for Horses, Dogs, and Cats'' by the National Research Council (Ref. 57), which identifies five factors to consider when selecting appropriate surrogates for horses, dogs and cats. In addition, it advises considering nutritional, metabolic, pharmacokinetic, and natural dietary patterns when selecting appropriate animal model species. Although the material is directed to only three target animals, some aspects of its approach can be generalized.

If you submit your conclusion of GRAS status to FDA, you must explain how the data and information in your GRAS notice provide the basis for your conclusion; we would then evaluate whether the data, information, and narrative in your GRAS notice support your conclusion.

H. Data and Information in a GRAS Notice About the Safety for Humans Consuming Human Food Derived From a Food-Producing Animal (§§ 570.235 and 570.250)

(Comment 151) Some comments support clarifying the rule to explicitly require the submission of information about safety for both the target animal and for humans consuming human food derived from food-producing animals. One comment states that the safety and wholesomeness of food given to animals that eventually end up in human food must be held to the same standard as for a substance intended for use in human food. Another comment asks us to specify that the submission of data and information about both target animal and human safety is required when such data and information are developed for food-producing animals.

One comment states that it is the responsibility of the notifier to determine the extent of the safety assessment of a substance intended for use in the food of a food-producing animal. This comment asserts that there is no need to set explicit standards for addressing both target animal and human food safety in applicable sections of the rule, because whether new data, such as tissue residue data, would be warranted would be determined through application of general scientific principles from the fields of animal nutrition and metabolism.

Another comment asserts that neither human feeding studies nor tissue residue accumulation data should be required when available scientific information can be used to draw conclusions using a weight of the evidence approach, as CFSAN does for human food substances. This comment asserts that CVM must clarify what data need to be provided regarding safety for humans consuming human food derived from food-producing animals before industry could agree to the requirement.

(Response 151) We are clarifying the requirement to address safety for humans consuming human food derived from food-producing animals in Parts 3 and 6 of a GRAS notice.

In the requirements for Part 3 of a GRAS notice for a substance intended for use in animal food, we have modified the title of the regulatory text to specify that Part 3 addresses exposures to both the target animal and to humans consuming human food derived from food-producing animals (see § 570.235). When the intended use of the notified substance is in food for food-producing animals, you must provide: (1) The potential quantities of any residues that humans may be exposed to in edible animal tissues; and (2) the data and information you rely on to establish the potential quantities of such residues (see § 570.235(b)). These requirements parallel the requirements for target animal exposure, but are directed to the quantity of potential residues of the notified substance, and of any other substance that is expected to be formed in or on the animal food because of the use of the notified substance, and those residues from any other substances present with the notified substance, whether naturally, due to its manufacture (*e.g.,* contaminants or by-products), or produced as a metabolite in edible animal tissues when the notified substance is consumed by a food-producing animal. It is well established that substances consumed by food-producing animals, and substances such as metabolites produced by a food-producing animal, can accumulate in edible animal tissues and have an adverse impact on public health. For example, aflatoxin M1 is a metabolite of aflatoxin B1 that is produced during normal biological processes of animals ingesting the toxin (*e.g.,* from food contaminated with aflatoxin B1) and has been shown to cause liver cancer in certain animals (Ref. 58). As another example, there can be human food safety concerns about the level of selenium in animal tissues when food-producing animals consume large amounts of a substance that contains selenium in their diets.

We agree that the specific data and information that are necessary to determine the safety for humans consuming human food derived from a food-producing animal would be determined through the application of general scientific principles from the fields of animal nutrition and metabolism and that it is the notifier's responsibility to determine what those specific data and information are. Therefore, we have modified the requirements for the narrative in Part 6 of a GRAS notice to clarify that the narrative must address the safety for both the target animal and for humans consuming human food derived from food-producing animals (see § 570.250(a)(1) and (b)).

I. Filing Decision, Opportunity for a Notifier To Submit an Amendment, and Asking Us To Cease To Evaluate a GRAS Notice for a Substance Intended for Use in Animal Food (§§ 570.260 and 570.265)

(Comment 152) Some comments express concern about differences in how CFSAN and CVM administered GRAS notices during the Interim Pilot program. Some comments describe CFSAN's practice of using conference calls to obtain a clarification or additional information, with a reasonable period of time for the notifier to provide the clarification or additional information. These comments assert that CVM's practice is different from CFSAN's practice because CVM does not contact a notifier to discuss CVM's questions after a submission has been accepted for filing. One comment asserts that CVM has informally indicated that once a GRAS notice is accepted for filing, there will be no further communication with the notifier and the GRAS notice will be judged solely on what was accepted for filing. This comment further asserts that such a process is unreasonable because the error or omission may be trivial and/or easily remedied. This comment also asserts that allowing informal contacts (including telephone, email, and fax) to address minor issues would be consistent with how FDA has handled a wide range of submissions that require review. Another comment asserts that CVM's practice of not contacting the notifier is a major concern for the industry and that CVM's reviewers may have questions that could be easily answered by the notifier, if contacted.

Some comments ask CVM to engage in the same informal practice as CFSAN, with respect to contacting the notifier and allowing remedial action, if such action may be completed in a reasonable period of time. Some comments ask the Centers to establish a uniform system of contact and communication after a submission (and/or agreeing to evaluate an amendment to a GRAS notice) to prevent delays or other inefficiencies over issues that could easily be clarified and resolved. Some comments note that uniformity between CFSAN and CVM in the submission and handling of requests to cease to evaluate a GRAS notice is of great importance in maintaining transparency and efficiency in the GRAS notification procedure.

(Response 152) The regulatory text governing what CVM will do with a GRAS notice (§ 570.265) is the same as the regulatory text governing what CFSAN will do with a GRAS notice (§ 170.265). In addition, the regulatory text that provides for a notifier who submits a GRAS notice to CVM to submit a timely amendment to a filed GRAS notice, and to ask us to cease to evaluate a GRAS notice (§ 570.260), is the same as the regulatory text that provides for a notifier who submits a GRAS notice to CFSAN to submit a timely amendment to a filed GRAS

notice, and to ask us to cease to evaluate a GRAS notice (§ 170.260).

We disagree that CVM did not contact notifiers during the Interim Pilot program. As shown in table 1 in CVM's experience document (Ref. 20), CVM contacted the notifier regarding 9 of 18 GRAS notices during its evaluation process. CVM issued ''no questions letters'' to seven of these nine notices after the notifiers provided clarifying amendments.

Moving forward under the final rule, CVM intends to consider the same factors that CFSAN considers regarding whether to file a submission as a GRAS notice (see Response 85), the purpose of contacting a notifier (including whether to provide an opportunity for a notifier to ask us to cease to evaluate a GRAS notice) (see Response 80), and the transparency of the reasons for a ''cease to evaluate letter'' (see Response 81). Because our factors regarding the purpose of contacting a notifier, and the provisions that provide an opportunity for a notifier to submit an amendment, consider whether an amendment is (or could be) timely, the final rule does, as requested by the comments, consider whether an amendment could be prepared and submitted in a reasonable period of time. Importantly, as discussed in Response 101, the role of an amendment is to clarify questions that we have about your conclusion of GRAS status, rather than to substantively amend the notice. Whether we will evaluate an amendment to a GRAS notice before responding to the notice is a matter that we will consider on a case-by-case basis.

J. Opportunity for a Notifier To Submit a Supplement to a GRAS Notice for a Substance Intended for Use in Animal Food (§ 570.280)

(Comment 153) One comment asks CVM to adopt CFSAN's approach of allowing a notifier to submit information to a GRAS notice after FDA responds to the notice.

(Response 153) The rule provides that, if circumstances warrant, a notifier who submits a GRAS notice to CVM may submit a supplement to a filed GRAS notice after we respond to your notice by letter or cease to evaluate your notice (§ 570.280). As discussed in section VI of CVM's experience document (Ref. 20), as of December 31, 2015, CVM had not received any supplements to a GRAS notice.

K. GRAS Affirmation Petitions for Substances Used in Animal Food

CVM has no pending GRAS affirmation petitions and, thus, the final animal food regulations do not include provisions for the disposition of pending GRAS affirmation petitions for substances used in animal food.

XXVI. Editorial, Clarifying, and Conforming Amendments

The revised regulatory text includes several changes that we have made to make the requirements more clear and improve readability. The revised regulatory text also includes several conforming changes that we have made when a change to one provision affects other provisions. We summarize the principal editorial and conforming changes in table 29.

TABLE 29—PRINCIPAL EDITORIAL, CLARIFYING, AND CONFORMING CHANGES

Designation in the regulatory text (§)	Revision	Explanation
§ 20.100(c)(46)	Add new paragraph (c)(46) to clarify applicability of § 20.100 (the handling of FDA records upon a request for public disclosure) to GRAS notices in §§ 170.36(h) and 570.36(h).	Conforming change in light of the new GRAS notification procedures established in §§ 170.36 and 570.36.
§ 25.20(k)	• Replace ''Affirmation of a food substance as GRAS for humans or animals, on FDA's initiative or in response to a petition, under parts 182, 184, 186, or 582 of this chapter'' with ''Establishment or amendment of a regulation for a food substance as GRAS under the conditions of its intended use for humans or animals under parts 182, 184, 186, 582, or 584 of this chapter''. • Replace ''unless categorically excluded in § 25.32(f), (k), or (r)'' with ''unless categorically excluded in § 25.32(f), (i), (j), (k), or (r)''.	• Conforming change in light of the deletion of the GRAS affirmation petition process. • Correct the list of applicable categorical exclusions that apply to include the categorical exclusions listed in § 25.32(i) and (j).
§ 25.32(f)	Replace ''Affirmation of a food substance as GRAS for humans or animals on FDA's initiative or in response to a petition, under parts 182, 184, 186, or 582 of this chapter'' with ''Establishment or amendment of a regulation for a food substance as GRAS under the conditions of its intended use for humans or animals under parts 182, 184, 186, 582, or 584 of this chapter''.	• Clarify that GRAS affirmation applies to the intended conditions of use of a substance, not the substance itself. • Conforming change in light of the deletion of the GRAS affirmation petition process.
§ 25.32 (i), (j), (k), and (r)	Replace ''or GRAS affirmation petition'' with ''establishment or amendment of a regulation for a food substance as GRAS under the conditions of its intended use for humans or animals under parts 182, 184, 186, 582, or 584 of this chapter''.	• Clarify that GRAS affirmation applies to the intended conditions of use of a substance, not the substance itself. • Conforming change in light of the deletion of the GRAS affirmation petition process.
§ 170.3(h), § 570.3(h)	• Specify ''data from human, animal, analytical, or other scientific studies'' rather than ''data from human, animal, analytical, and other scientific studies''.	• Clarify that the four listed types of studies (human, animal, analytical, and other) do not necessarily apply in all circumstances.
	• Replace ''appropriate to establish the safety of a substance'' with ''appropriate to establish the safety of a substance under the conditions of its intended use''.	• Include statutory language from section 201(s) of the FD&C Act to clarify that GRAS status applies to the intended conditions of use of a substance, not the substance itself.

