(2) *Identification of the averaging group.* An averaging group will consist of subject merchandise that is identical or virtually identical in all physical characteristics and that is sold to the United States at the same level of trade. In identifying sales to be included in an averaging group, the Secretary also will take into account, where appropriate, the region of the United States in which the merchandise is sold, and such other factors as the Secretary considers relevant.

(3) *Time period over which weighted average is calculated.* When applying the average-to-average method in an investigation, the Secretary normally will calculate weighted averages for the entire period of investigation. However, when normal values, export prices, or constructed export prices differ significantly over the course of the period of investigation, the Secretary may calculate weighted averages for such shorter period as the Secretary deems appropriate. When applying the average-to-average method in a review, the Secretary normally will calculate weighted averages on a monthly basis and compare the weighted-average monthly export price or constructed export price to the weighted-average normal value for the contemporaneous month.

(e) *Application of the average-to-transaction method*—In applying the average-to-transaction method in a review, when normal value is based on the weighted average of sales of the foreign like product, the Secretary will limit the averaging of such prices to sales incurred during the contemporaneous month.

(f) *Contemporaneous Month.* Normally, the Secretary will select as the contemporaneous month the first of the following months which applies: (1) The month during which the particular U.S. sales under consideration were made;

(2) If there are no sales of the foreign like product during this month, the most recent of the three months prior to the month of the U.S. sales in which there was a sale of the foreign like product.

(3) If there are no sales of the foreign like product during any of these months, the earlier of the two months following the month of the U.S. sales in which there was a sale of the foreign like product.

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BILLING CODE 3510–DS–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 170, 184, 186, and 570

[Docket No. FDA–1997–N–0020; Formerly Docket No. 1997N–0103]

Substances Generally Recognized as Safe; Reopening of the Comment Period

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; reopening of the comment period.

SUMMARY: The Food and Drug Administration (FDA) is reopening the comment period for the proposed rule published in the **Federal Register** of April 17, 1997 (the 1997 proposed rule). The 1997 proposed rule would replace the voluntary petition process to affirm the generally recognized as safe (GRAS) status of a substance intended for use in food for humans or animals with a voluntary notification procedure. FDA is reopening the comment period to update comments. The proposed rule would also clarify the criteria for exempting the use of a substance as GRAS.

DATES: The comment period for the proposed rule published April 17, 1997 (62 FR 18938), is reopened. Submit either electronic or written comments on the proposed rule by March 28, 2011. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by February 28, 2011, (*see* the "Paperwork Reduction Act of 1995" section of this document).

ADDRESSES: You may submit comments, including comments regarding the proposed collection of information, identified by Docket No. FDA–1997–N–0020, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- *FAX:* 301–827–6870.
- *Mail/Hand delivery/Courier (for paper, disk, or CD–ROM submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA–1997–N–0020, for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov,* including any personal information provided. For additional information on submitting comments, *see* the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: *With regard to substances that would be used in human food:* Paulette M. Gaynor, Center for Food Safety and Applied Nutrition (HFS–255), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–1192.

With regard to substances that would be used in food for animals: Geoffrey K. Wong, Center for Veterinary Medicine (HFV–224), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, 240–453–6879.

With regard to the information collection: Denver Presley Jr., Office of Information Management, Food and Drug Administration, 1350 Piccard Dr., PI50–400B, Rockville, MD 20850, 301–796–3793.

SUPPLEMENTARY INFORMATION:

I. Background

In the 1997 proposed rule, FDA proposed to replace the voluntary GRAS affirmation petition process in §§ 170.35(c) and 570.35(c) (21 CFR 170.35(c) and 570.35(c)) with a voluntary notification procedure whereby any person may notify us of a determination that a particular use of a substance in human food (proposed § 170.36) or in food for animals (proposed § 570.36) is GRAS.[1] We also proposed to clarify the criteria in §§ 170.30 (21 CFR 170.30) and 570.30 (21 CFR 570.30) whereby the use of a substance is not subject to the premarket approval requirements of the FD&C Act because it is GRAS. To simplify the discussion in this document, in general,

[1] As an error, the authority citation we listed for the proposed amendments to part 570 (21 CFR part 570) did not include an existing authority citation, *i.e.,* section 408 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 346a). Nothing in the 1997 proposed rule would alter the citation to section 408. Therefore, the authority citation for part 570 will continue to include section 408.

we refer to provisions of the 1997 proposed rule and issues for further comment from the perspective of the regulations that would be established in part 170 (21 CFR part 170). Unless we say otherwise, however, the issues discussed also apply to the corresponding provisions for part 570.

Under the proposed notification procedure, a GRAS notice would include: (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, including information about the method of manufacture (excluding any trade secrets); (3) information about any self-limiting levels of use; and (4) a comprehensive discussion of the basis for the GRAS determination. We would evaluate whether the notice provides a sufficient basis for a GRAS determination and would respond to the notifier in writing. We would immediately make available to the public the notice's "GRAS exemption claim" and our response to the notice, and disclose other releasable information in a notice in accordance with our regulations, in part 20 (21 CFR part 20), implementing the Freedom of Information Act.

