DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 170, 184, 186, and 570

[Docket No. 97N–0103]

Substances Generally Recognized as Safe

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to clarify the criteria for exempting the use of a substance in human food or in animal feed from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the act) because such use is generally recognized as safe (GRAS). FDA is also proposing to replace the current GRAS affirmation process with a notification procedure whereby any person may notify FDA of a determination that a particular use of a substance is GRAS. Under the proposed notification procedure, the agency intends to evaluate whether the submitted notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to FDA raises issues that lead the agency to question whether use of the substance is GRAS. This proposal reflects FDA's commitment to achieving the goals for the Reinventing Food Regulations part of the President's National Performance Review (hereinafter referred to as Reinventing Food Regulations). The proposed notification procedure would allow FDA to direct its resources to questions about GRAS status that are a priority with respect to public health protection.

DATES: Written comments by July 16, 1997, except that comments regarding information collection should be submitted by May 19, 1997. The agency proposes that any final rule that may issue based on this proposal become effective 60 days after its date of publication.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

Regarding Human Food Issues: Linda S. Kahl, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3101.

Regarding Animal Feed Issues: George Graber, Center for Veterinary Medicine (HFV–220), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1731.

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I. Background

A. The 1958 Amendment

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 act. The basic thrust of the 1958 amendment was to require that, before a new additive could be used in food, its producer demonstrate the safety of the additive to FDA. The 1958 amendment defined the terms ''food additive'' (section 201(s) of the act (21 U.S.C. 321(s))) and ''unsafe food additive'' (section 409(a) of the act (21 U.S.C. 348(a))), established a premarket approval process for food additives (section 409(b) through (h)), and amended the food adulteration provisions of the act to deem adulterated any food that is, or bears or contains, any food additive that is unsafe within the meaning of section 409 (section 402(a)(2)(C) of the act (21 U.S.C. 342(a)(2)(C))).

Congress recognized that, under this scheme, the safety of an additive could not be established with absolute certainty, and thus provided for a science-based safety standard that requires producers of food additives to demonstrate to a reasonable certainty that no harm will result from the intended use of an additive (Ref. 1). FDA has incorporated this safety standard into its regulations (§ 170.3(i) (21 CFR 170.3(i))). If FDA finds an additive to be safe, based ordinarily on data submitted by the producer to the agency in a food additive petition (FAP), the agency issues 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 substances, their customary or projected conditions of use, and the information generally available to scientists about the substances. Congress thus adopted, in section 201(s) of the act, 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 act, it is the use of a substance, rather than the substance itself, that is eligible for the GRAS exemption. In addition, it is well settled that a mere showing that use of a substance is ''safe'' is not sufficient to exempt the substance from the act's definition of ''food additive'' (*United States* v. *An Article of Food * * * Coco Rico, Inc.*, 752 F.2d 11, 15 n. 4 (1st Cir. 1985)). Instead, the substance must be shown to be ''generally recognized'' as safe under the conditions of its intended use (*Id.*; *United States* v. *Articles of Food and Drug * * * Coli-Trol 80*, 518 F.2d 743, 745 (5th Cir. 1975)). The proponent of the exemption has the burden of proving that the use of the substance is ''generally recognized'' as safe (*Id*). To establish such recognition, the proponent must show that there is a consensus of expert opinion regarding the safety of the use of the substance. (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).) Unanimity among experts regarding safety of a substance is not required. (See *United States* v. *Articles of Drug * * * 5,906 boxes*, 745 F.2d 105, 119 n. 22 (1st Cir. 1984); *United States* v. *An Article of Drug * * * 4,680 Pails*, 725 F.2d 976, 990 (5th Cir. 1984); *Coli-Trol* 80, *supra*, 518 F.2d at 746; *Promise Toothpaste, supra*, 624 F.Supp. at 782.) However, the existence of a severe conflict among experts regarding the safety of the use of a substance precludes a finding of general recognition (*4,680 Pails, supra*, 725 F.2d at 990; *Premo Pharmaceutical Laboratories* v. *United States*, 629 F.2d 795, 803 (2d Cir. 1980)) (*Cf. Coli-Trol 80, supra*, 518 F.2d at 746 (mere conflict among experts is not enough to preclude a finding of general recognition)).

It is on the basis of the GRAS exemption to the food additive definition that many substances (such as vinegar, vegetable oil, baking powder, and many salts, 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 agency review and approval. However, when a use of a substance does not qualify for the GRAS exemption or other exemptions provided under section 201(s) of the act, that use of the substance is a food additive use subject to the premarket approval mandated by the act. In such circumstances, the agency 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.

Importantly, under section 201(s) of the act, the GRAS exemption applies to the premarket approval requirements for food additives only. There is no corresponding exemption to the premarket approval requirements for color additives, which are defined in section 201(t) of the act.

B. History of FDA's Approach to the GRAS Exemption

1. The GRAS List

Shortly after passage of the 1958 amendment, FDA clarified the regulatory status of a multitude of food substances that were used in food prior to 1958 and amended its regulations to include a list of food substances that, when used for the purposes indicated and in accordance with current good manufacturing practice, are GRAS. This list was incorporated into the agency's regulations as § 121.101(d) (now parts 182 and 582 (21 CFR parts 182 and 582)) (24 FR 9368, November 20, 1959). As part of that rulemaking, however, FDA acknowledged that it would be impracticable to list all substances that are GRAS for their intended use (formerly § 121.101(a); current § 182.1(a)).

Section 121.101(d) became commonly referred to as ''the GRAS list.'' FDA 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).

2. Opinion Letters

Many substances that were considered GRAS by the food industry were not included in the agency's GRAS list. Under the 1958 amendment, a substance that is GRAS for a particular use may be marketed for that use without agency review and approval. Nonetheless, as a practical matter, manufacturers who determined on their own initiative that use of a substance qualified for the GRAS exemption frequently decided to obtain the agency's opinion on whether their determination was justified. Many manufacturers wrote to FDA 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 the agency at the time they were issued and were in fact formally revoked in 1970 (21 CFR 170.6, 35 FR 5810, April 9, 1970).

3. Agency-Initiated GRAS Review

In 1969 (34 FR 17063, October 21, 1969), FDA removed 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 FDA to reexamine the safety of GRAS substances (Ref. 3), and FDA announced that the agency was 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 issue 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.

4. GRAS Criteria and the GRAS Affirmation Process

In the notice announcing the comprehensive agency review of presumed GRAS substances, FDA 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 the agency's regulations as § 121.3 (precursor of current § 170.30 (21 CFR 170.30)) (36 FR 12093, June 25, 1971).

FDA made a second announcement that it was conducting a study of presumed GRAS substances (36 FR 20546, October 23, 1971) and subsequently instituted a rulemaking to establish procedures that the agency could use, on its 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) (21 CFR 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 GRAS determination), that rulemaking included a mechanism (the current GRAS petition process; § 170.35(c)) whereby an individual could petition FDA to review the GRAS status of substances not being considered as part of the agency's GRAS review.

In 1974, the agency 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 (current § 170.30) to distinguish a determination of GRAS status through scientific procedures (scientific procedures GRAS determination; current § 170.30(b)) from a determination of GRAS status through experience based on common use in food (common use GRAS determination; current § 170.30(c)) (41 FR 53600, December 7, 1976). Those final regulations also established definitions for ''common use in food'' (current § 170.3(f)) and ''scientific procedures'' (current § 170.3(h)). FDA 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).