TABLE 29—PRINCIPAL EDITORIAL, CLARIFYING, AND CONFORMING CHANGES—Continued

Designation in the regulatory text (§)	Revision	Explanation
170.3(i)	In the definition of ''safe'' or ''safety,'' replace ''under the intended conditions of use'' with ''under the conditions of its intended use''.	Conforming change to consistently use the exact statutory language in section 201(s) ''under the conditions of its intended use'' rather than variations (such as under the intended conditions of use).
§ 170.3(k)	Replace ''General recognition of safety shall be determined in accordance with 170.30'' with ''General recognition of safety shall be in accordance with § 170.30''.	Conforming change. See Response 41.
Throughout § 170.30	Replace ''§ 186.1'' with ''part 186''	Correction to clarify that the provision applies to all of part 186, not just § 186.1.
§ 170.30(a)	Replace the proposed regulatory text ''there is reasonable certainty that the substance is not harmful under the intended conditions of use'' with ''there is reasonable certainty that the substance is not harmful under the conditions of its intended use''.	Conforming change to consistently use the exact statutory language in section 201(s) ''under the conditions of its intended use'' rather than variations (such as under the intended conditions of use).
§ 170.30(b), § 570.30(b)	Replace ''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'' with ''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''.	• Clarify that FDA approves a food additive, not a ''food additive regulation''. • Clarify that the same quantity and quality of scientific evidence is required regardless of whether the substance is intended for use as an ''ingredient''.
§ 170.30(c)(1), § 570.30(c)(1)	Replace ''General recognition of safety through experience based on common use in food prior to January 1, 1958, may be determined without the quantity or quality of scientific procedures required for approval of a food additive regulation'' with ''General recognition of safety through experience based on common use in food prior to January 1, 1958, may be achieved without the quantity or quality of scientific procedures required for approval of a food additive''.	• Conforming change. See Response 41. • Clarify that FDA approves a food additive, not a ''food additive regulation''.
§ 170.30(c)(2)	• Replace ''if the information about the experience establishes that the use of the substance is safe within the meaning of the act (see § 170.3(i))'' with ''if the information about the experience establishes that the substance is safe under the conditions of its intended use within the meaning of section 201(u) of the Federal Food, Drug, and Cosmetic Act (see also § 170.3(i))''. • Replace ''in this country'' with ''in the United States''	• Conforming change to consistently use the exact statutory language in section 201(s) ''under the conditions of its intended use'' rather than variations (such as ''the use of the substance''). • Clarify that the applicable section of the FD&C Act is section 201(u). Section 170.3(i) is in our regulations, not in the FD&C Act. • Editorial change to include the full name of the statute. • Editorial change to be specific that ''this country'' means ''the United States''.
170.30(c)(2), 170.38(a), 570.38(a).	Replace ''the act'' with ''the Federal Food, Drug, and Cosmetic Act'' in any provision that we otherwise revised.	Editorial. It is now our practice to include the full name of this statute when we refer to it.
§ 170.30(e)	• Replace ''Beginning in 1969, the Food and Drug Administration has undertaken a systematic review of the status of all ingredients used in food on the determination that they are GRAS or subject to a prior sanction'' with ''Beginning in 1969, the Food and Drug Administration has undertaken a systematic review of the status of all ingredients used in food based on the view that they are GRAS under the conditions of their intended use or subject to a prior sanction''. • Replace ''All determinations of GRAS status or food additive status or prior sanction status pursuant to this review shall be handled pursuant to §§ 170.35, 170.38, and 180.1 of this chapter. Affirmation of GRAS status shall be announced in part 184 or § 186.1 of this chapter'' with ''All affirmations of GRAS status or determinations of food additive status or prior sanction status pursuant to this review shall be handled pursuant to §§ 170.35, 170.38, and 180.1 of this chapter. Affirmation of GRAS status shall be announced in part 184 or part 186 of this chapter''.	• See Response 41. • Include statutory language from section 201(s) of the FD&C Act to clarify that GRAS status applies to the intended conditions of use of a substance, not the substance itself. • Clarify that GRAS status pursuant to parts 184 and 186 is affirmed by FDA.

TABLE 29—PRINCIPAL EDITORIAL, CLARIFYING, AND CONFORMING CHANGES—Continued

Designation in the regulatory text (§)	Revision	Explanation
§ 170.30(l)	Replace ''Any change in part 182, part 184, or § 186.1 of this chapter shall be accomplished pursuant to § 170.38'' with ''Any change to the GRAS status of a food ingredient in part 182, part 184, or part 186 of this chapter shall be accomplished pursuant to § 170.38''.	Clarify the applicability of the requirement.
§ 170.35(a), § 570.35(a)	Replace ''may affirm the GRAS status of substances'' with ''may affirm that a substance that directly or indirectly becomes a component of food is GRAS under the conditions of its intended use''.	• Editorial change to use the singular. • Include statutory language from section 201(s) of the FD&C Act to clarify that GRAS affirmation applies to the intended conditions of use of a substance, not the substance itself.
§ 170.35(b)(1), § 570.35(b)(1).	Replace ''If the Commissioner proposes on his own initiative that a substance is entitled to affirmation as GRAS'' with ''If the Commissioner proposes on his own initiative that a substance is entitled to affirmation as GRAS under the conditions of its intended use''.	Include statutory language from section 201(s) of the FD&C Act to clarify that GRAS affirmation applies to the intended conditions of use of a substance, not the substance itself.
§ 170.35(b)(3), § 570.35(b)(3).	• Replace ''convincing evidence that the substance is GRAS'' with ''convincing evidence that the substance is GRAS under the conditions of its intended use''. • Replace ''listing the substance as GRAS in part 182, part 184, or part 186 of this chapter'' with ''listing the GRAS conditions of use of the substance in part 184 or part 186 of this chapter''.	• Include statutory language from section 201(s) of the FD&C Act to clarify that GRAS affirmation applies to the intended conditions of use of a substance, not the substance itself. • Deleted reference to parts 182 and 582. If FDA affirms GRAS status, the affirmation regulation would appear in part 184 or 186.
§ 170.35(b)(4), § 570.35(b)(4).	Replace ''there is a lack of convincing evidence that the substance is GRAS'' with ''there is a lack of convincing evidence that the substance is GRAS under the conditions of its intended use''.	Include statutory language from section 201(s) of the FD&C Act to clarify that GRAS affirmation applies to the intended conditions of use of a substance, not the substance itself.
§ 170.38(a), § 570.38(a)	• Replace ''may, in accordance with § 170.35(b)(4) or (c)(5), publish a notice in the **Federal Register** determining that a substance is not GRAS'' with ''may, in accordance with § 170.35(b)(4), publish a notice in the **Federal Register** determining that a substance is not GRAS under the conditions of its intended use''. • Replace ''may, in accordance with § 570.35(b)(4) or (c)(5), publish a notice in the **Federal Register** determining that a substance is not GRAS'' with ''may, in accordance with § 570.35(b)(4), publish a notice in the **Federal Register** determining that a substance is not GRAS under the conditions of its intended use''.	• See Response 41. • Conforming change in light of the deletion of the GRAS affirmation petition process. • Include statutory language from section 201(s) of the FD&C Act to clarify that GRAS affirmation applies to the intended conditions of use of a substance, not the substance itself.
• Throughout part 170, subpart E. • Throughout part 570, subpart E.	Replace variations of ''data or other information'' with ''data and information''.	Editorial change. Although data is a type of ''information,'' it is simpler and clearer to say ''data and information.''
• Throughout part 170, subpart E. • Throughout part 570, subpart E.	Replace variations of ''determine'' and ''determination'' with ''conclude'' and ''conclusion''.	See Response 41.
• Throughout part 170, subpart E. • Throughout part 570, subpart E.	• Replace ''exempt'' with ''not subject to: • Replace ''claim'' with ''view''	See Response 42.
§ 170.203, § 570.203	In the definition of ''notifier,'' add a parenthetical with examples of what we mean by ''person'' (*e.g.,* an individual, partnership, corporation, association, or other legal entity).	Clarification by including text from the definition of ''person'' in § 10.3.
§ 170.225(c)(4)	Replace the proposed phrase ''applicable conditions of use'' with ''intended conditions of use''.	Clarifying change to use the statutory term ''intended'' in place of ''applicable''.
§ 184.1(a)	Replace ''The direct human food ingredients listed in this part have been reviewed by the Food and Drug Administration and determined to be generally recognized as safe (GRAS) for the purposes and conditions prescribed'' with ''The direct human food ingredients listed in this part have been reviewed by the Food and Drug Administration and affirmed to be generally recognized as safe (GRAS) for the purposes and under the conditions prescribed''.	Clarify that the GRAS status of the uses of substances listed in part 184 has been affirmed by FDA, either on FDA's initiative or in response to a GRAS affirmation petition.

TABLE 29—PRINCIPAL EDITORIAL, CLARIFYING, AND CONFORMING CHANGES—Continued

Designation in the regulatory text (§)	Revision	Explanation
§ 184.1(b)(1)	• Replace ''shall independently establish'' with ''shall have a basis to conclude''. • Remove the last sentence, *i.e.,* ''Persons seeking FDA approval of an independent determination that a use of an ingredient is GRAS may submit a GRAS petition in accordance with 170.35 of this chapter.''.	• Conforming change to reflect ''conclusions'' of GRAS status. • Conforming change in light of the deletion of the GRAS affirmation petition process.
§ 186.1(a)	Replace ''The indirect human food ingredients listed in this part have been reviewed by the Food and Drug Administration and determined to be generally recognized as safe (GRAS)'' with ''The indirect human food ingredients listed in this part have been reviewed by the Food and Drug Administration and affirmed to be generally recognized as safe (GRAS)''.	Clarify that the GRAS status of the uses of substances listed in part 186 has been affirmed by FDA, either on FDA's initiative or in response to a GRAS affirmation petition.
§ 186.1(b)(1)	• Replace ''shall independently establish'' with ''shall have a basis to conclude''. • Remove the last sentence, *i.e.,* ''Persons seeking FDA approval of an independent determination that a use of an ingredient is GRAS may submit a GRAS petition in accordance with 170.35 of this chapter.''.	Conforming change in light of the deletion of the GRAS affirmation petition process.
§ 570.3(f)	• Add ''of the species to which the substance is intended to be fed'' in describing the animals consuming the substance. • Delete ''in the United States'' • Add ''(and, for food-producing animals fed with such substance, also means a substantial history of consumption by humans consuming human foods derived from those food-producing animals) prior to January 1, 1958.	Changes to • Conform with revisions to § 570.30(a) and (c) • Conform with the corresponding definition for human food in § 170.3(f), which does not specify ''in the United States.'' • Clarify that substantial history of consumption should be demonstrated by the same animal species as the species intended to be fed to conform with the submission requirements in part 5 of a GRAS notice when the basis for the conclusion of GRAS status is through experience based on common use in food (§ 570.245). • Clarify that substantial history of consumption for food-producing animals also should be demonstrated by a substantial history of consumption by humans consuming human foods derived from those food-producing animals prior to January 1, 1958 to conform with the submission requirements in part 5 of a GRAS notice.
§ 570.3(k)	Replace ''General recognition of safety shall be determined in accordance with § 570.30'' with ''General recognition of safety shall be in accordance with § 570.30''.	Conforming change. The GRAS notification procedure does not use the term ''determine.''
§ 570.3	Define ''food-producing animal'' to mean an animal used to produce human food.	Clarify the meaning of this term for the purpose of part 570, subpart E in light of provisions that address the safety of a substance for humans consuming human food derived from an animal used to produce human food.
§ 570.30(c)	Replace ''General recognition of safety through experience based on common use in food prior to January 1, 1958, may be determined without the quantity or quality of scientific procedures required for approval of a food additive regulation'' with ''General recognition of safety through experience based on common use in food prior to January 1, 1958, may be achieved without the quantity or quality of scientific procedures required for approval of a food additive''.	• Conforming change. The GRAS notification procedure does not use the term ''determine.'' • Clarify that FDA approves a food additive, not a ''food additive regulation''.
§ 570.30(d)	• Replace ''ingredients listed as GRAS in part 582 of this chapter'' with ''ingredients listed as GRAS in part 582 of this chapter or affirmed as GRAS in part 584 of this chapter''. • Replace ''without specific inclusion in part 582 of this chapter'' with ''without specific inclusion in part 582 or part 584 of this chapter''.	Clarify that the provisions apply regardless of whether an ingredient is listed as GRAS in part 582 or affirmed as GRAS in part 584.
§ 570.30(i)	Replace ''Any use of such and ingredient'' with ''Any use of such an ingredient''.	Editorial correction of ''and'' to ''an''.
570.225(c)(4), 570.225(c)(5), 570.230(c), 570.235, 570.240, 570.245.	Replace ''food'' with ''animal food''	Clarification for part 570.