We invited interested persons who determine that a use of a substance is GRAS to notify us of those determinations, under the framework of the 1997 proposed rule, during the interim between the proposed and final rules (62 FR 18938 at 18954). We said that we would determine whether our experience in administering such notices suggested that modifications to the proposed notification procedure were necessary (62 FR 18938 at 18954). During the period from February 1, 1999, through December 31, 2009 (the interim period), our Center for Food Safety and Applied Nutrition (CFSAN) received approximately 26 GRAS notices per year about substances intended for use in human food. The Center for Veterinary Medicine (CVM) established a pilot notification program only recently. (*See* the **Federal Register** of June 4, 2010; 75 FR 31800.)

The memorandum in reference 1 of this document describes CFSAN's experience (through December 31, 2009). In the remainder of this document, we refer to this memorandum as the "experience document." Because CVM's pilot program began relatively recently, the experience document does not describe any experience under CVM's pilot notification program.

Also, from 2008 to 2010, the Government Accountability Office (GAO) conducted a study related to food ingredients determined to be GRAS and, in 2010, issued a report (Ref. 2, the GAO report) that included a number of recommendations for FDA's food ingredient program. FDA responded to the GAO's recommendations, and that response is also included in the GAO report.

II. Request for Comments

Because of the length of time that has elapsed since publication of the 1997 proposed rule, we are interested in updating comments before issuing a final rule. In addition, based on CFSAN's experience with GRAS notices during the interim period, comments we received on the proposed rule, and GAO's recommendations, we have identified a number of issues within the scope of the proposed rule that may require further clarification. Specifically, these issues relate to the proposed revisions to § 170.30 (Issue 1), the proposed establishment of a notification procedure (Issues 2 through 16), and the effect of the proposed notification procedure on existing GRAS petitions (Issue 17).[2] Accordingly, we are requesting comments on the entire 1997 proposed rule as well as on the specific issues identified in this document.

Comments previously submitted to the Division of Dockets Management (previously the Dockets Management Branch), including comments submitted to the Division of Dockets Management after the comment period closed on July 16, 1997, but before December 28, 2010, do not need to be resubmitted in response to this notice because all such comments will be considered in any final rule based on the 1997 proposed rule and this document.[3]

[2] With regard to GAO's recommendations, we are requesting comment on the recommendations that FDA obtain more information about the use of engineered nanomaterials (Issue 10(c)), that FDA strive to minimize the potential for conflict of interest (Issue 15), and that FDA issue guidance on how to document GRAS determinations (Issue 16). GAO also recommended that FDA develop a strategy to finalize the proposal to establish a notification program for GRAS ingredients, and this notice reopening the comment period is the first step of such a strategy. FDA is not seeking comment on the remaining GAO recommendations, that FDA request that any company conducting a GRAS determination provide the Agency with basic information about that determination, and that FDA develop a strategy to reconsider the safety of certain GRAS substances. We consider those recommendations, and any comments on them, to be beyond the scope of this comment request because they raise issues about matters other than how a notification program should be run.

[3] After we issued the 1997 proposed rule, a Presidential Memorandum dated June 1, 1998 (the Plain Language Memorandum) (Ref. 3) prescribed a government-wide initiative (the Plain Language Initiative, or "PLI") to write regulations using "Plain Language." As outlined in that memorandum, documents written in plain language use "you" and other pronouns. Any final rule based on the 1997 proposed rule and this document would use such pronouns.

A. Issue 1. Description of Common Knowledge Element and Related Definition of "Scientific Procedures"

In the 1997 proposed rule, we proposed to revise § 170.30 to broaden the description of the common knowledge element to clarify the types of technical evidence of safety that would form the basis of a GRAS determination, and to clarify the role of publication in satisfying the common knowledge element. Specifically, we proposed revising § 170.30(b) from "* * * ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information." to "based upon generally available and accepted scientific data, information, methods, or principles, which ordinarily are published and may be corroborated by unpublished scientific data, information, or methods." We also proposed a companion change to the definition of scientific procedures (§ 170.3(h)) from "Scientific procedures include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance." to "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."

Most of the comments addressing these proposed amendments supported the amendments. In general, these comments expressed the opinion that the proposed amendments would more accurately reflect the state of contemporary science than the provisions they would replace. One comment objected to the proposed amendment to § 170.30(b). This comment asserted that the proposed amendment would de-emphasize or eliminate the existing criterion for peer-reviewed studies. One comment objected to the proposed amendment to § 170.3(h) because, under the proposed amendment, an "unpublished principle" could inappropriately be considered a sufficient scientific procedure for demonstrating the safety of a food substance.