5. The Plant Policy Statement

FDA's ''Statement of Policy: Foods Derived From New Plant Varieties'' (the plant policy statement) (57 FR 22984, May 29, 1992) is an example of a recent agency policy announcement regarding agency priorities in reviewing the GRAS status of substances added to food. In the plant policy statement, FDA reviewed its position on the applicability of the food additive definition and section 409 of the act to foods derived from new plant varieties in light of the intended changes in the composition of foods that might result from the newer techniques of genetic modification such as recombinant deoxyribonucleic acid (rDNA) techniques:

> The statutory definition of ''food additive'' makes clear that it is the intended or expected introduction of a substance into food that makes the substance potentially subject to food additive regulation. Thus, in the case of foods derived from new plant varieties, it is the transferred genetic material and the intended expression product or products that could be subject to food additive regulation, if such material or expression products are not GRAS.

(57 FR 22984 at 22990)

In the plant policy statement, FDA provided extensive guidance, including criteria and analytical steps that producers could follow, on situations in which producers should consult with FDA to determine whether an FAP is appropriate. FDA also stated its intent to use its food additive authority in regulating foods and their byproducts derived from new plant varieties to the extent necessary to protect public health.

C. Elements of the GRAS Standard

Under section 201(s) of the act, a substance is exempt from the definition of food additive and thus, from premarket approval requirements, if its safety is generally recognized by qualified experts. Accordingly, a determination that a particular use of a substance is GRAS requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted. In contrast, a determination that a food additive is safe requires only technical evidence of safety.[1] Thus, a GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use rather than on the basis of what the substance is or the types of data and information that are necessary to establish its safety. To emphasize this distinction between a GRAS substance and a food additive, and to simplify discussion about the standard for general recognition of safety, in this document, FDA uses the term ''technical element'' when discussing technical evidence of safety and ''common knowledge element'' when discussing general knowledge and acceptance of safety.

The technical element of the GRAS standard requires that information about the substance establish that the intended use of the substance is safe. As discussed in section I.A of this document, FDA has defined ''safe'' (§ 170.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. Current § 170.30(b) provides that general recognition of safety through scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive. Similarly, current § 170.30(c)(1) provides that 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 and must be based solely on food use of the substance prior to that date. Current § 170.3(f) defines ''common use in food'' as a substantial history of consumption for food use by a significant number of consumers.

The common knowledge element of the GRAS standard includes two facets: (1) The data and information relied on to establish the technical element must be generally available; and (2) there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use. Neither facet is, by itself, sufficient to satisfy the common knowledge element of the GRAS standard.

The usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. However, mechanisms to establish the basis for concluding that there is expert consensus about the safety of a substance are more varied. In some cases, publication in a peer-reviewed scientific journal of data (such as toxicity studies) on a test substance has been used to establish expert consensus in addition to general availability. In other cases, such publication of data and information in the primary

[1] In issuing a food additive regulation, the agency considers technical evidence of safety but does not address the GRAS standard of general recognition. Thus, in most cases, the agency's issuance of a food additive regulation means that FDA did not consider the possible GRAS status of that substance. In a few cases (e.g., 21 CFR 173.357, cellulose triacetate used as a fixing agent in the immobilization of lactase enzyme preparation), FDA concluded, in evaluating the GRAS status of a substance, that the safety of a use of a substance was not generally recognized and authorized its use as a food additive rather than affirm it as GRAS (59 FR 36935, July 20, 1994).

scientific literature has been supplemented by: (1) Publication of data and information in the secondary scientific literature, such as scientific review articles, textbooks, and compendia; (2) documentation of the opinion of an ''expert panel'' that is specifically convened for this purpose; or (3) the opinion or recommendation of an authoritative body such as the National Academy of Sciences (NAS) or the Committee on Nutrition of the American Academy of Pediatrics (CON/AAP) on a broad or specific issue that is related to a GRAS determination.

In this document, FDA is using the term ''consensus'' in discussing the common knowledge element of the GRAS standard. Such consensus does not require unanimity among qualified experts (*5,906 boxes, supra,* 745 F.2d at 119 n. 22; United *4,680 Pails, supra,* 725 F.2d at 990; *Coli-Trol 80, supra,* 518 F.2d at 746; *Promise Toothpaste, supra,* 624 F.Supp. at 782). For example, FDA would evaluate a single published report questioning the safety of use of a substance in food in the context of all the publicly available and corroborative information rather than conclude that such a report automatically disqualifies the substance from satisfying the GRAS standard (*Cf. Coli-Trol 80, supra,* 518 F.2d at 746).

D. The GRAS Petition Process

The rulemaking process in § 170.35(c) whereby manufacturers may petition FDA to affirm that a substance is GRAS under certain conditions of use was designed as a voluntary administrative process whose purpose was to provide a mechanism for official recognition of lawfully made GRAS determinations. To the extent that a person elected to submit a GRAS petition, the process could facilitate an awareness, by the agency as well as the domestic and international food industry, of independent GRAS determinations. However, GRAS affirmation involves the resource-intensive rulemaking process, including: (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**. FDA believes that, in practice, this resource-intensive process deters many persons from petitioning the agency to affirm their independent GRAS determinations.

II. Scope of the Proposed Regulations

Based on its experience applying the provisions of § 170.30, FDA is proposing to clarify when use of a substance is exempt from the act's premarket approval requirements because such use is GRAS. In proposing these changes, FDA is: (1) Emphasizing that a GRAS substance is distinguished from a food additive by the common knowledge about the safety of the substance for its intended use rather than by what the substance is, or on the basis of the types of data and information that are necessary to establish its safety; (2) identifying the types of technical evidence of safety that could form the basis of a GRAS determination; and (3) clarifying the role of publication in satisfying the general recognition standard. For consistency with the proposed changes to § 170.30, FDA is also proposing to amend the definition in § 170.3(h) of ''scientific procedures.''

In addition, in keeping with the Reinventing Food Regulations, FDA is proposing to replace the current GRAS affirmation petition process (§ 170.35(c)) with a notification procedure (proposed § 170.36) whereby any person may notify FDA of a determination that a particular use of a substance is GRAS. The submitted notice would include a ''GRAS exemption claim'' that would provide specific information about a GRAS determination in a consistent format. This GRAS exemption claim would include a succinct description of the ''notified substance'' (i.e., the substance that is the subject of the notice), the applicable conditions of use, and the basis for the GRAS determination (i.e., through scientific procedures or through experience based on common use in food) and would be dated and signed by the notifier. The GRAS exemption claim also would include a statement that the information supporting the GRAS determination was available for FDA review and copying or would be sent to FDA upon request. In addition to the GRAS exemption claim, the notice would include detailed information about the identity and properties of the notified substance and a detailed discussion of the basis for the notifier's GRAS determination.

Under the proposed notification procedure, the agency intends to evaluate whether the notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to FDA raises issues that lead the agency to question whether use of the substance is GRAS. Within 90 days of receipt of the notice, FDA would respond to the notifier in writing and could advise the notifier that the agency has identified a problem with the notice. Although information in a notice would be publicly available consistent with the Freedom of Information Act (FOIA), FDA would make readily accessible to the public the notice's GRAS exemption claim, as well as the agency's response to the notice. However, FDA does not intend to conduct its own detailed evaluation of the data that the notifier relies on to support a determination that a use of a substance is GRAS or to affirm that a substance is GRAS for its intended use.