XXVII. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. The final rule replaces the voluntary GRAS affirmation petition process with a voluntary GRAS notification procedure. Similar to the petition process, we expect that profit-maximizing firms will only submit the GRAS notice when the private benefits equal or exceed the costs of the GRAS notice, regardless of the size of the firm. Because small firms face the same voluntary business decision as large firms, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule will not result in an expenditure in any year that meets or exceeds this amount.

The final rule will eliminate the petition process to affirm a substance is GRAS and replace the petition process with a GRAS notification procedure. The level of effort required by a firm to reach a conclusion that a substance is GRAS for its intended use remains unchanged by the final rule. However, the rule will require that firms submit some additional information to support their conclusion with their notices. Although uncertain, we estimate that notifiers will spend between 5 more hours and 20 more hours to prepare and submit each notice. We estimate that this will cost notifiers less than $0.1 million each year.

For all affected notifiers, we expect that they will spend time reading and understanding the requirements of the final rule and revising standard operating procedures for preparing and submitting GRAS notices. We estimate that it will take from 20 hours to 80 hours for notifiers to perform this action. Firms with outstanding GRAS affirmation petitions may choose to submit GRAS notices and incorporate the information included in their petition. To account for the additional effort by these firms, we include the one-time cost to prepare and submit a GRAS notice for all outstanding petitions. We estimate that notifiers will spend between 170 and 190 hours to submit GRAS notices for each outstanding petition. The total one-time costs of the final rule range from $0.8 million to $2.7 million.

We estimate that over 10 years with a 7 percent discount rate, the present value of the total costs of the final rule range from $0.9 million to $3.3 million; with a 3 percent discount rate, the present value of the total costs range from $0.9 million to $3.4 million. The annualized costs of the rule range from $0.1 million to $0.4 million with a 7 percent discount rate and range from $0.1 million to $0.5 million with a 3 percent discount rate.

We do not quantify the benefits of the final rule. However, based on the differences in review time between the GRAS petition process and the GRAS notification procedure, we anticipate that industry will benefit from the more speedy notification procedure. For example, we have filed more than 600 GRAS notices for human food substances since 1998. During this time, it took an average of 200 days for us to respond to 588 GRAS notices; it took an average of 7.9 years to complete 24 previous GRAS affirmation petitions. We began to accept GRAS notices for animal food substances in 2010 and we have filed 18 GRAS notices for animal food substances since that time. It took an average of 294 days for us to respond to 12 GRAS notices with a ''no questions letter'' or ''insufficient basis letter''; it took an average of 4.9 years to respond to the three previous GRAS affirmation petitions. With the GRAS notification procedure, we can complete our evaluation within the timelines specified in the final rule.

The Economic Analysis of Impacts of the final rule performed in accordance with Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act (Ref. 51) is available at *http://www.regulations.gov* under the docket number for this final rule and at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm*.

XXVIII. Analysis of Environmental Impact

We have carefully considered the potential environmental effects of this action. We have concluded under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XXIX. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by OMB under the PRA (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown in the following paragraphs with an estimate of the one-time and annual reporting burdens. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Substances Generally Recognized as Safe Notification Procedure (21 CFR parts 170 and 570) (OMB Control No. 0910–0342)—Revision.

Description: The FD&C Act requires that all food additives (as defined by section 201(s)) be approved by FDA before they are marketed (sections 402(a)(2)(C) and 409 of the FD&C Act). Section 201(s) of the FD&C Act excludes from the definition of a food additive a substance ''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.'' This final rule amends our regulations in parts 170 and 570 and revises the information collection provisions regarding the notification procedures for GRAS substances. The

regulations implement the GRAS provision of section 201(s) of the FD&C Act in part 170 and part 570 for human food and animal food, respectively.

Description of Respondents: Respondents to the collection of information are manufacturers of substances used in human food and animal food. We estimate there are 480 such respondents. As estimated in the Final Regulatory Impact Analysis (Ref. 51), approximately 340 to 460 notifiers (for human food) and approximately 10 to 20 notifiers (for animal food) will be affected by the final rule. The Final Regulatory Impact Analysis reflects an overall increase in respondents to the program and we have therefore adjusted our respondent numbers accordingly.

As discussed in section II.B of the preamble to this final rule, previously manufacturers were invited to submit notices of their independent GRAS determinations for review under the framework of the proposed rule during the period between issuance of the proposed rule and any final rule based on the proposed rule. The proposed regulations provided a standard format for the voluntary submission of a notice. To date, the GRAS program has been administered under these proposed procedures. Comments regarding the information collection topics solicited in the proposed rule and subsequent 2010 notice are discussed in the preamble in sections IV, VII, and X through XVIII. While none of the comments suggested we modify the estimated annual burden associated with the information collection, we have revised the underlying notification procedures and, consequently, have revised the underlying information collection provisions consistent with the final rule.

Specifically the final rule establishes a voluntary administrative procedure for notifying FDA about a conclusion that a substance is GRAS under the conditions of its intended use in human food or animal food. The final rule explains that a GRAS notice must include the following seven parts:

TABLE 30—INFORMATION TO BE INCLUDED IN EACH PART OF A GRAS NOTICE

Part No.	Information to be included
Part 1	Signed statements and a certification.
Part 2	The identity, method of manufacture, specifications, and physical or technical effect of the notified substance.
Part 3	Dietary exposure to the notified substance.
Part 4	Self-limiting levels of use in circumstances where the amount of the notified substance that can be added to human food or animal food is limited because the food containing levels of the notified substance above a particular level would become unpalatable or technologically impractical.
Part 5	The history of consumption of the substance for food use by a significant number of consumers (or animals in the case of animal food) prior to January 1, 1958, if a conclusion of GRAS status is based on common use of the substance in food prior to 1958.
Part 6	A narrative that provides the basis for the notifier's conclusion of GRAS status, including why the scientific data, information, methods, and principles described in the notice provide a basis for the conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use.
Part 7	A list of the generally available data, information, and methods the notifier cites in the GRAS notice.

The information submitted to us in a GRAS notice is necessary to allow us to administer efficiently the FD&C Act's various provisions that apply to the use of substances added to food, specifically with regard to whether a substance is GRAS under the conditions of its intended use or is a food additive subject to premarket review. We will use the information collected through the GRAS notification procedure to complete our evaluation within the timelines specified in the final rule.

One-Time Reporting Burden

Table 31 shows the estimated one-time reporting burden associated with the final rule. We expect that all respondents to the information collection will spend time reading and understanding the requirements of the final rule and revising standard operating procedures for preparing and submitting GRAS notices. As noted, we estimate that approximately 340 to 460 notifiers (for human food) and approximately 10 to 20 notifiers (for animal food) will be affected by the final rule. We use the upper-bound estimates of 460 and 20 respondents as shown in rows 1 and 2. We estimate that it will take from 20 to 80 hours for respondents to perform this action. We use the upper-bound estimate of 80 hours as shown in rows 1 and 2. Of the 480 affected respondents, some will have outstanding GRAS petitions. Firms with outstanding GRAS petitions regarding substances intended for use in human food may choose to submit GRAS notices and incorporate the information included in their petition. As estimated in the Final Regulatory Impact Analysis (Ref. 51), up to 45 petitions (for human food) will be submitted as GRAS notices and incorporated. We use the upper-bound estimate of 45 as shown in row 3. To account for the additional effort by these firms, we include the one-time burden to prepare and submit a GRAS notice for all outstanding petitions. Because there are no outstanding GRAS petitions regarding substances intended for use in animal food, we do not account for any burden for the submission of a GRAS notice that incorporates a GRAS petition regarding a substance intended for use in animal food. We estimate that respondents will spend between 170 and 190 hours to submit GRAS notices for each outstanding petition and have used, therefore, an average estimate of 185 hours as shown in row 3.

TABLE 31—ESTIMATED ONE-TIME REPORTING BURDEN [1]

Activity/21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Notifier's review of final rule and revision of procedures for preparing and submitting GRAS notices for human food, 170.210 through 170.270.	460	1	460	80	36,800
Notifier's review of final rule and revision of procedures for preparing and submitting GRAS notices for animal food, 570.210 through 570.270	20	1	20	80	1,600
Prepare and submit GRAS notice for an outstanding GRAS petition, 170.285	45	1	45	185	8,325
Total					46,725

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Recurring Reporting Burden

Table 32 shows the estimated recurring annual reporting burden associated with the final rule. As previously discussed, the final rule replaces the petition process with a GRAS notification procedure. The level of effort required by a firm to reach a conclusion that a substance is GRAS for its intended use remains unchanged by the final rule. However, the final rule requires that firms submit some additional information to support the conclusions found within their notices. The additional information might include an amendment (§§ 170.260 and 570.260); a supplement (§§ 170.280 and 570.280); a request for FDA to cease to evaluate a GRAS notice (§§ 170.260 and 570.260); an incorporation into a GRAS notice (§§ 170.215 and 570.215); and, information required when the intended conditions of use of a notified substance includes use in a product subject to regulation by FSIS, including authorization to us to share any trade secrets with FSIS (§ 170.270). Because the amount of additional information may vary, we estimate that respondents will spend between 155 and 170 hours to prepare and submit each notice. Using the upper-bound figure of 170 hours, we therefore estimate that the 50 notifiers for human food and 25 notifiers for animal food will expend 12,750 hours annually as shown, respectively, in rows 1 and 2.