In light of these comments, we reviewed our proposed inclusion of scientific "principles" in the proposed amendments to §§ 170.3(h) and 170.30(b). "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 (Shorter Oxford English Dictionary, 5th Edition, 2002). Thus, a principle is a different genre than data, information, and methods and is, by its very nature, generally available and accepted. An "unpublished principle" is a non-sequitur. Therefore, the adjectives "published" and "unpublished" should not modify scientific "principles."

We also reviewed our use of the term "study" in the proposed companion change to the definition of scientific procedures. A procedure can be defined as a particular mode or course of action (Shorter Oxford English Dictionary, 5th Edition, 2002); a "study" can be defined as the devotion of time and attention to acquiring information or knowledge or as applying the mind to acquiring knowledge, especially devoting time and effort to this end (Id.). The terms "procedure" and "study" each carry the connotation of an action. However, "data and information" would be the outcome of a study or procedure and do not carry the connotation of an action. To be a "procedure," data, information, methods or principles would need to be acquired or applied.

We are seeking comment on the use of those terms. For example, we are considering whether to revise the second sentence of § 170.30(b) to 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, and may be corroborated by the application of unpublished scientific data, information, or methods. We also are considering whether to revise the definition of scientific procedures 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.

B. Issue 2. Terms

In the 1997 proposed rule, we used the terms "determine" and "determination" to describe the action of a person who informs us that the use of a food substance is GRAS under the proposed notification procedure. However, as discussed in the experience document, during the interim period CFSAN responded to approximately 5 percent of submitted GRAS notices with a letter informing the notifier that the notice did not provide a basis for a "GRAS determination" (Ref. 1). Clearly, in these cases it was CFSAN's view that the notifier had not "determined" GRAS status. To clarify that the submission of a GRAS notice reflects the view of the notifier and may not necessarily provide an adequate basis for a GRAS determination, we have tentatively concluded that the terms "conclude" and "conclusion" in lieu of "determine" and "determination" would be more appropriate, and therefore in this document we use the terms "conclude" and "conclusion." We seek comment on these terms.

C. Issue 3. Definitions

In the 1997 proposed rule, we did not propose definitions of terms that would be associated with the GRAS notification procedure. However, it would be consistent with the Plain Language Initiative for a final rule to include definitions of terms used in the rule. While the meanings of some terms (such as "notified substance") were implicit in the discussion of the proposed notification procedure, to ensure the opportunity to comment on these definitions, we include them here. In addition, some terms not used in the 1997 proposed rule may be useful in light of comments already received. We seek comment on the definitions described in the following paragraphs.

(Issue 3a). "Amendment" and "supplement." Several comments asked FDA to allow a notifier to address questions FDA had about a GRAS notice by submitting an amendment to the notice. As discussed in the experience document (Ref. 1), during the interim period several notifiers submitted one or more amendments to their GRAS notices. We would define "amendment" to mean any data or other information that you submit regarding a filed GRAS notice before we respond to the notice.

As discussed in the experience document (Ref. 1), during the interim period several notifiers submitted information to a GRAS notice after CFSAN responded to the notice. We would define "supplement" to mean any data or other information that you submit regarding a filed GRAS notice after we respond to the notice.

(Issue 3b) "Notified substance," "notifier," and "qualified expert." We would define "notified substance" to mean the substance that is the subject of your GRAS notice. We would define "notifier" to mean the person 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. Consistent with section 201(s) of the FD&C Act (21 U.S.C. 321(s)), we would define "qualified expert" to mean an individual who is qualified by scientific training and experience to evaluate the safety of substances added to food.

D. Issue 4. Incorporation by Reference

One comment requested that a notifier be permitted to reference a previously submitted GRAS notice to support a view that an additional use of the applicable substance is GRAS. In the comment's view, this process, known as "incorporation by reference," would be administratively efficient. As discussed in the experience document (Ref. 1), during the interim period CFSAN encouraged notifiers to use a process such as that recommended in the comment.

We are therefore seeking comment on whether to include a provision in the final rule to expressly permit the notifier to incorporate by reference either 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, such as data and information contained in a previous GRAS notice, a food additive petition, or a food master file.

While the data and information in a previously submitted GRAS notice are generally publicly available, other data and information that have been submitted to us may be confidential. We do not anticipate that a notifier would have access to another party's confidential data or information.

We note that, regardless of whether a notifier incorporates by reference data or information, we may consider taking into account other relevant data or information that we have from other sources. As discussed in the experience document (Ref. 1), during the interim period CFSAN did review information that was available in its files but not available to the applicable notifier.

E. Issue 5. Request That FDA Cease To Evaluate a GRAS Notice

Several comments requested that the notification procedure provide for a notifier to withdraw a notice in light of our questions about the notice. These comments considered such a provision would provide the notifier with an opportunity to resubmit a notice addressing our questions.