FDA has tentatively concluded that the proposed notification procedure has advantages over the current petition process because the resource-intensive rulemaking that is associated with a petition would be eliminated. This streamlining would allow FDA to redirect its resources to questions about GRAS status that are a priority with respect to public health protection. In addition, the proposed notice is simpler than a GRAS affirmation petition and therefore conceivably would provide an incentive for manufacturers to inform FDA of their GRAS determinations. This would result in increased agency awareness of the composition of the nation's food supply and the cumulative dietary exposure to GRAS substances. FDA has also tentatively concluded that the public health would be better served if some resources that are currently directed to the GRAS petition process were redirected to the preparation of documents that would provide the industry with guidance on certain food safety issues for complex substances (e.g., macroingredients or biological polymers, such as proteins, carbohydrates, and fats and oils). Finally, the reduction in resources devoted to the evaluation of GRAS substances would allow FDA to shift resources to its statutorily mandated task of reviewing food and color additive petitions.

In light of its experience in reviewing GRAS petitions, FDA believes that the substitution of the proposed notification procedure for the current GRAS petition process would not adversely affect the public health because the agency would be replacing one voluntary administrative process with a different voluntary administrative procedure that would utilize FDA's resources more effectively and efficiently. Under both the current and the proposed procedures, a manufacturer may market a substance that the manufacturer determines is GRAS without informing the agency or, if the agency is so

informed, while the agency is reviewing that information. Thus, from a legal and regulatory perspective, this substitution is neutral.

FDA is also proposing to remove § 170.30(f), which expresses the agency's intent to review the GRAS status of certain food substances, because § 170.30(f) is redundant with the provisions of § 170.35 (a) and (b) that the agency may, on its own initiative, affirm the GRAS status of substances that directly or indirectly become components of food (§ 170.35(a)) or publish a notice announcing its conclusion that there is a lack of convincing evidence that the substance is GRAS and that it should be considered a food additive (§ 170.35(b)).

FDA's regulations regarding the eligibility of substances used in animal food or feeds for classification as GRAS, and the procedures for affirmation of GRAS status for such substances, are codified at §§ 570.30 and 570.35 (21 CFR 570.30 and 570.35), respectively. FDA is proposing the following: (1) To amend the provisions of § 570.30 that are parallel to the provisions of current § 170.30 (i.e., § 570.30 (a) and (b)); (2) to eliminate the GRAS affirmation petition process provided for in § 570.35 (a) and (c); and (3) to provide the option of a GRAS notification procedure for animal food or feeds that would be parallel to proposed § 170.36. FDA is proposing these changes because the regulations in part 570 (21 CFR part 570) implement the same statutory provisions as the regulations in part 170 (21 CFR part 170).

Finally, FDA is proposing to make certain conforming amendments to §§ 170.38, 184.1, 186.1, and 570.38.

As FDA gains experience with the questions raised by industry in preparing notices, FDA expects, from time to time, to prepare guidance documents on issues of particular interest. However, such guidance documents are not a subject of this proposal.

III. Proposed Revisions to § 170.30—Eligibility for Classification as GRAS

A. General Criteria

FDA is proposing to expand the description of the general criteria provided in current § 170.30(a) for a GRAS determination. FDA is not proposing any changes to the first two sentences of current § 170.30(a), which reflect the language of the GRAS exemption as set out in section 201(s) of the act.

The final sentence of current § 170.30(a) provides that general recognition of safety requires that there be common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food. FDA is proposing to amend this provision to define what that common knowledge is (i.e., that there is reasonable certainty that the substance is not harmful under the intended conditions of use). In other words, proposed § 170.30(a) would clarify that the safety standard for a GRAS substance is identical to the safety standard in § 170.3(i) and that a GRAS substance is neither more safe nor less safe than an approved food additive. Rather, the distinction between a GRAS substance and an approved food additive is that, for a GRAS substance, there is common knowledge of safety within the expert community.

B. Scientific Procedures GRAS Determination

1. Establishing General Recognition of Safety

Current § 170.30(b) describes the technical element of a scientific procedures GRAS determination (i.e., that it requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive). Current § 170.30(b) also describes the common knowledge element of a scientific procedures GRAS determination (i.e., that it ordinarily is based upon published studies, which may be corroborated by unpublished studies and other data and information).

FDA is proposing two changes to the description of the common knowledge element in current § 170.30(b). First, FDA is proposing to broaden this description to clarify the types of technical evidence of safety (currently described only as ''studies'') that could form the basis of a GRAS determination. FDA is proposing this change because the quantity and quality of scientific evidence required to obtain approval of a substance as a food additive vary considerably depending upon the estimated dietary exposure to the substance and the chemical, physical, and physiological properties of the substance; there can likewise be a comparable variation in the scientific evidence that forms the basis of a GRAS determination. Second, FDA is proposing to amend this description to clarify the role of publication in satisfying the common knowledge element. FDA is proposing this change because publication is ordinarily required, but may not always be sufficient, to satisfy the common knowledge element of the GRAS standard.

Specifically, FDA is proposing to revise § 170.30(b) to provide that general recognition of safety through scientific procedures be based upon generally available and accepted scientific data, information, methods, or principles, which ordinarily are published. Thus, under proposed § 170.30(b), ''studies'' would be one of several types of scientific ''data and information'' that could support the technical element of a scientific procedures GRAS determination. However, depending on the circumstances, other scientific data and scientific information such as that relating to chemical identity or characteristic properties of a substance, as well as methods of manufacture, could support, and in some cases be sufficient to satisfy that element.

In addition, under this proposed revision of § 170.30(b), generally available and accepted scientific principles could be applied to, and relied on as part of, the technical element of a scientific procedures GRAS determination. *Webster's New World Dictionary of the American Language* defines a ''principle'' as ''a fundamental truth, law, doctrine or motivating force upon which others are based.'' For example, the common scientific principle ''the dose makes the poison,'' underlies a determination that a substance is safe for use in food at certain levels even if it exhibits toxicity when present at higher levels. A related scientific principle is that the toxicity of a substance may vary between animal species. FDA relies on both of these scientific principles when determining whether the proposed use of a substance added to food is safe within the meaning of section 409 of the act.

For consistency with this proposed amendment, FDA is also proposing to amend the current definition of ''scientific procedures'' in § 170.3(h). Under the current definition, scientific procedures include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance. FDA is proposing to amend § 170.3(h) by broadening it so that scientific procedures would include scientific data (such as human, animal, analytical, and other scientific studies), information, methods, or principles, whether published or unpublished, appropriate to establish the safety of a substance. In both this proposed definition and the proposed amendment to § 170.30(b), the descriptor ''scientific'' applies equally to ''data,''

''information,'' ''methods,'' and ''principles.''

FDA is proposing to clarify the role of publication in satisfying the common knowledge element of the GRAS standard by adding the phrases ''generally available and accepted'' and ''which ordinarily are published'' as descriptors of ''scientific data, information, methods, or principles'' in proposed § 170.30(b). Thus, under proposed § 170.30(b), publication of data and information about a GRAS substance is usually necessary, but may not always be sufficient, to satisfy the common knowledge element of the GRAS standard.

The descriptor ''which ordinarily are published'' reflects that the usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. This descriptor maintains the explicit emphasis of current § 170.30(b) on the importance of publication in satisfying the common knowledge element. However, current § 170.30(b) does not explicitly emphasize the second facet of the common knowledge element (i.e., that there is a basis to conclude that there is the requisite expert consensus that the generally available data and information establish the safety of the substance for its intended use). For example, 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. On the other hand, the published results of a particular safety study may not be sufficient to satisfy the common knowledge element if the study raises safety questions that require additional data to be resolved. In such cases, the general recognition standard usually requires more than a publication in the primary scientific literature. As mentioned, the basis for concluding that there is expert consensus historically has included publication in secondary sources, convening an expert panel, or relying on an opinion or recommendation of an authoritative body.