TABLE 32—ESTIMATED ANNUAL REPORTING BURDEN [1]

Activity/21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
GRAS notification procedure for human food, 170.210 through 170.270	50	1	50	170	8,500
GRAS notification procedure for animal food, 570.210 through 570.270	25	1	25	170	4,250
Total					12,750

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Recordkeeping

The final rule does not contain recordkeeping requirements. We believe that documentation used by respondents in support of a conclusion of GRAS status is information that is collected and retained as a part of usual and customary business practices for a firm engaged in the manufacture of substances used in human food and animal food. We have, therefore, not provided an estimate for these activities (5 CFR 1320.3(b)(2)).

This final rule also refers to other currently approved collections of information found in our regulations. These collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR 25.32(i) are approved under OMB control number 0910–0541. The collections of information in 21 CFR 10.33 are approved under OMB control number 0910–0191.

The information collection provisions of this final rule have been submitted to OMB for review as required by section 3507(d) of the PRA. Before the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

XXX. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we have concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XXXI. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *http://*

www.regulations.gov. FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register,** but Web sites are subject to change over time.

1. House Report No. 2284, July 28, 1958. See Reference 1 to the proposed rule.
2. Price, J.M., C.G. Biava, B.L. Oser, et al., ''Bladder Tumors in Rats Fed Cyclohexylamine or High Doses of a Mixture of Cyclamate and Saccharin,'' *Science,* 167:1131–1132, 1970. See Reference 2 to the proposed rule.
3. *New York Times,* p. 22, October 31, 1969. See Reference 3 to the proposed rule.
4. United States Government Accountability Office, ''Report to Congressional Requestors on Food Safety: FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe (GRAS),'' Report No. GAO–10–246, (*http://www.gao.gov/new.items/d10246.pdf*), February 2010. Accessed and printed on May 3, 2010. See Reference 2 to the 2010 notice.
5. FDA, ''Draft Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives,'' (*http://www.regulations.gov* in Docket No. FDA–2011–D–0490), 2012. Accessed and printed on February 19, 2016.
6. FDA, ''Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives,'' (*http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm300661.htm*), 2014. Accessed and printed on January 15, 2016.
7. FDA, ''Draft Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology,'' (*http://www.regulations.gov* in Docket No. FDA–2010–D–0530), 2011. Accessed and printed on February 19, 2016.
8. FDA, ''Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology,'' (*http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm*), 2014. Accessed and printed on January 15, 2016.
9. The Pew Charitable Trusts, ''Fixing the Oversight of Chemicals Added to Our Food,'' (*http://www.pewtrusts.org/~/media/legacy/uploadedfiles/phg/content_level_pages/reports/foodadditivescapstonereportpdf.pdf*), 2013. Accessed and printed on February 19, 2016.
10. Letter dated November 17, 2010, from Joann M. Givens of FDA to Mr. Tim Baggs, Charge Beverages Corporation, (*http://www.fda.gov/iceci/enforcementactions/warningletters/2010/ucm233990.htm*). Accessed and printed on January 31, 2016.
11. Letter dated November 17, 2010, from Joann M. Givens of FDA to Rhonda Kallman of New Century Brewing Company, (*http://www.fda.gov/iceci/enforcementactions/warningletters/2010/ucm234028.htm*). Accessed and printed on January 31, 2016.
12. Letter dated November 17, 2010, from Joann M. Givens of FDA to Jaisen Freeman, Chris Hunter, and Jeff Wright of Phusion Projects, (*http://www.fda.gov/iceci/enforcementactions/warningletters/2010/ucm234023.htm*). Accessed and printed on January 31, 2016.
13. Letter dated November 17, 2010, from Joann M. Givens of FDA to Michael Michail of United Brands Company, (*http://www.fda.gov/iceci/enforcementactions/warningletters/2010/ucm234002.htm*). Accessed and printed on January 31, 2016.
14. TTB, Industry Circular 2010–8, (*http://www.ttb.gov/industry_circulars/archives/2010/10–08.html*), 2010. Accessed and printed on January 21, 2016.
15. The National Academies of Sciences, Health and Medicine Division, ''Caffeine in Food and Dietary Supplements: Examining Safety—Workshop Summary,'' (*http://www.nationalacademies.org/hmd/Reports/2014/Caffeine-in-Food-and-Dietary-Supplements-Examining-Safety.aspx*), 2014. Accessed and printed on May 27, 2016.
16. Memorandum of Meeting Held on December 11, 2014, between Representatives of FDA and Representatives of the Caffeine Technical Working Group on the American Beverage Association (ABA) Caffeine Technical Working Group (CTWG) Research Plans.
17. International Life Sciences Institute (ILSI North America), ''Caffeine Working Group,'' (*http://ilsina.org/our-work/food-safety/caffeine/*), 2015. Accessed and printed on June 8, 2016.
18. Experience With GRAS Notices Under the 1997 Proposed Rule, Memorandum Dated November 4, 2010, from Linda S. Kahl of FDA to Docket No. FDA–1997–N–0020. See Reference 1 to the 2010 notice.
19. ''Substances that Are Generally Recognized as Safe (GRAS); Updated Experience With GRAS Notices,'' Memorandum Dated June 1, 2016, from Paulette M. Gaynor of FDA to Docket No. FDA–1997–N–0020.
20. ''Experience With GRAS Notices Under CVM's Interim Pilot Program,'' Memorandum Dated June 10, 2016, from David Edwards of FDA to Docket No. FDA–1997–N–0020.
21. Memorandum for the Heads of Executive Departments and Agencies, Dated June 1, 1998, Signed by President William J. Clinton, (*http://www.plainlanguage.gov/whatisPL/govmandates/memo.cfm*). Accessed and printed on July 14, 2008. See Reference 3 to the 2010 notice.
22. eRulemaking Program, ''Improving Electronic Dockets on *Regulations.gov* and the Federal Docket Management System: Best Practices for Federal Agencies,'' (*http://www.regulations.gov/docs/FactSheet_eRulemaking_Best_Practices.pdf*), 2010. Accessed and printed on January 15, 2016.
23. Dictionary.com. Dictionary.com Unabridged. Random House, Inc. (*http://dictionary.reference.com/browse/corroborate*), 2016. Accessed and printed on February 23, 2016.
24. Food and Agriculture Organization of the United Nations and the World Health Organization, ''Chapter 6, Dietary Exposure Assessment of Chemicals in Food'' in *Environmental Health Criteria 240. Principles and Methods for the Risk Assessment of Chemicals in Food,* (*http://apps.who.int/iris/bitstream/10665/44065/9/WHO_EHC_240_9_eng_Chapter6.pdf*), 2009. Accessed and printed on February 13, 2006.
25. FDA, ''Guidance for Industry: Estimating Dietary Intake of Substances in Food,'' (*http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm074725.htm*), 2006. Accessed and printed on January 15, 2016.
26. Renwick, A.G., ''The Use of a Sweetener Substitution Method to Predict Dietary Exposures for the Intense Sweetener Rebaudioside A.,'' *Food and Chemical Toxicology,* 46:S61–S69, 2008.
27. Mitchell, D.C., C.A. Knight, J. Hockenberry, et al., ''Beverage Caffeine Intakes in the U.S.,'' *Food and Chemical Toxicology,* 63:136–142, 2014.
28. Fulgoni, V.L., D.R. Keast, and H.R. Lieberman, ''Trends in Intake and Sources of Caffeine in the Diets of US Adults: 2001–2010,'' *The American Journal of Clinical Nutrition,* 101:1081–1087, 2015.
29. Branum, A.M., L.M. Rossen, and K.C. Schoendorf, ''Trends in Caffeine Intake Among U.S. Children and Adolescents,'' *Pediatrics,* 133(3):386–393, 2014.
30. Food and Agriculture Organization and World Health Organization, ''Joint FAO/WHO Expert Consultation on Biotechnology and Food Safety,'' (*ftp://ftp.fao.org/es/esn/food/biotechnology.pdf*), 1996. See Reference 6 to the proposed rule.
31. FDA, ''Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions,'' (*http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm124917.htm*), 2009. Accessed and printed on January 15, 2016.
32. FDA, ''Guidance for Industry: Microbiological Considerations for Antimicrobial Food Additive Submissions,'' (*http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm230417.htm*), 2008. Accessed and printed on January 15, 2016.
33. FDA, ''Guidance for Industry: Enzyme Preparations: Recommendations for Submission of Chemical and Technological Data for Food Additive

Petitions and GRAS Notices,'' (*http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm217685.htm*), 2010. Accessed and printed on January 15, 2016.
34. FDA, ''Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food,'' (*http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm054658.htm*), 2006. Accessed and printed on January 15, 2016.
35. FDA, ''Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients. Redbook 2000,'' (*http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm*), 2007. Accessed and printed on January 15, 2016.
36. 225–00–2000 ''Amendment 1: Memorandum of Understanding Between the United States Department of Agriculture Food Safety Inspection Service and the United States Department of Health and Human Services Food and Drug Administration, (*http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm441552.htm*), 2000. Accessed and printed on November 25, 2015.
37. FDA, ''Guidance for Industry: Providing Regulatory Submissions in Electronic or Paper Format to the Office of Food Additive Safety; Draft Guidance,'' (*http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2021277.htm*), 2010. Accessed and printed on January 15, 2016.
38. Form FDA 3667. ''Generally Recognized As Safe (GRAS) Notice,'' (*http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM350015.pdf*), 2016. Accessed and printed on June 1, 2016.
39. Form FDA 3480. ''Food Contact Substance: Notification for New Use, Pre-Notification Consultation, Food Master File'', (*http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM076880.pdf*), 2016. Accessed and printed on June 1, 2016.
40. Form FDA 3537. ''DHHS/FDA Food Facility Registration,'' (*http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm071977.pdf*), 2014. Accessed and printed on January 15, 2016.
41. FSIS, ''Contact Us,'' (*http://www.fsis.usda.gov/wps/portal/informational/contactus*). Accessed and printed on January 28, 2016.
42. Pariza, M.W. and M. Cook, ''Determining the Safety of Enzymes Used in Animal Feed,'' *Regulatory Toxicology and Pharmacology,* 56:332–342, 2010.
43. Olempska-Beer Z.S., R.I Merker, M.D. Ditto, and M.J. DiNovi, ''Food-Processing Enzymes From Recombinant Microorganisms—A Review,'' *Regulatory Toxicology and Pharmacology,* 45(2):144–158, 2006.
44. ''Guidance for Industry: Use of Nanomaterials in Food for Animals (# 220),'' (*http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM401508.pdf*), 2015. Accessed and printed on January 15, 2016.
45. ''GRAS Notices, Search Results, Common Use in Food,'' 2016.
46. GRAS Notice Inventory, (*http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm*), 2016. Accessed and printed on January 15, 2016.
47. Current Animal Food GRAS Notices Inventory, (*http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/GenerallyRecognizedasSafeGRASNotifications/ucm243845.htm*), 2016. Accessed and printed on February 23, 2016.
48. FDA, List of Pending GRAS Affirmation Petitions as of December 31, 2015.
49. FDA, ''Guidance for Industry: Frequently Asked Questions About GRAS,'' (*http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm061846.htm*), 2004. Accessed and printed on October 13, 2010. See Reference 6 to the 2010 notice.
50. FDA, Memorandum of Telephone Conference Held on May 19, 1998, between Linda S. Kahl and Gloria Overholser of FDA and Carlton Kempter and Jonathan Fleuchaus, U.S. Environmental Protection Agency.
51. FDA, ''Substances Generally Recognized as Safe Final Rule: Final Regulatory Impact Analysis, Final Regulatory Flexibility Analysis, Final Unfunded Mandates Reform Act Analysis,'' 2016.
52. FDA, ''Compliance Policy Guide CPG Sec. 665.100 Common or Usual Names for Animal Feed Ingredients,'' (*http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074687.htm*), 1995. Accessed and printed on January 7, 2016.
53. Selle, P.H. and V. Ravindran, ''Microbial Phytase in Poultry Nutrition,'' *Animal Feed Science and Technology,* 135:1–41, 2007.
54. Hatten., L.F., D.R. Ingram., and S.T. Pittman, ''Effect of Phytase on Production Parameters and Nutrient Availability in Broilers and Laying Hens: A Review,'' *The Journal of Applied Poultry Research,* 10(3):274–278, 2001.
55. Angel, C.R., W. Saylor, S.L. Vieira, and N. Ward, ''Effects of a Monocomponent Protease on Performance and Protein Utilization in 7- to 22-Day-Old Broiler Chickens,'' *Poultry Science,* 90:2281–2286, 2011.
56. FDA, ''Guidance for Industry: Recommendations for Preparation and Submission of Animal Food Additive Petitions (# 221),'' (*http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM367746.pdf*), 2015. Accessed and printed on January 15, 2016.
57. National Research Council, ''General Considerations in Determining Safety of Animal Dietary Supplements,'' in *Safety of Dietary Supplements for Horses, Dogs, and Cats,* Washington, DC, Chapter 9, pp. 169–175, The National Academies Press, 2009.
58. FDA, ''Compliance Policy Guide CPG Sec. 527.400. Whole Milk, Lowfat Milk, Skim Milk—Aflatoxin M1,'' (*http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074482.htm*), 2005. Accessed and printed on January 15, 2016.