Under § 20.29, no person may withdraw records submitted to FDA. While a notifier cannot withdraw a GRAS notice submitted to FDA, when

we issued the proposed rule, we considered a request that FDA cease to evaluate a GRAS notice to be an implicit prerogative not needing explicit authorization in the rule. For GRAS notices that FDA has ceased to evaluate at the request of the notifier, the GRAS notices remain in our files and, thus, are available for public disclosure, subject to procedures established in part 20.

As discussed in the experience document (Ref. 1), at the request of the notifier, CFSAN ceased to evaluate approximately 16 percent of GRAS notices that came to closure by December 31, 2009. Persons who rely only on the provisions of proposed § 170.36, without referring to our letters responding to GRAS notices, may not be aware of the implicit prerogative to request that FDA cease to evaluate a GRAS notice.

Therefore, we are seeking comment on whether the rule should explicitly state that you may request in writing that we cease to evaluate your GRAS notice at any time during our evaluation of your GRAS notice.

F. Issue 6. Notifier's Responsibility for a GRAS Conclusion

(Issue 6a) Under proposed § 170.36(c)(1), the GRAS notice would be dated and signed by the notifier or by the notifier's attorney or agent or (if the notifier is a corporation) by an authorized official. As discussed in the experience document (Ref. 1), during the interim period CFSAN received some GRAS notices in which the combination of an illegible signature and the lack of a typed or printed name to accompany the signature made it impossible to identify the person who was signing the document. Therefore, we are seeking comment on how to best ensure that the identity and authority of the person who is signing the GRAS notice is made clear. For example, we are considering requiring that the GRAS notice state the name and the position or title of the person who signs it.

(Issue 6b) Under the GRAS affirmation petition process, a petitioner is required to submit a petition for GRAS affirmation under 21 CFR part 10 (§ 170.35(c)(1)(v)). As part of this petition, a petitioner is required to submit a statement that, "to the best of his knowledge, it [the GRAS affirmation petition] 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." (§ 170.35(c)(1)(v)). We implicitly proposed this provision under proposed § 170.36(c)(4), which proposed to require, among other things, that a GRAS notice include a comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with the conclusion of GRAS status. We are seeking comment on whether the GRAS notification procedure should be as explicit on this point as the GRAS affirmation petition process it would replace.

We also are seeking comment on whether to require a notifier to certify to this statement, which would be consistent with the certification in item *E. Certification* in § 10.30(b). Such certification also would be consistent with the procedures established for another notification program in CFSAN, the premarket notification program for food contact substances. (*See* § 171.101(e) and FDA Form No. 3480 (Ref. 4).)

G. Issue 7. Appropriately Descriptive Term for the Notified Substance

In the 1997 proposed rule, we proposed to require that the GRAS notice include the common or usual name of the notified substance (proposed § 170.36(c)(1)(ii)). We also advised that notifiers with questions concerning the common or usual name for a substance consult with CFSAN's Office of Food Labeling (now the Office of Nutrition, Labeling and Dietary Supplements) (for a substance that would be used in human food) or with CVM's Division of Animal Feeds (for a substance that would be used in animal food).[4] As discussed in the experience document (Ref. 1), in 2004, CFSAN began to routinely advise notifiers that its use of a particular term to identify the notified substance in a letter responding to a GRAS notice should not be considered an endorsement or recommendation of that term as an appropriate common or usual name for the purpose of complying with the labeling provisions of the FD&C Act.

A GRAS notice addresses sections 201(s) and 409 of the FD&C Act and does not address the labeling provisions of the FD&C Act or FDA's corresponding regulations. We are seeking comment on whether to revise proposed § 170.36(c)(1)(ii) to make this more clear. For example, instead of requiring that the GRAS notice include the common or usual name of the notified substance, we are considering requiring that the GRAS notice include the name of the notified substance, using an appropriately descriptive term. We note that this may be the same as the term which you may believe would be the common or usual name of the substance under 21 CFR parts 102 (human food) and 502 (animal food).

H. Issue 8. Public Disclosure

Under proposed § 170.36(f)(1), the elements listed in proposed § 170.36(c)(1)) would be immediately available for public disclosure on the date the notice is received. As a practical consequence of this proposed provision, the fact that we had received a GRAS notice (*i.e.,* the existence of the GRAS notice) would be immediately available to the public. As discussed in the experience document (Ref. 1), we have made this information readily accessible to the public. CFSAN currently is making a "GRAS Notice Inventory" available on its Internet site. CFSAN presents notice-specific information (such as the name and address of the notifier, the name of the notified substance, and the intended conditions of use) extracted from the information submitted under proposed § 170.36(c)(1). CFSAN expects that the ways by which we make this information readily accessible to the public will evolve over time.