The body of information published in secondary sources (such as review articles, articles describing scientific methods, general reference materials, and textbooks) can be more useful than the primary scientific literature for showing a basis for a conclusion that the necessary expert consensus exists because the existence of the secondary sources implies that the primary scientific literature has been evaluated after its publication. For example, FDA sometimes relies on generally available and accepted compendia such as *Bergey's Manual of Systematic Bacteriology* (Ref. 4) when evaluating the common knowledge element of the GRAS standard for food substances derived from a bacterial source.

The opinion of a specially-convened expert panel can provide a basis for showing expert consensus when an individual published study raises safety questions. The opinion of an expert panel is also useful when multiple studies bearing on the safety of a substance are published but there are no secondary sources that evaluate these studies and draw general conclusions based on this comprehensive body of knowledge. For example, during the agency-initiated GRAS review, FDA commissioned, through the Life Sciences Research Office of the Federation of American Societies for Experimental Biology, the ''Select Committee on GRAS Substances'' (the Select Committee). The charge to the Select Committee was to summarize the available scientific literature and to provide a recommendation as to what restrictions, if any, on the use of the substance would be needed to ensure its safe use in food.

In FDA's view, the common knowledge element of the GRAS standard precludes a GRAS determination if the data and information evaluated by such an expert panel are only available in files that are not publicly accessible, such as in confidential industry files. For example, in response to GRAS petitions requesting that FDA affirm the GRAS status of lactase from *Kluyveromyces lactis* entrapped in cellulose triacetate fibers for use in reducing the lactose content of milk, FDA affirmed that the lactase enzyme was GRAS (49 FR 47384, December 4, 1984) but issued a food additive regulation authorizing the secondary direct food additive use of cellulose triacetate as an immobilizing agent because the information that the petitioner relied on to establish the safety of the cellulose triacetate was not generally available (59 FR 36935, July 20, 1994).

The opinions or recommendations of an authoritative body such as NAS or CON/AAP frequently bear on an issue that is related to a GRAS determination. For example, CON/AAP may recommend the use in infant formula of a food substance whose regulatory status is not explicitly identified in FDA's regulations. Similarly, NAS's *Recommended Dietary Allowances* (Ref. 5) are useful in establishing the safe level of an added nutrient source in foods, particularly when the safe level of intake is a narrow range because the difference between the recommended dietary intake and the intake at which the substance exhibits toxic properties is small. In cases such as these, the opinions or recommendations of the authoritative body may provide a basis for concluding that there is expert consensus regarding the safety of a substance for its intended use in food.

2. Corroboration of Safety

FDA is proposing to retain the concept in current § 170.30(b) that unpublished data and information that bear on safety may be used to corroborate published data and information that establish general recognition of safety. FDA is proposing to amend current § 170.30(b) by removing the phrase ''unpublished studies and other data and information'' and substituting the phrase ''unpublished scientific data, information, or methods.'' This proposed revision is comparable to the proposed broadening of the description of the common knowledge element of the GRAS standard and likewise reflects the variation in the nature of the scientific evidence that would be required to obtain approval of the substance as a food additive.

C. Common Use GRAS Determination

FDA is not proposing any changes to current § 170.30(c)(1), which sets out criteria for a common use GRAS determination. However, FDA is proposing to amend current § 170.30(c)(2), which sets out these criteria in the more narrow circumstance of that use occurring exclusively or primarily outside of the United States. FDA is proposing to revise the final sentence of current § 170.30(c)(2) by replacing the recommendation that persons who claim GRAS status on such basis obtain FDA concurrence that the use of the substance is GRAS (*i.e.*, through submission of a GRAS affirmation petition) with a recommendation that persons who assert such a claim for a substance notify FDA of that claim in accordance with proposed § 170.36. This revision is a necessary conforming amendment because, as discussed in sections V and VI of this document, FDA is proposing to replace the current affirmation process in § 170.35(c)(1) with a notification procedure (proposed § 170.36). The recommendation in proposed § 170.30(c)(2) is appropriate because notice will facilitate the lawful entry of GRAS substances into the United States. FDA will be aware that a

substance offered for import is the subject of a GRAS exemption claim and will also be aware of the basis for such claim. Absent notice, the substance may appear to be adulterated and thus, be detained under section 801(a) of the act (21 U.S.C. 381(a)). Therefore, it is prudent for an individual who claims that a substance is GRAS through experience based on its common use in food outside of the United States to notify FDA of that claim. The language of proposed § 170.30(c)(2) is comparable to the language of current § 170.30(c)(2) in that it is not a requirement.

D. Other Provisions of Current § 170.30

FDA is not proposing any changes to the remainder of current § 170.30, except § 170.30(f) as discussed below, because the changes that the agency is proposing in this document require no conforming amendments to those sections.

Current § 170.30(f) was issued under the auspices of the agency-initiated GRAS review (36 FR 12093, June 25, 1971) and expresses the agency's intent to review the GRAS status of certain food substances. As discussed in section V of this document), FDA is proposing to remove the provision in § 170.35(a) that the Commissioner of Food and Drugs (the Commissioner), on the petition of an interested person, may affirm the GRAS status of substances that directly or indirectly become components of food. The agency is proposing to retain, however, the provision in § 170.35(a) that the Commissioner, on his/her own initiative, may affirm the GRAS status of such substances. In addition, the agency is proposing no changes to the provision in § 170.35(b) that if the Commissioner concludes that there is a lack of convincing evidence that a substance is GRAS and that it should be considered a food additive, he/she shall publish a notice thereof in the **Federal Register** in accordance with § 170.38. Therefore, § 170.30(f) is redundant with § 170.35 (a) and (b). Accordingly, in keeping with the agency's goals for the Reinventing Food Regulations, FDA is proposing to remove current § 170.30(f).

IV. The Technical Element of a GRAS Determination Through Scientific Procedures

A GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use rather than on the basis of what the substance is or the types of data and information that are necessary to establish its safety. Nonetheless, FDA is frequently asked about the types of data and information that are appropriate to establish the safety of a GRAS substance. Accordingly, FDA discusses below two topics that pertain to the technical element of a scientific procedures GRAS determination: (1) The importance of dietary exposure; and (2) the role of substantial equivalence.

A. Consideration of Dietary Exposure

Section 409(c)(5) of the act requires that, in evaluating the proposed use of a food additive, FDA consider the probable consumption of the substance and of any substance formed in or on food because of its use, as well as the cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet. FDA has incorporated this requirement into the definition of ''safe'' and ''safety'' with respect to substances added to food (§ 170.3(i)). Thus, the technical element of a scientific procedures GRAS determination must consider the probable consumption and cumulative effect of the substance in the diet because a scientific procedures GRAS determination requires the same quantity and quality of evidence as is required to obtain approval of the substance as a food additive. If the dietary exposure to the substance under the intended conditions of use presents a basis for concern about the safety of its use, data or information addressing those concerns are necessary to satisfy the technical element. As with other data and information that support a GRAS determination, data or information addressing a safety question raised by dietary exposure must also satisfy the common knowledge element by being generally available to, and accepted by, qualified experts.