List of Subjects

21 CFR Part 20

Confidential business information, Courts, Freedom of information, Government employees.

21 CFR Part 25

Environmental impact statements, Foreign relations, Reporting and recordkeeping requirements.

21 CFR Part 170

Administrative practice and procedure, Food additives, Reporting and recordkeeping requirements.

21 CFR Part 184

Food additives.

21 CFR Part 186

Food additives, Food packaging.

21 CFR Part 570

Animal feeds, Animal foods, Food additives.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR chapter I is amended as follows:

PART 20—PUBLIC INFORMATION

■ 1. The authority citation for part 20 continues to read as follows:

Authority: 5 U.S.C. 552; 18 U.S.C. 1905; 19 U.S.C. 2531–2582; 21 U.S.C. 321–393, 1401–1403; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–300u–5, 300aa–1.

■ 2. In § 20.100, add paragraph (c)(46) to read as follows:

§ 20.100 Applicability; cross-reference to other regulations.

* * * * *

(c) * * *

(46) Generally recognized as safe (GRAS) notices, in part 170, subpart E and part 570, subpart E of this chapter.

PART 25—ENVIRONMENTAL IMPACT CONSIDERATIONS

■ 3. The authority citation for part 25 continues to read as follows:

Authority: 21 U.S.C. 321–393; 42 U.S.C. 262, 263b–264; 42 U.S.C. 4321, 4332; 40 CFR parts 1500–1508; E.O. 11514, 35 FR 4247, 3 CFR, 1971 Comp., p. 531–533 as amended by E.O. 11991, 42 FR 26967, 3 CFR, 1978 Comp., p. 123–124 and E.O. 12114, 44 FR 1957, 3 CFR, 1980 Comp., p. 356–360.

■ 4. In § 25.20, revise paragraph (k) to read as follows:

§ 25.20 Actions requiring preparation of an environmental assessment.

* * * * *

(k) Establishment or amendment of a regulation for a food substance as GRAS under the conditions of its intended use for humans or animals under parts 182, 184, 186, 582, or 584 of this chapter, or establishment or amendment of a regulation for a prior-sanctioned food ingredient, as defined in §§ 170.3(l) and 181.5(a) of this chapter, unless categorically excluded in § 25.32(f), (i), (j), (k), or (r).

* * * * *

■ 5. In § 25.32, revise paragraphs (f), (i), (j), (k), and (r) to read as follows:

§ 25.32 Foods, food additives, and color additives.

* * * * *

(f) Establishment or amendment of a regulation for a food substance as GRAS under the conditions of its intended use for humans or animals under parts 182, 184, 186, 582, or 584 of this chapter, and establishment or amendment of a regulation for a prior-sanctioned food ingredient, as defined in §§ 170.3(l) and 181.5(a) of this chapter, if the substance or food ingredient is already marketed in the United States for the proposed use.

* * * * *

(i) Approval of a food additive petition, establishment or amendment of a regulation for a food substance as GRAS under the conditions of its intended use for humans or animals under parts 182, 184, 186, 582, or 584 of this chapter, the granting of a request for exemption from regulation as a food additive under § 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is present in finished food-packaging material at not greater than 5 percent-by-weight and is expected to remain with finished food-packaging material through use by consumers or when the substance is a component of a coating of a finished food-packaging material.

(j) Approval of a food additive petition, establishment or amendment of a regulation for a food substance as GRAS under the conditions of its intended use for humans or animals under parts 182, 184, 186, 582, or 584 of this chapter, the granting of a request for exemption from regulation as a food additive under § 170.39 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, when the substance is to be used as a component of a food-contact surface of permanent or semipermanent equipment or of another food-contact article intended for repeated use.

(k) Approval of a food additive petition or color additive petition, establishment or amendment of a regulation for a food substance as GRAS under the conditions of its intended use for humans or animals under parts 182, 184, 186, 582, or 584 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective, for substances added directly to food that are intended to remain in food through ingestion by consumers and that are not intended to replace macronutrients in food.

* * * * *

(r) Approval of a food additive petition or color additive petition, establishment or amendment of a regulation for a food substance as GRAS under the conditions of its intended use for humans or animals under parts 182, 184, 186, 582, or 584 of this chapter, or allowing a notification submitted under 21 U.S.C. 348(h) to become effective for a substance that occurs naturally in the environment, when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

PART 170—FOOD ADDITIVES

■ 6. The authority citation for part 170 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 346a, 348, 371.

■ 7. In § 170.3, revise paragraph (h), the first sentence of paragraph (i), and paragraph (k), to read as follows:

§ 170.3 Definitions.

* * * * *

(h) *Scientific procedures* 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 its intended use.

(i) *Safe* or *safety* means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use. * * *

* * * * *

(k) *General recognition of safety* shall be in accordance with § 170.30.

* * * * *

■ 8. Amend § 170.30 as follows:
■ a. Revise the last sentence of paragraph (a);
■ b. Revise paragraph (b).
■ c. Revise the the first sentence of paragraph (c)(1) and revise paragraph (c)(2);
■ d. Remove ''§ 186.1'' and add in its place ''part 186'' wherever it appears in paragraph (d);
■ e. Revise paragraph (e);
■ f. Remove and reserve paragraph (f);
■ g. Remove ''§ 186.1'' and add in its place ''part 186'' in paragraphs (h) introductory text, (h)(1), (i), (j), and (k); and
■ h. Revise the last sentence of paragraph (l).

The revisions read as follows:

§ 170.30 Eligibility for classification as generally recognized as safe (GRAS).

(a) * * * 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 (see § 170.3(i)).

(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. General recognition of safety through scientific procedures shall be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

(c)(1) General recognition of safety through experience based on common use in food prior to January 1, 1958, may be achieved without the quantity or quality of scientific procedures required for approval of a food additive. * * *

(2) A substance used in food prior to January 1, 1958, may be generally recognized as safe through experience based on its common use in food when that use occurred exclusively or primarily outside of the United States if

the information about the experience establishes that the substance is safe under the conditions of its intended use within the meaning of section 201(u) of the Federal Food, Drug, and Cosmetic Act (see also § 170.3(i)). Common use in food prior to January 1, 1958, that occurred outside of the United States shall be documented by published or other information and shall be corroborated by information from a second, independent source that confirms the history and circumstances of use of the substance. The information used to document and to corroborate the history and circumstances of use of the substance must be generally available; that is, it must be widely available in the country in which the history of use has occurred and readily available to interested qualified experts in the United States. A person who concludes that a use of a substance is GRAS through experience based on its common use in food outside of the United States should notify FDA of that view in accordance with subpart E of this part.

* * * * *

(e) Food ingredients were listed as GRAS in part 182 of this chapter during 1958–1962 without a detailed scientific review of all available data and information relating to their safety. Beginning in 1969, the Food and Drug Administration has undertaken a systematic review of the status of all ingredients used in food based on the view that they are GRAS under the conditions of their intended use or subject to a prior sanction. All affirmations of GRAS status or determinations of food additive status or prior sanction status pursuant to this review shall be handled pursuant to §§ 170.35, 170.38, and 180.1 of this chapter. Affirmation of GRAS status shall be announced in part 184 or part 186 of this chapter.

* * * * *

(l) * * * Any change to the GRAS status of a food ingredient in parts 182, 184, or 186 of this chapter shall be accomplished pursuant to § 170.38.

■ 9. In § 170.35, revise paragraphs (a), (b)(1), (3), and (4), and remove paragraph (c) to read as follows:

§ 170.35 Affirmation of generally recognized as safe (GRAS) status.

(a) The Commissioner, on his own initiative, may affirm that a substance that directly or indirectly becomes a component of food is GRAS under the conditions of its intended use.

(b)(1) If the Commissioner proposes on his own initiative that a substance is entitled to affirmation as GRAS under the conditions of its intended use, he will place all of the data and information on which he relies on public file in the office of the Division of Dockets Management and will publish in the **Federal Register** a notice giving the name of the substance, its proposed uses, and any limitations proposed for purposes other than safety.

* * * * *

(3) The Commissioner will evaluate all comments received. If he concludes that there is convincing evidence that the substance is GRAS under the conditions of its intended use as described in § 170.30, he will publish a notice in the **Federal Register** listing the GRAS conditions of use of the substance in part 184 or part 186 of this chapter, as appropriate.

(4) If, after evaluation of the comments, the Commissioner concludes that there is a lack of convincing evidence that a substance is GRAS under the conditions of its intended use and that it should be considered a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic Act, he shall publish a notice thereof in the **Federal Register** in accordance with § 170.38.

■ 10. In § 170.38, revise paragraph (a) to read as follows:

§ 170.38 Determination of food additive status.

(a) The Commissioner may, in accordance with § 170.35(b)(4), publish a notice in the **Federal Register** determining that a substance is not GRAS under the conditions of its intended use and is a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic Act.

* * * * *

■ 11. Add subpart E, consisting of §§ 170.203 through 170.285, to read as follows:

Subpart E—Generally Recognized as Safe (GRAS) Notice

Sec.

Subpart E—Generally Recognized as Safe (GRAS) Notice

§ 170.203 Definitions.

The definitions and interpretations of terms in § 170.3 apply to such terms when used in this subpart. The following definitions also apply:

Amendment means any data and information that you submit regarding a filed GRAS notice before we respond to your notice by letter in accordance with § 170.265(b)(1) or cease to evaluate your notice in accordance with § 170.265(b)(3).