Because, under proposed § 170.36(f)(1), the information submitted under proposed § 170.36(c)(1) would be immediately available for public disclosure, it is implicit in this provision that a person submitting information under proposed § 170.36(c)(1) should not include in this portion any non-public information such as trade secret information, confidential commercial or financial information, and personal privacy information. Based on our experience, notifiers did not identify any information in the information submitted under proposed § 170.36(c)(1) as being confidential. We are seeking comment on whether the final rule should explicitly require that the information submitted under proposed § 170.36(c)(1) exclude non-public information.

I. Issue 9. Including Confidential Information in a GRAS Notice

We proposed that the method of manufacture in a GRAS notice exclude any trade secrets (proposed § 170.36(c)(2)). However, we stated that a notifier who considers that certain information in a submission should not be available for public disclosure should identify as confidential the relevant portions of the submission for our consideration (62 FR 18938 at 18952). We further stated we would review the identified information, determine

[4] For example, a notifier may have a question about the common or usual name where it is not established by regulation.

whether that information is exempt from public disclosure under part 20 and release or protect the information in accordance with our determination. We advised that, in most cases, we would be likely to determine all information in a GRAS notice is available for public disclosure, because a conclusion of GRAS status must be based on generally available data and information.

We received several comments about whether confidential information should be included in a GRAS notice. In essence, these comments suggested that we both provide for the submission of trade secrets or other confidential information in a GRAS notice and protect the trade secrets or other confidential information from public disclosure, just as we would in the case of submissions such as food additive petitions.

As discussed in the experience document (Ref. 1), during the interim period CFSAN did accept some GRAS notices that included information identified by the notifier as confidential. When a GRAS notice included such information, in no case did CFSAN disclose the identified information. In some cases, including confidential information in a GRAS notice did not present a problem because it was corroborative information. However, in other cases CFSAN questioned whether there could be a basis for a conclusion of GRAS status if qualified experts generally did not have access to the confidential information.

In light of both the comments and CFSAN's experience, we are seeking comments relevant to including confidential information in a GRAS notice. We note that, while 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.

(Issue 9a) We are seeking comment on whether proposed § 170.36(c)(2) should stipulate that the method of manufacture exclude any trade secrets, as it was proposed.

(Issue 9b) We are seeking comment on 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 GRAS without access to the trade secret(s).

(Issue 9c) We are seeking comment on 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 GRAS without access to such information.

J. Issue 10. Describing the Identity of a Notified Substance

Under proposed § 170.36(c)(2), a GRAS notice would include "Detailed information about the identity of the notified substance, including, as applicable, its chemical name, Chemical Abstracts Service Registry Number, Enzyme Commission number, empirical formula, structural formula, quantitative composition, method of manufacture (excluding any trade secrets and including, for substances 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."

(Issue 10a) Based on our experience, we have found that when the source of a notified substance is a biological material (*e.g.,* a plant, animal, or microorganism), taxonomic information about genus and species may be insufficient to identify a biological source. The experience document (Ref. 1) provides examples of GRAS notices including information such as genus, species, variety, strain, part of a plant source (such as fruit, seeds or seed husks, expressed oil, flowers, roots, leaves, pulp, wood, or bark), and part of an animal source (such as fluid, muscle mass, egg, shells, or extracted oil). We note that some GRAS substances are derived from animal organs (*e.g.,* the enzyme preparation "catalase" is manufactured from cow's liver (21 CFR 184.1034)) or tissue (*e.g.,* the enzyme preparation "animal lipase" is manufactured from edible forestomach tissue or from animal pancreatic tissue (21 CFR 184.1415)). We request comment on what scientific information would be sufficient to identify the biological source.

(Issue 10b) Based on our experience, 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. For example, during the interim period CFSAN evaluated a GRAS notice about a substance derived from a biological source that is known to contain mutagenic substances (Ref. 1). Therefore, we are seeking comment on whether to require that information about the identity of the notified substance specify any known toxicants that could be in the source.

(Issue 10c) Substances that have a small particle size often have chemical, physical, or biological properties that are different from those of their larger counterparts (Ref. 5) and, thus, particle size and associated chemical and physical properties may be relevant to the identity of the notified substance. GAO's recent recommendations also encouraged us to obtain more information about the use of engineered nanomaterials (Ref. 2). Therefore, we are seeking 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.

K. Issue 11. Dietary Exposure

We proposed to require 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)). This proposed provision restated the statutory language of section 409(c)(5) of the FD&C Act regarding dietary exposure.

We proposed to require that a notice regarding a conclusion of GRAS status through experience based on common use in food 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 [5] (proposed § 170.36(c)(4)(ii)(A)). This proposed provision was silent on the probable consumption of the substance by present-day consumers.

We are seeking comment on issues related to the proposed provisions for information about dietary exposure to a notified substance.

(Issue 11a) We are seeking comment on whether proposed § 170.36(c)(4)(i)(A) 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

[5] In this document, references to "consumers" for the purposes of part 170 are references to "animals" for the purposes of part 570.

dietary exposure (*i.e.,* the amount of the notified substance that consumers are likely to eat or drink as part of a total diet).