In some cases, dietary exposure is unlikely to present a basis for a safety concern. For example, dietary exposure to an enzyme preparation that is derived from a controlled fermentation of a nonpathogenic, nontoxigenic microorganism that does not produce antibiotics, and that is processed using substances that are acceptable for use in foods generally, would not ordinarily present a basis for a safety concern. On the other hand, consumption of a component of a commonly consumed food may present a basis for a safety concern if the dietary exposure to the isolated component under its intended conditions of use is many times greater than its dietary exposure when consumed as a component of food.

For example, a fiber may be extracted from a vegetable that has a relatively low dietary exposure (such as beets) and added, at the same level, to other foods that have a relatively high dietary exposure. The probable cumulative intake of the fiber likely will be many times higher from the consumption of the foods to which it is added than from the consumption of beets. The probable intake of the fiber from consumption of foods to which it is added may present a basis for a safety concern, especially if the foods containing the added beet fiber will not replace beets in the diet. Likewise, in the case of a chemically synthesized substance that is structurally identical to a naturally occurring substance in commonly consumed food, technical evidence of safety would include consideration of whether the cumulative exposure to both the synthetic and the natural substance exceeds the exposure to the natural substance and whether the combined exposure presents a basis for a safety concern.

B. Substantial Equivalence to a GRAS Substance

A report of a joint Food and Agriculture Organization (FAO) and World Health Organization (WHO) consultation (the 1996 FAO/WHO report) recommended that ''[s]afety assessment based on the concept of substantial equivalence * * * be applied in establishing the safety of foods and food components derived from genetically modified organisms'' (Ref. 6). The 1996 FAO/WHO report stated that:

> [s]ubstantial equivalence embodies the concept that if a new food or food component is found to be substantially equivalent to an existing food or food component, it can be treated in the same manner with respect to safety (i.e. the food or food component can be concluded to be as safe as the conventional food or food component). Account should be taken of any processing that the food or food component may undergo as well as the intended use and the intake by the population.

The 1996 FAO/WHO report relied, in part, on previous expert reports that had discussed the concept of substantial equivalence, including the 1990 joint FAO/WHO consultation, ''[s]trategies for assessing the safety of foods produced by biotechnology'' (Ref. 7); a report prepared by an expert group of the Organization for Economic Co-operation and Development (OECD), ''[s]afety evaluation of foods produced by modern biotechnology: Concepts and principles'' (Ref. 8); and a report of a WHO workshop, ''[a]pplication of the principles of substantial equivalence to the safety evaluation of foods or food components from plants derived by modern biotechnology'' (Ref. 9).

FDA believes that in certain instances the concept of substantial equivalence may have applicability to the technical element of a GRAS determination, and the agency has already applied this concept when evaluating the safety of new or modified food substances. For example, the agency's approach (57 FR 22984 and Ref. 10) to assessing the safety of foods derived from new plant varieties, including the safety of newly introduced substances in the food (primarily proteins, carbohydrates, and fatty acids) and unintended changes in the food's composition, is similar to the concept of substantial equivalence posited by FAO, WHO, and OECD.[2] As another example, FDA has applied this concept in affirming the GRAS status of several microbially-derived chymosin (i.e., rennet) enzyme preparations (55 FR 10932 at 10935, March 23, 1990; 57 FR 6476 at 6479, February 25, 1992; 58 FR 27197 at 27202, May 7, 1993) and several animal-and plant-derived enzyme preparations (60 FR 32904 at 32911, June 26, 1995).

However, the concept of substantial equivalence may be of minimal relevance in circumstances where the differences between two substances outweigh the similarities. Thus, a critical factor that must be considered when applying the concept of substantial equivalence is any difference in composition or characteristic properties between the substances being compared. In the example of a microbially-derived enzyme preparation, its principal enzyme component may show substantial equivalence in structure and function to that of a GRAS enzyme preparation derived from an animal source but exhibit different properties such as specific activity (i.e., the rate at which the enzyme catalyzes a reaction) or optimum reaction conditions of pH and temperature because of changes, either through natural selection or through selective chemical modification, in the particular amino acid sequence of the enzyme's active site. Such differences, which are common when comparing enzyme preparations derived from different sources, generally do not outweigh the similarities between the enzyme preparations.

[2] In the plant policy statement, FDA used the term ''substantial similarity,'' rather than ''substantial equivalence,'' to avoid possible confusion with the agency's use of the concept of ''substantial equivalence'' with respect to the premarket notification process for medical devices. For consistency with current thinking from international expert groups such as the FAO/WHO and OECD consultation groups, FDA is now using the term ''substantial equivalence'' with respect to food products.

On the other hand, the product resulting from the chemical reaction of two or more GRAS substances is a discrete new substance that may have properties that are distinctly different from the individual GRAS substances from which it is synthesized or from a simple mixture of those GRAS substances. The concept of substantial equivalence may not be relevant here unless the reaction product is widely recognized to be metabolized in the same way as the individual components from which it is synthesized. Likewise, in the case of a chemically synthesized substance that is structurally identical to a naturally occurring substance in commonly consumed food, compositional differences between the synthesized and naturally occurring substance may include the presence of any residues of potentially harmful chemicals carried over to the synthetic substance from the manufacturing process.

FDA invites comment on the applicability of the concept of substantial equivalence to the technical element of a GRAS determination.

V. Proposed Revisions to § 170.35—Affirmation of GRAS Status

As a result of the agency's experience in processing FAP's and GRAS affirmation petitions, FDA has tentatively concluded that the petition process, which is the statutorily mandated process for food additives, should no longer be applied to GRAS substances, where the conditions of safe use of a substance have already been recognized by qualified experts. FDA believes that the lengthy rulemaking associated with the GRAS petition process deters many persons who independently determine that use of a substance is GRAS from informing the agency of such determinations. Moreover, FDA believes that the current commitment of its resources to the GRAS petition process provides limited public health benefit because manufacturers who submit an affirmation petition frequently market the substance at issue before FDA reaches a decision on the GRAS status of its intended use.

Accordingly, FDA is proposing to amend current § 170.35(a) to remove the provision that FDA may review the GRAS status of a substance added to food in response to a petition from an interested party. FDA has tentatively concluded that the elimination of the GRAS petition process would not adversely affect public health because the agency is simultaneously proposing to establish a notification procedure for GRAS substances. FDA has also tentatively concluded that the proposed notification procedure, discussed more fully in section VI of this document, would allow the agency to direct its resources to the more significant questions about GRAS status.

Proposed § 170.35(a) would continue to provide a mechanism whereby FDA, on its own initiative, may affirm the GRAS status of the use of a substance that directly or indirectly becomes a component of food. FDA proposes to retain the option of agency-initiated affirmations for those circumstances where such action is necessary or useful. For example, FDA may propose to revise an existing regulation affirming the GRAS status of a use of a substance if the agency determines that the current regulation is confusing or unnecessarily restrictive. In addition, the agency may choose to complete a rulemaking already begun as part of the agency-initiated GRAS review.

Proposed § 170.35(a) includes a technical revision that amends current § 170.35(a) to place it in the singular. For consistency with the language of the statute, proposed § 170.35(a) also has been revised to clarify that the Commissioner might affirm the GRAS status of a use of a substance, rather than the substance itself.

In light of the increasing complexity of the food supply, FDA recognizes that members of the food industry may wish to engage in discussions with the agency concerning novel issues that accompany the technical element of some GRAS determinations. FDA believes that the elimination of the GRAS petition process will not constrain industry from consulting with the agency about such novel issues. Rather, FDA believes that the substitution of the proposed notification procedure for the current petition process will encourage industry to consult with FDA early in development of food substances to identify the critical aspects of the safety determination that would need general recognition to qualify for a GRAS exemption.