GRAS means generally recognized as safe.

GRAS notice means a submission that informs us of your view that a substance is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is GRAS under the conditions of its intended use in accordance with § 170.30.

Notified substance means the substance that is the subject of your GRAS notice.

Notifier means the person (*e.g.,* an individual, partnership, corporation, association, or other legal entity) who is responsible for the GRAS notice, even if another person (such as an attorney, agent, or qualified expert) prepares or submits the notice or provides an opinion about the basis for a conclusion of GRAS status.

Qualified expert means an individual who is qualified by scientific training and experience to evaluate the safety of substances under the conditions of their intended use in food.

Supplement means any data and information that you submit regarding a filed GRAS notice after we respond to your notice by letter in accordance with § 170.265(b)(1) or cease to evaluate your

notice in accordance with § 170.265(b)(3).

We, our, and *us* refer to the United States Food and Drug Administration (FDA).

You and *your* refer to a notifier.

§ 170.205 Opportunity to submit a GRAS notice.

Any person may notify FDA of a view that a substance is not subject to the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act based on that person's conclusion that the substance is GRAS under the conditions of its intended use.

§ 170.210 How to send your GRAS notice to FDA.

(a) Send your GRAS notice to the Office of Food Additive Safety (HFS–200), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Drive, College Park, MD 20740.

(b) When you submit your GRAS notice, you may do so either in an electronic format that is accessible for our evaluation or on paper. If you send your GRAS notice on paper, a single paper copy is sufficient.

§ 170.215 Incorporation into a GRAS notice.

You may incorporate into your GRAS notice either specifically identified data and information that you previously submitted to the Center for Food Safety and Applied Nutrition (CFSAN), or specifically identified publicly available data and information submitted by another party, when such data and information remain in CFSAN's records, such as data and information contained in a previous GRAS notice or a food additive petition.

§ 170.220 General requirements applicable to a GRAS notice.

(a) A GRAS notice has seven parts as required by §§ 170.225 through 170.255. You must submit the data and information specified in each of these parts on separate pages or sets of pages.

(b) You must include each of the seven parts in your GRAS notice. If you do not include a part, you must include with your GRAS notice an explanation of why that part does not apply to your GRAS notice.

§ 170.225 Part 1 of a GRAS notice: Signed statements and certification.

(a) Part 1 of your GRAS notice must be dated and signed by a responsible official of your organization, or by your attorney or agent.

(b) Except as required by paragraph (c)(8) of this section, you must not include any information that is trade secret or confidential commercial information in Part 1 of your GRAS notice.

(c) In Part 1 of your GRAS notice, you must:

(1) Inform us that you are submitting a GRAS notice in accordance with this subpart;

(2) Provide the name and address of your organization;

(3) Provide the name of the notified substance, using an appropriately descriptive term;

(4) Describe the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purposes for which the substance will be used, including, when appropriate, a description of a subpopulation expected to consume the notified substance;

(5) Inform us of the statutory basis for your conclusion of GRAS status (*i.e.,* through scientific procedures in accordance with § 170.30(a) and (b) or through experience based on common use in food in accordance with § 170.30(a) and (c));

(6) State your view that the notified substance is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the notified substance is GRAS under the conditions of its intended use;

(7) State that, if we ask to see the data and information that are the basis for your conclusion of GRAS status, either during or after our evaluation of your notice, you will:

(i) Agree to make the data and information available to us; and

(ii) Agree to both of the following procedures for making the data and information available to us:

(A) Upon our request, you will allow us to review and copy the data and information during customary business hours at the address you specify for where these data and information will be available to us; and

(B) Upon our request, you will provide us with a complete copy of the data and information either in an electronic format that is accessible for our evaluation or on paper;

(8) State your view as to whether any of the data and information in Parts 2 through 7 of your GRAS notice are exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552 (*e.g.,* as trade secret or as commercial or financial information that is privileged or confidential).

(9) Certify that, to the best of your knowledge, your GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to you and pertinent to the evaluation of the safety and GRAS status of the use of the substance;

(10) State both the name and position or title of the person who signs the GRAS notice; and

(11) When applicable, state as required by § 170.270 whether you:

(i) Authorize us to send any trade secrets to the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture; or

(ii) Ask us to exclude any trade secrets from the copy of the GRAS notice that we will send to FSIS.

§ 170.230 Part 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect.

In Part 2 of your GRAS notice, you must include:

(a) Scientific data and information that identifies the notified substance.

(1) Examples of appropriate data and information include the chemical name, applicable registry numbers (such as a Chemical Abstracts Service (CAS) registry number or an Enzyme Commission (EC) number), empirical formula, structural formula, quantitative composition, and characteristic properties.

(2) When the source of a notified substance is a biological material, you must include data and information sufficient to identify:

(i) The taxonomic source (*e.g.,* genus, species) including, as applicable, data and information at the sub-species level (*e.g.,* variety, strain);

(ii) The part of any plant or animal used as the source; and

(iii) Any known toxicants that could be in the source;

(b) A description of the method of manufacture of the notified substance in sufficient detail to evaluate the safety of the notified substance as manufactured;

(c) Specifications for food-grade material; and

(d) When necessary to demonstrate safety, relevant data and information bearing on the physical or other technical effect the notified substance is intended to produce, including the quantity of the notified substance required to produce such effect.

§ 170.235 Part 3 of a GRAS notice: Dietary exposure.

In part 3 of your GRAS notice, you must provide data and information about dietary exposure (*i.e.,* the amount of relevant substances that consumers are likely to eat or drink as part of a total diet), regardless of whether your conclusion of GRAS status is through

scientific procedures or through experience based on common use in food, as follows:

(a) You must provide an estimate of dietary exposure to the notified substance that includes exposure from its intended use and all sources in the diet; and

(b) When applicable, you must provide an estimate of dietary exposure to any other substance that is expected to be formed in or on food because of the use of the notified substance (*e.g.,* hydrolytic products or reaction products);

(c) When applicable, you must provide an estimate of dietary exposure to any other substance that is present with the notified substance either naturally or due to its manufacture (*e.g.,* contaminants or by-products);

(d) You must describe the source of any food consumption data that you use to estimate dietary exposure in accordance with paragraphs (a) through (c) of this section; and

(e) You must explain any assumptions you made to estimate dietary exposure in accordance with paragraphs (a) through (c) of this section.

§ 170.240 Part 4 of a GRAS notice: Self-limiting levels of use.

In circumstances where the amount of the notified substance that can be added to food is limited because food containing levels of the notified substance above a particular level would become unpalatable or technologically impractical, in Part 4 of your GRAS notice you must include data and information on such self-limiting levels of use.

§ 170.245 Part 5 of a GRAS notice: Experience based on common use in food before 1958.

If the statutory basis for your conclusion of GRAS status is through experience based on common use in food, in Part 5 of your GRAS notice you must include evidence of a substantial history of consumption of the notified substance for food use by a significant number of consumers prior to January 1, 1958.

§ 170.250 Part 6 of a GRAS notice: Narrative.

In Part 6 of your GRAS notice, you must include a narrative that provides the basis for your conclusion of GRAS status, in which:

(a)(1) You must explain why the data and information in your notice provide a basis for your view that the notified substance is safe under the conditions of its intended use. In your explanation, you must address the safety of the notified substance, considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet;

(2) In your explanation, you must identify what specific data and information that you discuss in accordance with paragraph (a)(1) of this section are generally available, and what specific data and information that you discuss in accordance with paragraph (a)(1) of this section are not generally available, by providing citations to the list of data and information that you include in Part 7 of your GRAS notice in accordance with § 170.255;

(b) You must explain how the generally available data and information that you rely on to establish safety in accordance with paragraph (a) of this section provide a basis for your conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use;

(c) You must either:

(1) Identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status, regardless of whether those data and information are generally available; or

(2) State that you have reviewed the available data and information and are not aware of any data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status;

(d) If you view any of the data and information in your notice as exempt from disclosure under the Freedom of Information Act, you must identify the specific data and information; and

(e) For non-public, safety-related data and information considered in reaching a conclusion of GRAS status, you must explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to such data and information.

§ 170.255 Part 7 of a GRAS notice: List of supporting data and information in your GRAS notice.

(a) In part 7 of your GRAS notice, you must include a list of all of the data and information that you discuss in Part 6 of your GRAS notice to provide a basis for your view that the notified substance is safe under the conditions of its intended use as described in accordance with § 170.250(a)(1).

(b) You must specify which data and information that you list in accordance with paragraph (a) of this section are generally available, and which data and information are not generally available.

§ 170.260 Steps you may take before FDA responds to your GRAS notice.

(a) You may submit a timely amendment to your filed GRAS notice, to update your GRAS notice or in response to a question from us, before we respond to your notice by letter in accordance with § 170.265(b)(1) or cease to evaluate your notice in accordance with § 170.265(b)(3).

(b) At any time before we respond to your GRAS notice in accordance with § 170.265(b)(1), you may request in writing that we cease to evaluate your GRAS notice. Your request does not preclude you from submitting a future GRAS notice in accordance with this subpart with respect to the notified substance.

§ 170.265 What FDA will do with a GRAS notice.

(a)(1) We will conduct an initial evaluation of your submission to determine whether to file it as a GRAS notice for evaluation of your view that the notified substance is GRAS under the conditions of its intended use.

(2) If we file your submission as a GRAS notice, we will send you a letter that informs you of the date of filing.

(3) If we do not file your submission as a GRAS notice, we will send you a letter that informs you of that fact and provides our reasons for not filing the submission as a GRAS notice.

(4) We will consider any timely amendment that you submit to a filed GRAS notice, to update your GRAS notice or in response to a question from us, before we respond to you by letter in accordance with paragraph (b)(1) of this section, if we deem that doing so is feasible within the timeframes established in paragraph (b) of this section. If we deem that considering your amendment is not feasible within the timeframes established in paragraph (b) of this section or if we have granted your request to cease to evaluate your notice, we will inform you that we are not considering your amendment.

(b)(1) Within 180 days of filing, we will respond to you by letter based on our evaluation of your notice. We may extend the 180 day timeframe by 90 days on an as needed basis.

(2) If we extend the timeframe, we will inform you in writing of the extension as soon as practicable but no later than within 180 days of filing.

(3) If you ask us to cease to evaluate your GRAS notice in accordance with § 170.260(b), we will send you a letter informing you of our decision regarding your request.

(c) If circumstances warrant, we will send you a subsequent letter about the notice.

§ 170.270 Procedures that apply when the intended conditions of use of a notified substance include use in a product or products subject to regulation by the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture.

If the intended conditions of use of the notified substance include use in a product or products subject to regulation by FSIS under statutes that it administers:

(a) When applicable, you must include in your GRAS notice a statement as to whether you:

(1) Authorize us to send any trade secrets to FSIS; or

(2) Ask us to exclude any trade secrets from the copy of the GRAS notice that we will send to FSIS.