(Issue 11b) Over 50 years have passed since passage of the 1958 Food Additives Amendment establishing the requirements for food additives and the corresponding provisions for GRAS substances in food. In evaluating whether use of a substance is GRAS through experience based on common use in food, we rely on information documenting that the "common use in food" of a substance satisfies the definition in § 170.3(f) such that adverse health effects, if they occurred, could be noted. In other words, a substance is not eligible for GRAS status merely because it was used in food before January 1, 1958, if such use were not sufficiently widespread (62 FR 18938 at 18949). Therefore, we are seeking comment on 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.

(Issue 11c) Some substances are administered to certain animal species through their drinking water. Section 201(f) of the FD&C Act defines food as "articles used for food or drink for man or other animals." In the proposed rule, we utilized the terms, "foods" and "diet," when addressing the intended use and safety evaluation of notified substances. We are seeking comment on 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 proposed § 570.36.

(Issue 11d) Under proposed § 570.36(c)(1)(iii), notifiers would submit information about the applicable conditions of use of the notified substance, including a description of the population expected to consume the substance. For substances added to animal food, the applicable population is the specific animal species intended to consume the substance. Animal species differ in their physical characteristics, digestive physiology, and metabolic pathways. Therefore, a substance that is safe for use in one animal species may not be safe for use in other species, and FDA would need to know the intended species in order to properly evaluate the notifier's safety assessment of the intended use of the substance. We are seeking comment on 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.

(Issue 11e) Proposed § 570.36(c)(2) would require that notifiers submit detailed information about the notified substance, including any content of potential human or animal toxicants. Additionally, proposed §§ 570.36(c)(4)(i)(A) and (c)(4)(ii)(A) would require that notifiers submit a comprehensive discussion of, and citations to, the information that the notifier relies on to establish safety. Where a substance is intended for use in the food of an animal used to produce human food, these sections of the proposed rule would require that the notifier include citations to information about both target animal (*i.e.,* the specific animal species that are fed the notified substance) and human safety. The information provided would need to be sufficient to show that the use of the substance is generally recognized among qualified experts to be safe for animals consuming food containing the substance as well as for humans consuming food derived from such animals (*i.e.,* under its intended conditions of use). A GRAS notice for a substance intended for use in the food of an animal used to produce human food submitted without such information would likely receive a response from FDA stating that FDA has identified questions regarding whether the intended use of the substance is GRAS. (*See* the proposed rule (62 FR 18938 at 18950).) Therefore, we are seeking comment on 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.

L. Issue 12. Filing Decision

Some comments to the 1997 proposed rule recommended that we conduct a preliminary review of a submission, before we file it as a GRAS notice, to determine whether it appears, on its face, to meet the format requirements. Some comments suggested that we "decline to file" a notice that appears to be inadequate, *e.g.,* because it lacks critical data or information. These comments considered that a preliminary review that resulted in a "filing decision" would be analogous to the current procedure whereby we review a GRAS affirmation petition to determine whether it appears, on its face, to meet the format requirements for the GRAS affirmation petition process.

As discussed in the experience document (Ref. 1), CFSAN routinely conducted such a preliminary review of each submitted GRAS notice. Based on our experience, it was the complete evaluation process that identified those data or information that are critical to establish GRAS status. Therefore, a decision on our part to file a submission as a GRAS notice has not reflected our judgment as to whether the notice addressed all issues or discussed all critical data or information.

We are seeking comment on whether we should make explicit the process by which FDA makes such a filing decision, including the factors we should use to determine whether to file a submission as a GRAS notice. Some potential factors could be the following:

- Whether your submission includes all required sections;
- Whether you provided all required copies;
- Where information provided is identified as being confidential, whether you explain the basis for your conclusion of GRAS status;
- Whether we still retain as a record any data or information that you ask us to incorporate by reference; and
- Whether the subject of your 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. For example, if we receive a submission about a mixture of substances, each of which is affirmed as GRAS under 21 CFR part 184 for use as an antimicrobial in human food, and the intended use of the mixture is as an antimicrobial, we may treat the submission as general correspondence and inform the notifier that we do not devote resources to evaluating the use of such mixtures under the GRAS notification procedure.

M. Issue 13. Substances Intended for Use in Products Subject to Regulation by the U.S. Department of Agriculture

Subsequent to the 1997 proposal, we issued a final rule amending the GRAS affirmation petition process to provide for simultaneous review of a GRAS notice by FDA and the U.S. Department of Agriculture's (USDA's) Food Safety and Inspection Service (FSIS) when the intended use of the notified substance includes use in products subject to regulation by FSIS (65 FR 51758, August 25, 2000). Under § 170.35(c)(3)(i), we forward a copy of a GRAS affirmation petition to FSIS for simultaneous review under the Poultry Products Inspection Act (PPIA) (21 U.S.C 451 *et seq.*) or the Federal Meat Inspection Act (FMIA) (21 U.S.C. 601 *et seq.*). Under

§ 170.35(c)(3)(ii), we ask USDA to advise whether the proposed uses comply with the FMIA or PPIA or, if not, whether use of the substance would be permitted in products under USDA jurisdiction under specified conditions or restrictions. The provisions of this review process reflect interagency coordination to ease the burden on regulated industries and consumers.