FDA is also proposing to remove current § 170.35(c), which prescribes the procedure for the submission of a GRAS affirmation petition. Under proposed § 170.35(a), FDA will no longer be bound to review such a petition. Therefore, if proposed § 170.35(a) becomes final, current § 170.35(c) will become obsolete.

VI. Proposed Establishment of a Notification Procedure

A. General Requirements

Proposed § 170.36(a)(1) provides 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 GRAS. The agency encourages manufacturers and developers of food substances and of new processes for producing food substances to use this notification procedure to inform FDA if such manufacturers or developers conclude that there is general recognition that use of a substance is safe.[3]

Current agency regulations concerning the eligibility of a substance for a health claim (§ 101.14(b)(3)(ii)) (21 CFR 101.14(b)(3)(ii)) require that a substance that is to be consumed as a component of conventional food at other than decreased dietary levels be a food, food ingredient, or a component of a food ingredient, whose use, at the levels necessary to justify a claim, be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the act. In the final rule establishing § 101.14(b)(3)(ii) (58 FR 2478 at 2502, January 6, 1993), FDA explained that the preliminary requirement that a substance be safe and lawful was necessary in the health claim regulation because FDA's authorization of a health claim places the agency's imprimatur on the claim. FDA further stated that it would be a violation of the agency's responsibility under the act to authorize a health claim for a substance without the agency being satisfied that the particular use of the substance is safe. As discussed in detail in section VI.D of this document, an agency response to a GRAS notice would not be equivalent to an agency affirmation of GRAS status. Therefore, if adopted, the GRAS notification procedure proposed in this notice will not satisfy a health claim petitioner's responsibilities under § 101.14(b)(3)(ii).

In addition, FDA recently proposed that good manufacturing practice for infant formula requires that only substances whose use in infant formula is safe and suitable under the applicable food safety provisions of the act be used to make this product; that is, that the substance be GRAS for such use, used in accordance with the agency's food additive regulations, or authorized for such use by a prior sanction (proposed § 106.40(a); 61 FR 36154 at 36212, July 9, 1996). FDA also proposed that a ''new infant formula'' submission required under section 412 (c) and (d) of the act (21 U.S.C. 350a (c) and (d)) include the basis on which each ingredient meets the requirements of proposed § 106.40(a), and that any claim that an ingredient is GRAS be supported by a citation to the agency's regulations or by an explanation as to why there is general recognition of the safety of the use of the ingredient in infant formula (proposed § 106.120(b)(6)(ii); 61 FR 36154 at 36217). Again, as discussed in detail in section VI.D of this document, an agency response to a GRAS notice would not be equivalent to an agency affirmation of GRAS status or place an agency imprimatur on the substance that is the subject of the notice. Therefore, if adopted, this proposed GRAS notification program will not substitute for the requirements proposed for new infant formula submissions.

The fact that the proposed GRAS notification program will not satisfy the requirements of either § 101.14(b)(3)(ii) or proposed § 106.120(b)(6)(ii) is reflected in proposed § 170.36(a)(2). Under proposed § 170.36(a)(2)(i), any person who submits a health claim petition under § 101.14 must comply in full with § 101.14(b)(3)(ii), regardless of whether the agency has been notified under proposed § 170.36 about a relevant GRAS determination and regardless of the nature of the agency's response to that notice. Similarly, proposed § 170.36(a)(2)(ii) provides that any person who makes a new infant formula submission under § 106.120 must comply in full with § 106.120(b)(6)(ii), regardless of whether the agency has been notified under proposed § 170.36 about a relevant GRAS determination and regardless of the nature of the agency's response to that notice.

Proposed § 170.36(b) requires that notice of a GRAS exemption claim be submitted in triplicate and provides the address for such a submission. FDA plans to use one copy of the notice for the agency's administrative record. FDA anticipates that at least two agency scientists, with food safety expertise relating to identity, dietary exposure and health effects, will evaluate most notices. Thus, for efficient administration of the notification procedure, FDA is stipulating that three copies of a notice be submitted.

FDA is aware that there is increasing interest in submitting an electronic copy of information prepared for regulatory purposes. FDA requests 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 required under proposed § 170.36(b).

B. Specific Requirements

Proposed § 170.36(c) provides details on information that must be included in a notice. FDA recognizes that a decision to submit a notice is voluntary. However, as discussed (see discussion of proposed § 170.36(e)), under the proposed notification procedure, FDA would respond to a notice within 90 days. In order for the agency to meet this timeframe, the information in the notice needs to be presented in an orderly and consistent fashion. Moreover, FDA believes that a prescribed format and a description of information that the agency considers important in supporting a GRAS determination would simplify the notifier's task of preparing the notice.

1. GRAS Exemption Claim

A GRAS determination must comply with the provisions of § 170.30 and the person making such determination is responsible for ensuring such compliance, regardless of whether that person notifies the agency about the determination. Accordingly, proposed § 170.36(c)(1) requires that the notice include a claim (hereinafter referred to as the ''GRAS exemption claim''), dated and signed by the notifier, that a particular use of a substance is exempt from the premarket approval requirements of the act because the notifier has determined that such use is GRAS. Proposed § 170.36(c)(1) would distinguish the notification procedure, in which the notifier explicitly accepts responsibility for the GRAS determination, from the GRAS petition process, in which the notifier is requesting that the agency affirm the GRAS status of use of a substance.

Proposed § 170.36 (c)(1)(i) through (c)(1)(iv) identify specific information required in a GRAS exemption claim in a prescribed format. This requirement will simplify the notifier's task of preparing this section of a notice and will enable the agency to use this section of a notice to effectively and efficiently inform the public about received notices (see discussion of proposed § 170.36(f)(2)).

FDA has requested comment on whether proposed § 170.36(b) should require or recommend that an electronic copy of the entire notice be submitted

[3] FDA considers that the current voluntary procedure whereby developers of new plant varieties modified through the use of rDNA techniques notify the agency about food derived from the plant is parallel to, and has some overlapping provisions with, the proposed GRAS notification procedure but is nonetheless distinct from this proposed procedure. For example, current notices to the agency concerning new plant varieties generally are broader in scope than the regulatory status of substances introduced into the new plant variety and usually include a safety and nutritional assessment of food derived from the new plant variety in addition to a basis for the notifier's determination that an FAP is not required for any of the substances introduced into that food.

in addition to three paper copies. In particular, receiving electronic copies of the GRAS exemption claim may make FDA's administration of the GRAS notification procedure more efficient, especially if the agency uses an electronic means to make those claims readily accessible to the public. Accordingly, FDA specifically requests comment on whether the regulation should include a recommendation or requirement that the notice include an electronic copy of the GRAS exemption claim required by proposed § 170.36(c)(1).

a. *Notifier.* Proposed § 170.36(c)(1)(i) requires that the GRAS exemption claim include the name and address of the notifier. This is necessary for full identification of the person who accepts responsibility for the claim. This is also necessary so that the agency can both acknowledge receipt of the notice (proposed § 170.36(d)) and inform the notifier of the agency's response to the notice (proposed § 170.36(e)).

b. *Name of notified substance.* Proposed § 170.36(c)(1)(ii) requires that the GRAS exemption claim include the common or usual name of the notified substance. This is necessary to identify the notified substance as well as to identify whether there are any labeling issues that need to be addressed. The notifier may include in the GRAS exemption claim additional information, such as that described in proposed § 170.36(c)(2), concerning the identity of the substance if such information is appropriate or necessary to fully and unambiguously describe it.