(b)(1) We will forward a copy of a GRAS notice or relevant portions thereof to FSIS;

(2) We will exclude any trade secrets unless you have authorized us to do so in accordance with paragraph (a)(1) of this section; and

(c) We will ask FSIS to advise whether the intended conditions of use comply with applicable statutes and regulations, or, if not, whether the use of the substance would be permitted in products under FSIS' jurisdiction under specified conditions or restrictions.

(d) As appropriate, we will inform you of the advice we receive from FSIS in the letter we send you in accordance with § 170.265(b)(1).

§ 170.275 Public disclosure of a GRAS notice.

(a) The data and information in a GRAS notice (including data and information submitted in any amendment or supplement to your GRAS notice or incorporated into your GRAS notice) are:

(1) Considered a mandatory, rather than voluntary, submission for purposes of their status under the Freedom of Information Act and our public information requirements in part 20 of this chapter; and

(2) Available for public disclosure in accordance with part 20 of this chapter as of the date that we receive your GRAS notice.

(b) We will make the following readily accessible to the public:

(1) A list of filed GRAS notices, including the information described in § 170.225(c)(2) through (c)(5);

(2) The text of any letter that we issue under § 170.265(b)(1) or (c); and

(3) The text of any letter that we issue under § 170.265(b)(3) if we grant your request that we cease to evaluate your notice.

(c) We will disclose all remaining data and information that are not exempt from public disclosure in accordance with part 20 of this chapter.

§ 170.280 Submission of a supplement.

If circumstances warrant, you may submit a supplement to a filed GRAS notice after we respond to your notice by letter in accordance with § 170.265(b)(1) or cease to evaluate your notice in accordance with § 170.265(b)(3).

§ 170.285 Disposition of pending GRAS affirmation petitions.

Because the procedure to submit a GRAS notice is replacing the former process to submit a GRAS affirmation petition, the following will happen to a filed GRAS affirmation petition that is pending on October 17, 2016.

(a) On October 17, 2016, we will close the docket for any GRAS affirmation petition that is still pending as of October 17, 2016.

(b) Any person who submitted a GRAS affirmation petition described in this section may submit a GRAS notice as described in this subpart and request that we incorporate the GRAS affirmation petition as described in § 170.215.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

■ 12. The authority citation for part 184 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 348, 371.

■ 13. In § 184.1, revise the first sentence of paragraph (a), and revise the fifth sentence and remove the last sentence of paragraph (b)(1) to read as follows.

§ 184.1 Substances added directly to human food affirmed as generally recognized as safe (GRAS).

(a) The direct human food ingredients listed in this part have been reviewed by the Food and Drug Administration and affirmed to be generally recognized as safe (GRAS) for the purposes and under the conditions prescribed. * * *

(b) * * *

(1) * * * In such a case, a manufacturer may not rely on the regulation as authorizing that use but shall have a basis to conclude that that use is GRAS or shall use the ingredient in accordance with a food additive regulation. * * *

* * * * *

PART 186—INDIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

■ 14. The authority citation for part 186 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 348, 371.

■ 15. In § 186.1, revise the first sentence of paragraph (a), and revise the fifth sentence and remove the last sentence of paragraph (b)(1) to read as follows.

§ 186.1 Substances added indirectly to human food affirmed as generally recognized as safe (GRAS).

(a) The indirect human food ingredients listed in this part have been reviewed by the Food and Drug Administration and affirmed to be generally recognized as safe (GRAS) for the purposes and under the conditions prescribed, providing they comply with the purity specifications listed in this part or, in the absence of purity specifications, are of a purity suitable for their intended use in accordance with § 170.30(h)(1) of this chapter.

* * *

(b) * * *

(1) * * * In such a case, a manufacturer may not rely on the regulation as authorizing that use but shall have a basis to conclude that the use is GRAS or shall use the ingredient in accordance with a food additive regulation. * * *

* * * * *

PART 570—FOOD ADDITIVES

■ 16. The authority citation for part 570 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 346a, 348, 371.

■ 17. In § 570.3, revise paragraphs (f), (h), the first sentence of (i), and (k), and add paragraph (n) to read as follows:

§ 570.3 Definitions.

* * * * *

(f) *Common use in food* means a substantial history of consumption of a substance by a significant number of animals of the species to which the substance is intended to be fed (and, for food-producing animals fed with such substance, also means a substantial history of consumption by humans consuming human foods derived from those food-producing animals), prior to January 1, 1958.

* * * * *

(h) *Scientific procedures* 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 its intended use.

(i) *Safe* or *safety* means that there is a reasonable certainty in the minds of

competent scientists that the substance is not harmful under the conditions of its intended use. * * *

* * * * *

(k) *General recognition of safety* shall be in accordance with § 570.30.

* * * * *

(n) *Food-producing animal* means an animal used to produce human food.

■ 18. In § 570.30, revise the last sentence of paragraph; (a); revise paragraphs (b) through (d); and revise the last sentence in paragraph (i) to read as follows:

§ 570.30 Eligibility for classification as generally recognized as safe (GRAS).

(a) * * * 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 to either the target animal or to humans consuming human food derived from food-producing animals under the conditions of its intended use (see § 570.3(i)).

(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. General recognition of safety through scientific procedures shall address safety for both the target animal and for humans consuming human food derived from food-producing animals and shall be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

(c)(1) General recognition of safety through experience based on common use in food prior to January 1, 1958, shall address safety for both the target animal and for humans consuming human food derived from food-producing animals and may be achieved without the quantity or quality of scientific procedures required for approval of a food additive. General recognition of safety through experience based on common use in food prior to January 1, 1958, shall be based solely on food use of the substance in the same animal species prior to January 1, 1958, and shall ordinarily be based upon generally available data and information. An ingredient not in common use in food prior to January 1, 1958, may achieve general recognition of safety only through scientific procedures.

(2) A substance used in food prior to January 1, 1958, may be generally recognized as safe through experience based on its common use in food when that use occurred exclusively or primarily outside of the United States if the information about the experience establishes that the substance is safe under the conditions of its intended use within the meaning of section 201(u) of the Federal Food, Drug, and Cosmetic Act (see also § 570.3(i)) for both the target animal and for humans consuming human food derived from food-producing animals. Common use in food prior to January 1, 1958, that occurred outside of the United States shall be documented by published or other information and shall be corroborated by information from a second, independent source that confirms the history and circumstances of use of the substance. The information used to document and to corroborate the history and circumstances of use of the substance must be generally available; that is, it must be widely available in the country in which the history of use has occurred and readily available to interested qualified experts in the United States. A person who concludes that a use of a substance is GRAS through experience based on its common use in food outside of the United States should notify FDA of that view in accordance with subpart E of this part.

(d) The food ingredients listed as GRAS in part 582 of this chapter or affirmed as GRAS in part 584 of this chapter do not include all substances that are generally recognized as safe for their intended use in food. Because of the large number of substances the intended use of which results or may reasonably be expected to result, directly or indirectly, in their becoming a component or otherwise affecting the characteristics of food, it is impracticable to list all such substances that are GRAS. A food ingredient of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effects, which is subject only to conventional processing as practiced prior to January 1, 1958, and for which no known safety hazard exists, will ordinarily be regarded as GRAS without specific inclusion in part 582 or part 584 of this chapter.

* * * * *

(i) * * * Any use of such an ingredient not in full compliance with each such established limitation shall require a food additive regulation.

* * * * *

■ 19. In § 570.35, revise paragraphs (a), (b)(1), (3), and (4), and remove paragraph (c) to read as follows:

§ 570.35 Affirmation of generally recognized as safe (GRAS) status.

(a) The Commissioner, on his own initiative, may affirm that a substance that directly or indirectly becomes a component of food is GRAS under the conditions of its intended use.

(b)(1) If the Commissioner proposes on his own initiative that a substance is entitled to affirmation as GRAS under the conditions of its intended use, he will place all of the data and information on which he relies on public file in the office of the Division of Dockets Management and will publish in the **Federal Register** a notice giving the name of the substance, its proposed uses, and any limitations proposed for purposes other than safety.

* * * * *

(3) The Commissioner will evaluate all comments received. If he concludes that there is convincing evidence that the substance is GRAS under the conditions of its intended use as described in § 570.30, he will publish a notice in the **Federal Register** listing the GRAS conditions of use in this subchapter E.

(4) If, after evaluation of the comments, the Commissioner concludes that there is a lack of convincing evidence that the substance is GRAS under the conditions of its intended use and that it should be considered a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic Act, he shall publish a notice thereof in the **Federal Register** in accordance with § 570.38.

■ 20. In § 570.38, revise paragraph (a) to read as follows:

§ 570.38 Determination of food additive status.

(a) The Commissioner may, in accordance with § 570.35(b)(4), publish a notice in the **Federal Register** determining that a substance is not GRAS under the conditions of its intended use and is a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic Act.

* * * * *

■ 21. Add and reserve subparts C and D.

■ 22. Add subpart E, consisting of §§ 570.203 through 570.280, to read as follows:

Subpart E—Generally Recognized as Safe (GRAS) Notice

Sec.

Subpart E—Generally Recognized as Safe (GRAS) Notice

§ 570.203 Definitions.

The definitions and interpretations of terms in § 570.3 apply to such terms when used in this subpart. The following definitions also apply:

Amendment means any data and information that you submit regarding a filed GRAS notice before we respond to your notice by letter in accordance with § 570.265(b)(1) or cease to evaluate your notice in accordance with § 570.265(b)(3).

GRAS means generally recognized as safe.

GRAS notice means a submission that informs us of your view that a substance is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is GRAS under the conditions of its intended use in accordance with § 570.30.

Notified substance means the substance that is the subject of your GRAS notice.

Notifier means the person (*e.g.,* an individual, partnership, corporation, association, or other legal entity) who is responsible for the GRAS notice, even if another person (such as an attorney, agent, or qualified expert) prepares or submits the notice or provides an opinion about the basis for a conclusion of GRAS status.

Qualified expert means an individual who is qualified by scientific training and experience to evaluate the safety of substances under the conditions of their intended use in animal food.

Supplement means any data and information that you submit regarding a filed GRAS notice after we respond to your notice by letter in accordance with § 570.265(b)(1) or cease to evaluate your notice in accordance with § 570.265(b)(3).

We, our, and *us* refer to the United States Food and Drug Administration (FDA).

You and *your* refer to a notifier.

§ 570.205 Opportunity to submit a GRAS notice.

Any person may notify FDA of a view that a substance is not subject to the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act based on that person's conclusion that the substance is GRAS under the conditions of its intended use.

§ 570.210 How to send your GRAS notice to FDA.

(a) Send your GRAS notice to the Division of Animal Feeds (HFV–220), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855.

(b) When you submit your GRAS notice, you may do so either in an electronic format that is accessible for our evaluation or on paper. If you send your GRAS notice on paper, a single paper copy is sufficient.

§ 570.215 Incorporation into a GRAS notice.

You may incorporate into your GRAS notice either specifically identified data and information that you previously submitted to the Center for Veterinary Medicine (CVM), or specifically identified publicly available data and information submitted by another party, when such data and information remain in CVM's records, such as data and information contained in a previous GRAS notice or a food additive petition.

§ 570.220 General requirements applicable to a GRAS notice.