In addition, as discussed in the experience document (Ref. 1), during the interim period CFSAN developed a Memorandum of Understanding (MOU) with USDA's FSIS (65 FR 33330, May 23, 2000), which provides for the same coordinated review process for GRAS notices when the intended use of the notified substance includes use in products subject to regulation by FSIS. Under the terms of the MOU, CFSAN forwards a copy of an applicable GRAS notice to FSIS. CFSAN then simultaneously evaluates the basis for GRAS status while FSIS evaluates whether the intended use of the notified substance in meat or poultry products complies with the FMIA or PPIA or, if not, whether use of the substance would be permitted in products under FSIS jurisdiction under specified conditions or restrictions. In addition, during the interim period responsibility to administer the Egg Products Inspection Act (EPIA) (21 U.S.C. 1031 *et seq.*) was transferred from the Agricultural Marketing Service of USDA to FSIS (69 FR 1647; January 12, 2004). In light of this transfer of responsibility, FSIS provided its review of the use of a notified substance in egg products when a GRAS notice that CFSAN sent to USDA for its review under the PPIA or the FMIA also described a use in egg products (Ref. 1).

As discussed in the experience document (Ref. 1), more than 25 percent of GRAS notices filed during the interim period included the use of the notified substance in products subject to regulation by FSIS under the FMIA or the PPIA, and FDA obtained FSIS review for these substances.

We are seeking comment on whether to make our coordinated review process with FSIS explicit in the final rule. We also are seeking comment on whether such a procedure should provide that a notifier who submits a GRAS notice for the use of a notified substance in products subject to regulation by FSIS provide an additional paper copy or an electronic copy of the GRAS notice that we could send to FSIS. This would improve the efficiency of a simultaneous review process. We note that FSIS, under statutes it administers, does not review the use of substances intended for use in food for animals and therefore there would be no need for a counterpart provision in proposed § 570.36 for substances intended for use in food for animals.

O. Issue 14. Timeframe for FDA's Evaluation of a GRAS Notice

Section 170.35 does not specify a timeframe for FDA to complete the rulemaking associated with a GRAS affirmation petition. However, we proposed to respond to a GRAS notice within 90 days to reflect both a commitment to operational efficiency and a belief that our evaluation of whether a notice provides a sufficient basis for a conclusion of GRAS status could likely be accomplished in such a period. We also considered whether the timeframe for our response should be longer than 90 days, and specifically requested comment on whether the proposed 90-day timeframe for an Agency response should be lengthened, *e.g.,* to 120 days or 150 days. In addition, we noted that comments on the proposal may justify a longer timeframe for notifications concerning substances used in animal food.

Several comments favored a 90-day timeframe because a 90-day timeframe would provide an incentive for manufacturers to submit GRAS notices. Other comments questioned whether the proposed 90-day timeframe would allow sufficient time for us to adequately evaluate a GRAS notice and urged us to establish a realistic timeframe that we would hold ourselves accountable to.

As shown in the experience document (Ref. 1), during the interim period CFSAN responded to approximately 12 percent of GRAS notices within 90 days, and required more than 180 days to respond to more than 31 percent of GRAS notices. As discussed in the experience document (Ref. 1), the scientific challenges associated with the safety assessment conducted by the notifier were a factor in the time CFSAN needed to respond to a GRAS notice. We request comment on 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.

O. Issue 15. Conflict of Interest

In the GAO report (Ref. 2), GAO 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. Further, GAO recommended that FDA 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. As discussed in the GAO report (Ref. 2), we consider that the use of an expert panel is one way to demonstrate consensus (*i.e.,* the common knowledge element of safety) and we do not consider the view of an expert panel alone to be determinative for establishing safety. We seek comment on whether companies would find it useful to have guidance on potential conflicts of interest of GRAS expert panelists. If such guidance would be useful, we seek comment on what companies currently do to mitigate such a conflict. We also seek comment on whether to require that GRAS notices include information regarding expert panelists' independence.

P. Issue 16. Additional Guidance on Documenting GRAS Conclusions

The GAO report recommended that FDA issue guidance on how to document GRAS conclusions (Ref. 2). In our response to GAO, we noted the guidance in the preamble to the GRAS proposal and the guidance on our Web site that answers common questions about the food ingredients classified as GRAS in the form of frequently asked questions (Ref. 6). We seek comment whether there is a need to clarify that this guidance also applies to a GRAS conclusion that is not submitted to FDA under the proposed notification procedure and whether there is a need for FDA to develop further guidance on documenting such a GRAS conclusion.