The agency recognizes that notifiers may have questions concerning the common or usual name for a notified substance. FDA advises that in such circumstances, a notifier should consult with the Office of Food Labeling in FDA's Center for Food Safety and Applied Nutrition (CFSAN).

c. *Conditions of use.* Proposed § 170.36(c)(1)(iii) requires that the GRAS exemption claim identify 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 (e.g., if the substance is intended for use in a limited population, such as ingredients used mainly in infant formula, medical foods, or in specially designed food products typically consumed as a sole source of the diet by persons who are unable to consume food in conventional form). Information describing the conditions of use is necessary to delineate the boundaries of the GRAS exemption claim consistent with section 201(s) of the act, which states that a GRAS substance must be generally recognized as safe ''under the conditions of its intended use.'' This information is also necessary to determine whether dietary exposure to the substance presents a basis for concern about the safety of its use.

d. *Basis for the GRAS determination.* Proposed § 170.36(c)(1)(iv) requires that the GRAS exemption claim identify the basis for the GRAS determination as either scientific procedures or experience based on common use in food. The act differentiates between these two bases for GRAS determination and, under § 170.30, the requirements for a scientific procedures GRAS determination are different from the requirements for a common use GRAS determination. The basis for a GRAS determination is thus fundamental to the GRAS exemption claim.

e. *Availability of information.* A GRAS determination must comply with the provisions of § 170.30 and the person making such determination is responsible for ensuring such compliance, regardless of whether that person notifies the agency about the determination. As discussed more fully below (see discussion of proposed § 170.36(c)(4)), and in keeping with the agency's commitment to achieving the goals for Reinventing Food Regulations, FDA is proposing to require that a notifier supply a detailed summary of the information that is the basis for a GRAS determination rather than the information itself. Proposed § 170.36(c)(1)(v) provides a mechanism for FDA to verify the information that supports a GRAS determination by requiring that the GRAS exemption claim include a statement that the data and information that are the basis for the determination are available for review and copying by FDA or will be sent to FDA upon request. Notifiers who voluntarily choose to notify FDA of a GRAS determination receive as a benefit a response that documents the agency's awareness of the determination. As a condition of that benefit, the notifier must consent to grant FDA access to the data and information that are the basis of the GRAS determination.

There is no burden on the notifier for developing the data and information that are the basis for the GRAS determination because such data and information must already be generally available in order to satisfy the common knowledge element of a GRAS determination. Additionally, any person who determines that a substance is GRAS should have assembled and evaluated the evidence that forms the basis of such a determination, regardless of whether the person subsequently notifies the agency about the claim. Therefore, FDA believes that the burden to the notifier of the proposed rule is the minimal burden of maintaining the information. Such preservation of the data and information that are the basis for the GRAS determination also represents prudent practice for those who claim an exemption from a statutory requirement.

The new procedure that FDA is proposing to establish will involve the submission of a detailed summary of the information that forms the basis for an exemption from a statutory requirement rather than the submission of the information itself. It therefore is prudent that FDA monitor compliance with the essence of the statutory requirement (i.e., that there is common knowledge among qualified experts that there is reasonable certainty that the substance is not harmful under the intended conditions of use). Accordingly, FDA intends to conduct random audits of data and information maintained by the notifier. Moreover, because the proposed substitution of a notification procedure for the current petition process would allow FDA to direct its resources to priority questions about GRAS status, FDA 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.

2. Identity and Specifications

Proposed § 170.36(c)(2) requires that the notice include detailed information about the identity of the notified substance, including, as applicable, the chemical name, Chemical Abstracts Service (CAS) registry number, Enzyme Commission (EC) number, empirical formula, structural formula, quantitative composition, method of manufacture (excluding any trade secret information), characteristic properties, any potential human toxicants, and specifications for food-grade material. This detailed information, which would be in addition to the substance's common or usual name that would be included under proposed § 170.36(c)(1)(ii), is necessary to describe accurately the notified substance using commonly accepted scientific nomenclature and practice.

For some substances, such as calcium acetate (21 CFR 184.1185), the most relevant information concerning identity may be chemical information such as its CAS registry number and empirical formula. For other substances, such as whey (21 CFR 184.1979), a

chemical formula cannot be used for identification; instead, source and quantitative composition (e.g., percent of protein, fat, ash, lactose, and moisture) appropriately describe the substance.

In many cases, the method of manufacture provides important identity information. For example, an enzyme preparation that is derived from an animal source and contains the enzyme chymosin as its principal enzyme component (§ 184.1685(a)(1) (21 CFR 184.1685(a)(1))) is chemically different from an enzyme preparation that is derived from a microbial source and contains the enzyme chymosin as its principal enzyme component (§ 184.1685(a)(2)) because the components and contaminants derived from the source material are distinctly different.

In some cases, the characteristic properties of a substance may be important when defining the conditions under which the substance may safely be used. For example, if an isolated or chemically processed fiber is intended for use as a replacement for part of the flour used in baked goods, information about its physicochemical properties, such as its ability to swell due to high water absorption or to bind physiologically important ions, may be important in establishing a safe level of the fiber in baked goods.

The proposed requirement that information relating to identity include any potential human toxicants in the notified substance derives from the known presence of such toxicants in substances of natural biological origin. For example, it is well known that potatoes contain the naturally occurring toxicant, solanine. In the plant policy statement (57 FR 22984 at 22987), FDA discussed the importance of ensuring that new plant varieties do not contain significantly higher levels of toxicants than are present in other edible varieties of the same species. This consideration applies to all food products that derive from a source known to contain naturally occurring toxicants.

Specifications are an important factor in establishing food-grade quality for any substance intended for use in food. Substances that do not meet the specifications may not be suitable for use in food. Specifications may be general or particular and may relate to identity, purity, or both.

General specifications governing both identity and purity are common for GRAS substances. For example, the regulations for microbially-derived GRAS substances usually stipulate, as a general identity specification, that the source microorganism be a nontoxigenic, nonpathogenic strain. Similarly, the regulations for many GRAS substances stipulate, as a general purity specification, the maximum permissible level of a heavy metal toxicant such as lead.

In addition, GRAS substances frequently require a particular identity specification to adequately define the substance whose safety is generally recognized. For example, in affirming that canola oil (i.e., low erucic acid rapeseed oil) is GRAS for use as an edible fat and oil, FDA only considered the GRAS status of oil that contains levels of a specific fatty acid (erucic acid) that are no more than 2 percent of the component fatty acids. Therefore, the identity specification for low erucic acid rapeseed oil (21 CFR 184.1555(c)(1)) stipulates that, chemically, the oil is a mixture of triglycerides, composed of both saturated and unsaturated fatty acids, with an erucic acid content of no more than 2 percent of the component fatty acids.

In some cases, FDA expects that the specifications for a notified substance may be generally available in a standard reference such as the Food Chemicals Codex (FCC), which contains general and specific requirements for more than 900 substances used in food. In other cases, the specifications for the notified substance may be the same as, or similar to, specifications in the agency's GRAS regulations but not available in any other standard reference. For example, the specifications for an oil that is substantially similar to hydrogenated and partially hydrogenated menhaden oil, which FDA has affirmed as GRAS for use as an edible fat or oil, could be based on the specifications in 21 CFR 184.1472.