(a) A GRAS notice has seven parts as required by §§ 570.225 through 570.255. You must submit the data and information specified in each of these parts on separate pages or sets of pages.

(b) You must include each of the seven parts in your GRAS notice. If you do not include a part, you must include with your GRAS notice an explanation of why that part does not apply to your GRAS notice.

§ 570.225 Part 1 of a GRAS notice: Signed statements and certification.

(a) Part 1 of your GRAS notice must be dated and signed by a responsible official of your organization, or by your attorney or agent.

(b) Except as required by paragraph (c)(8) of this section, you must not include any information that is trade secret or confidential commercial information in Part 1 of your GRAS notice.

(c) In Part 1 of your GRAS notice, you must:

(1) Inform us that you are submitting a GRAS notice in accordance with this subpart;

(2) Provide the name and address of your organization;

(3) Provide the name of the notified substance, using an appropriately descriptive term;

(4) Describe the intended conditions of use of the notified substance, including stating whether the substance will be added to food (including drinking water) for animals in which the substance will be used; identifying the foods to which it will be added, the levels of use in such foods, and the animal species for which these foods are intended (including, when appropriate, a description of a subpopulation expected to consume the notified substance); and the purposes for which the substance will be used;

(5) Inform us of the statutory basis for your conclusion of GRAS status (*i.e.,* through scientific procedures in accordance with § 570.30(a) and (b) or through experience based on common use in animal food in accordance with § 570.30(a) and (c));

(6) State your view that the notified substance is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the notified substance is GRAS under the conditions of its intended use;

(7) State that, if we ask to see the data and information that are the basis for your conclusion of GRAS status, either during or after our evaluation of your notice, you will:

(i) Agree to make the data and information available to us; and

(ii) Agree to both of the following procedures for making the data and information available to us:

(A) Upon our request, you will allow us to review and copy the data and information during customary business hours at the address you specify for where these data and information will be available to us; and

(B) Upon our request, you will provide us with a complete copy of the data and information either in an electronic format that is accessible for our evaluation or on paper;

(8) State your view as to whether any of the data and information in Parts 2 through 7 of your GRAS notice are exempt from disclosure under the

Freedom of Information Act, 5 U.S.C. 552 (*e.g.,* as trade secret or as commercial or financial information that is privileged or confidential);

(9) Certify that, to the best of your knowledge, the GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to you and pertinent to the evaluation of the safety and GRAS status of the use of the substance; and

(10) State both the name and the position or title of the person who signs the GRAS notice.

§ 570.230 Part 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect.

In Part 2 of your GRAS notice, you must include:

(a) Scientific data and information that identifies the notified substance.

(1) Examples of appropriate data and information include the chemical name, applicable registry numbers (such as a Chemical Abstracts Service (CAS) registry number or an Enzyme Commission (EC) number), empirical formula, structural formula, quantitative composition, and characteristic properties.

(2) When the source of a notified substance is a biological material, you must include data and information sufficient to identify:

(i) The taxonomic source (*e.g.,* genus, species), including as applicable data and information at the sub-species level (*e.g.,* variety, strain);

(ii) The part of any plant or animal used as the source; and

(iii) Any known toxicants that could be in the source;

(b) A description of the method of manufacture of the notified substance in sufficient detail to evaluate the safety of the notified substance as manufactured;

(c) Specifications for material that is of appropriate grade for use in animal food; and

(d) When necessary to demonstrate safety, relevant data and information bearing on the physical or other technical effect the notified substance is intended to produce, including the quantity of the notified substance required to produce such effect.

§ 570.235 Part 3 of a GRAS notice: Target animal and human exposures.

In part 3 of your GRAS notice, you must provide data and information about exposure to the target animal and to humans consuming human food derived from food-producing animals, regardless of whether your conclusion of GRAS status is through scientific procedures or through experience based on common use in food, as follows:

(a) For exposure to the target animal, you must provide:

(1) The amount of the notified substance that different target animal species are likely to consume in the animal food (including drinking water) as part of the animal's total diet, including the intended use and all other sources in the total diet; and

(2) When applicable, the amount of any other substance that is expected to be formed in or on food because of the use of the notified substance (*e.g.,* hydrolytic products or reaction products);

(3) When applicable, the amount of any other substance that is present with the notified substance either naturally or due to its manufacture (*e.g.,* contaminants or by-products);

(4) The data and information you rely on to establish the amount of the notified substance and the amounts of any other substance in accordance with paragraphs (a)(1) through (a)(3) of this section that different target animal species are likely to consume in the animal food (including drinking water) as part of the animal's total diet; and

(b) When the intended use is in food for food-producing animals, you must provide:

(1) The potential quantities of any residues that humans may be exposed to in edible animal tissues, including:

(i) Residues of the notified substance;

(ii) Residues of any other substance that is expected to be formed in or on the animal food because of the use of the notified substance; and

(iii) Residues from any other substance that is present with the notified substance whether naturally, due to its manufacture (*e.g.,* contaminants or by-products), or produced as a metabolite in edible animal tissues when the notified substance is consumed by a food-producing animal; and

(2) The data and information you rely on to establish, in accordance with paragraph (b)(1) of this section, the potential quantities of any residues that humans may be exposed to in edible animal tissues.

§ 570.240 Part 4 of a GRAS notice: Self-limiting levels of use.

In circumstances where the amount of the notified substance that can be added to animal food is limited because animal food containing levels of the notified substance above a particular level would become unpalatable or technologically impractical, in Part 4 of your GRAS notice you must include data and information on such self-limiting levels of use.

§ 570.245 Part 5 of a GRAS notice: Experience based on common use in food before 1958.

If the statutory basis for your conclusion of GRAS status is through experience based on common use in animal food, in Part 5 of your GRAS notice you must include evidence of a substantial history of consumption of the notified substance for food use by a significant number of animals of the species to which the substance is intended to be fed prior to January 1, 1958, and evidence of a substantial history of consumption by humans consuming human foods derived from food-producing animals prior to January 1, 1958.

§ 570.250 Part 6 of a GRAS notice: Narrative.

In Part 6 of your GRAS notice, you must include a narrative that provides the basis for your conclusion of GRAS status, in which:

(a)(1) You must explain why the data and information in your notice provide a basis for your view that the notified substance is safe under the conditions of its intended use for both the target animal and for humans consuming human food derived from food-producing animals. In your explanation, you must address the safety of the notified substance, considering all animal food (including drinking water) as part of the animal's total diet, taking into account any chemically or pharmacologically related substances in such diet. In your explanation, you must also address the safety of the notified substance in regard to human exposure, considering all dietary sources and taking into account any chemically or pharmacologically related substances;

(2) In your explanation, you must identify what specific data and information that you discuss in accordance with paragraph (a)(1) of this section are generally available, and what specific data and information that you discuss in accordance with paragraph (a)(1) of this section are not generally available, by providing citations to the list of data and information that you include in Part 7 of your GRAS notice in accordance with § 570.255;

(b) You must explain how the generally available data and information that you rely on to establish safety in accordance with paragraph (a) of this section provide a basis for your conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use for both the target animal and for humans consuming human food derived from food-producing animals;

(c) You must either:

(1) Identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status, regardless of whether those data and information are generally available; or

(2) State that you have reviewed the available data and information and are not aware of any data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status;

(d) If you view any of the data and information in your notice as exempt from disclosure under the Freedom of Information Act, you must identify the specific data and information; and

(e) For non-public, safety-related data and information considered in reaching a conclusion of GRAS status, you must explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to such data and information.

§ 570.255 Part 7 of a GRAS notice: List of supporting data and information in your GRAS notice.

(a) In part 7 of your GRAS notice, you must include a list of all of the data and information that you discuss in Part 6 of your GRAS notice to provide a basis for your view that the notified substance is safe under the conditions of its intended use as described in accordance with § 570.250(a)(1).

(b) You must specify which data and information that you list in accordance with paragraph (a) of this section are generally available, and which data and information are not generally available.

§ 570.260 Steps you may take before FDA responds to your GRAS notice.

(a) You may submit a timely amendment to your filed GRAS notice, to update your GRAS notice or in response to a question from us, before we respond to your notice by letter in accordance with § 570.265(b)(1) or cease to evaluate your notice in accordance with § 570.265(b)(3).

(b) At any time before we respond to your notice by letter in accordance with § 570.265(b)(1), you may request in writing that we cease to evaluate your GRAS notice. Your request does not preclude you from submitting a future GRAS notice in accordance with this subpart with respect to the notified substance.

§ 570.265 What FDA will do with a GRAS notice.

(a)(1) We will conduct an initial evaluation of your submission to determine whether to file it as a GRAS notice for evaluation of your view that the notified substance is GRAS under the conditions of its intended use.

(2) If we file your submission as a GRAS notice, we will send you a letter that informs you of the date of filing.

(3) If we do not file your submission as a GRAS notice, we will send you a letter that informs you of that fact and provide our reasons for not filing the submission as a GRAS notice.

(4) We will consider any timely amendment that you submit to a filed GRAS notice, to update your GRAS notice or in response to a question from us, before we respond to you by letter in accordance with paragraph (b)(1) of this section, if we deem that doing so is feasible within the timeframes established in paragraph (b) of this section. If we deem that considering your amendment is not feasible within the timeframes established in paragraph (b) of this section or if we have granted your request to cease to evaluate your notice, we will inform you that we are not considering your amendment.

(b)(1) Within 180 days of filing, we will respond to you by letter based on our evaluation of your notice. We may extend the 180 day timeframe by 90 days on an as needed basis.

(2) If we extend the timeframe, we will inform you in writing of the extension as soon as practicable but no later than within 180 days of filing.

(3) If you ask us to cease to evaluate your GRAS notice in accordance with § 570.260(b), we will send you a letter informing you of our decision regarding your request.

(c) If circumstances warrant, we will send you a subsequent letter about the notice.

§ 570.275 Public disclosure of a GRAS notice.

(a) The data and information in a GRAS notice (including data and information submitted in any amendment or supplement to your GRAS notice, or incorporated into your GRAS notice) are:

(1) Considered a mandatory, rather than voluntary, submission for purposes of their status under the Freedom of Information Act and our public information requirements in part 20 of this chapter; and

(2) Available for public disclosure in accordance with part 20 of this chapter as of the date that we receive your GRAS notice.

(b) We will make the following readily accessible to the public:

(1) A list of filed GRAS notices, including the information described in § 570.225(c)(2) through (c)(5);

(2) The text of any letter that we issue under § 570.265(b)(1) or (c); and

(3) The text of any letter that we issue under § 570.265(b)(3) if we grant your request that we cease to evaluate your notice.

(c) We will disclose all remaining data and information that are not exempt from public disclosure in accordance with part 20 of this chapter.

§ 570.280 Submission of a supplement.

If circumstances warrant, you may submit a supplement to a filed GRAS notice after we respond to your notice by letter in accordance with § 570.265(b)(1) or cease to evaluate your notice in accordance with § 570.265(b)(3).

Dated: August 8, 2016.

Jeremy Sharp,

Deputy Commissioner for Policy, Planning, Legislation and Analysis.

[FR Doc. 2016–19164 Filed 8–12–16; 11:15 am]

BILLING CODE 4164–01–P