Q. Issue 17. Pending GRAS Affirmation Petitions

In the 1997 proposed rule, we proposed to presumptively convert any filed, GRAS affirmation petition that is pending on the effective date of the rule (hereinafter referred to as a "pending petition") to a GRAS notice. The conversion would take place on the effective date of the final rule. Any person (hereinafter referred to as an "affected petitioner") who had submitted a GRAS affirmation petition could amend the converted petition by submitting the dated and signed document that would be required under proposed § 170.36(c)(1). In essence, we would waive the requirement for an affected petitioner who submitted such a document to agree to provide us with access to applicable data and information upon request if the affected petitioner informed us that the complete record that supports the conclusion of GRAS status had been submitted in the applicable GRAS petition. The proposed procedures for our review and administration of a converted petition would be similar to those for a newly

submitted GRAS notice. However, by 90 days after the effective date of the final rule,[6] we would inform any affected petitioner who had not submitted a certification that the converted petition was inadequate as a notice.

A few comments stated that the 1997 proposed rule did not discuss the fate of a pending petition if the petitioner elected not to submit a conversion amendment. These comments did not understand the implications of the proposed provisions which, in essence, would consider that the affected petitioner had not provided a basis for a conclusion of GRAS status.

Many comments objected to the proposed provisions regarding pending petitions. In general, these comments expressed the opinion that our proposal was fundamentally unfair to an affected petitioner because an affected petitioner had invested considerable time and resources in the petition process. Some comments suggested that we "grandfather" a pending petition (*i.e.,* complete the rulemaking that began under the petition process), as a matter of course, in those circumstances where we had completed our scientific review and had no outstanding scientific questions. Other comments suggested that such a "grandfather" provision be an option available to an affected petitioner rather than a matter of course. One comment recommended that the final rule provide a petitioner with a period of 180, rather than 90, days to submit the dated and signed document providing information in proposed § 170.36(c)(1). This comment argued that many of these petitions had been pending for years, that the subjects of the petitions had been marketed during those years, and that there would therefore be no urgency in closing the applicable files.

In light of the view of the comments that our proposed disposition of pending petitions was unfair, in this document we are seeking comments regarding pending petitions. Specifically, we seek comment on how to reduce the impact on affected petitioners while retaining the principle that we will not devote resources to pending petitions. We seek comment on 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. We are seeking comment on whether an affected petitioner could request that we incorporate by reference a withdrawn GRAS affirmation petition into a GRAS notice, and if so, if any requirements of the GRAS notification procedure should be waived.

We also note that, as discussed in the experience document (Ref. 1), during the interim period we processed a pending petition as a food additive petition and issued a food additive regulation for the petitioned substance (21 CFR 172.780; 70 FR 8032, February 17, 2005). We note that CVM has no pending GRAS petitions and thus, this discussion is not applicable to GRAS affirmation petitions for food for animals.

[6] Proposed § 170.36(g)(3)(iii) stated that we would inform a petitioner who did not submit a conversion amendment that the notice was inadequate within 90 days of publication of the final rule, rather than within 90 days of the effective date of the final rule. This was an error.

III. Costs and Benefits

FDA requests comments on how the issues discussed in this document could affect the costs and benefits estimated in the 1997 proposed rule, *e.g.,* whether these issues would result in costs or benefits that would be either greater than, or less than, those estimated in the 1997 proposed rule (62 FR 18938 at 18958).

IV. Paperwork Reduction Act of 1995

The 1997 proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Interested persons are requested to send comments regarding information collection to FDA (*see* **DATES** and **ADDRESSES**).

V. Comments

Interested persons may submit to the Division of Dockets Management (*see* **ADDRESSES**) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

VI. References

We have placed the following references on display in the Division of Dockets Management (*see* **ADDRESSES**). You may see them between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to Web sites after this document publishes in the **Federal Register.**)

1. 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.

2. 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, February 2010, Accessible at *http://www.gao.gov/new.items/d10246.pdf,* Accessed and printed on May 3, 2010.

3. Memorandum for the Heads of Executive Departments and Agencies, Dated June 1, 1998, Signed by President William J. Clinton, Accessible at *http://www.plainlanguage.gov/whatisPL/govmandates/memo.cfm,* Accessed and printed on July 14, 2008.

4. FDA Form No. 3480, Notification for New Use of a Food Contact Substance, Accessible at *http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm076880.pdf,* Accessed and printed on October 13, 2010.

5. FDA, 2007, Nanotechnology Task Force Report 2007, Accessible at *http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm,* Accessed and printed on October 13, 2010.

6. Guidance for Industry: Frequently Asked Questions About GRAS, Accessible at *http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm061846.htm,* Accessed and printed on October 13, 2010.

Dated: December 17, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[REG–132554–08]

RIN 1545–BI16

Additional Rules Regarding Hybrid Retirement Plans; Correction

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Correction to a notice of proposed rulemaking.