3. Self-limiting Levels of Use

Proposed § 170.36(c)(3) requires that the notice include any self-limiting levels of use of the substance. If a substance is added to food above its technologically self-limiting level, the food becomes unpalatable, unappealing or otherwise unfit for consumption. Information on a technologically self-limiting level of use of a substance would be important in addressing concerns about the level of use of the substance as a food component. For example, it is generally known that the taste associated with many GRAS synthetic flavoring substances limits the levels at which the flavoring substances can be used to levels below those known to exhibit toxic properties.

4. Scientific Procedures GRAS Determination

The technical element of a scientific procedures GRAS determination requires that information about the substance show that there is reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. The nature of the information that the notifier relies on to establish the technical element of the GRAS standard may vary from substance to substance. Such information may include, but is not limited to, the identity, characteristic properties, and methods of manufacture of the notified substance, applicable toxicological studies, and information relating to dietary exposure.

The common knowledge element requires both that the information relied on be generally available and that there be a basis to conclude that there is expert consensus about the safety of the substance for its intended use. A notice summary that fully describes the technical evidence of safety, but does not provide a basis to conclude that the technical evidence is generally available and accepted, would be incomplete. The common knowledge element applies to all of the evidence that is the basis for the safety determination.

a. *Technical evidence of safety.* Proposed § 170.36(c)(4)(i)(A) requires that the notice include a detailed summary of the basis for the notifier's determination that a particular use of the substance is GRAS through scientific procedures. This summary would 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.

Proposed § 170.36 (c)(2) and (c)(3) of the notice would require that information relating to the identity, characteristic properties, and methods of manufacture of the notified substance be described in detail; therefore, the comprehensive discussion in the notice summary should focus on how that information is relevant to the GRAS determination. Under proposed § 170.36(c)(4), the comprehensive discussion in the notice summary of any applicable toxicological studies should fully describe such studies, identify the conclusions drawn from such studies, and explain how these conclusions are relevant to the GRAS determination. FDA is not proposing to require that the notice include the raw data supporting the conclusions of applicable toxicological studies because the agency does not intend, in most cases, to conduct its own detailed evaluation of those data.

Proposed § 170.36(c)(4)(i)(A) specifies that the discussion in the notice summary include a consideration of the probable consumption of the substance and the cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substances in such diet. This consideration of dietary exposure is mandated for food additives by section 409(c)(5) of the act; § 170.30(b) further provides that a scientific procedures GRAS determination requires the same quantity and quality of scientific evidence as would be required to approve a food additive. Thus, such information should be included in the notice summary. Several technical documents that discuss the practical details of estimating consumer exposure to a food substance are available from the agency.[4]

The notice summary may also include a comprehensive discussion of scientific data, information, and methods that, in the notifier's view, corroborate the GRAS determination. For example, for a substance whose safety is established based on its identity, method of manufacture, and characteristic properties, a notifier may describe a toxicological study and rely on these data as corroborative. However, as with studies that are relied on to support a GRAS determination, the comprehensive discussion should fully describe such studies, identify the conclusions drawn from such studies, and explain how these conclusions are relevant to the GRAS determination.

b. *General availability of information supporting safety.* The inclusion of citations to published articles is customary scientific practice and is the simplest way to demonstrate the general availability of the information on which the notifier relies. Proposed § 170.36(c)(4)(i)(A) does not require that a notifier submit copies of published information identified in the notice summary because, in most cases, the agency does not intend to conduct its own detailed evaluation of the data that the notifier relies on to support a determination that a use of a substance is GRAS. Rather, the agency intends to evaluate whether the notice summary establishes a basis to conclude that there is expert consensus regarding the safety of use of the substance.

Under proposed § 170.36(c)(4)(i)(A), notifiers should limit published information citations to those that the notifier discusses and relies on to support a GRAS determination or that are appropriately discussed and explained because they may appear to be inconsistent with a GRAS determination (see discussion of proposed § 170.36(c)(4)(i)(B)). Accordingly, the notifier should not cite published information unless the cited information bears directly on the GRAS determination. For example, a bibliography describing an exhaustive literature search about a notified substance is of limited or no value in supporting the common knowledge element of a GRAS determination if the relevance of the cited literature is not readily apparent or fully discussed. Moreover, such a bibliography would not, absent a discussion of the relevance of the material cited to the GRAS determination in question, fulfill the technical element of a GRAS determination.

c. *Unfavorable information.* Proposed § 170.36(c)(4)(i)(B) requires that the notice summary of a scientific procedures GRAS determination include a comprehensive discussion of any reports of investigations or other information (e.g., adverse event reports and consumer complaints) that may appear to be inconsistent with the GRAS determination. FDA is proposing this requirement as a prelude to proposed § 170.36(c)(4)(i)(C), which would require that the notice summary include a basis to conclude that there is expert consensus regarding the safety of use of the substance. In other words, in order to meet the act's general recognition standard, all information, both favorable and unfavorable, that bears on the safety of the substance for its intended use must be considered.

Proposed § 170.36(c)(4)(i)(B) is consistent with the provision in current § 170.35(c)(1)(iv) and (c)(1)(v) (which are proposed for deletion) that a GRAS affirmation petition include adverse information or consumer complaints and be a representative and balanced submission that includes known information, both favorable and unfavorable. Proposed § 170.36(c)(4)(i)(B) is also consistent with a similar provision (§ 171.1(c) (21 CFR 171.1(c))) in the FAP regulations, which requires that the petition must not omit without explanation any reports of investigations that would bias an evaluation of the safety of the food additive. Thus, the requirement in proposed § 170.36(c)(4)(i)(B) is appropriate because general recognition of safety based upon scientific procedures requires the same quantity and quality of scientific evidence required to obtain approval of the substance as a food additive.

d. *Basis for concluding expert consensus.* Proposed § 170.36(c)(4)(i)(C) requires that the notice summary of a scientific procedures GRAS determination include the basis for concluding, in light of the data and information described in the notice, that there is a consensus among qualified experts that there is reasonable certainty that the substance is not harmful under the intended conditions of use. Thus, the notice summary must consider the totality of the publicly available and corroborative evidence about the safety of the substance for its intended use, including both favorable and potentially unfavorable information.

As discussed in section I.C of this document, the bases for concluding that there is the requisite expert consensus may be quite varied. For example, there could be a basis to conclude that the necessary expert consensus exists if data published in the primary scientific literature establish the safety of a substance for its intended use and such data raise no safety questions that experts would need to resolve. On the other hand, data published in the primary scientific literature may not provide a basis for expert consensus if those data raise unresolved safety questions. Alternatively, the opinions of a specially convened expert panel or of an authoritative body such as NAS may provide a basis for expert consensus. However, an ongoing scientific discussion or controversy about safety concerns raised by available data would make it difficult to provide a basis for expert consensus about the safety of a substance for its intended use.

5. Common Use GRAS Determination

a. *Technical evidence of safety.* Proposed § 170.36(c)(4)(ii)(A) requires that the notice summary of a common use GRAS determination 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. Under current § 170.30(c)(1), in evaluating whether use of a substance is GRAS through experience based on common use in food prior to January 1, 1958, FDA relies 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 the

[4] For example, ''Recommendations for Submission of Chemical and Technological Data for Direct Food Additive and GRAS Food Ingredient Petitions'' (1993); ''Estimating Exposure to Direct Food Additives and Chemical Contaminants in the Diet'' (1995); and ''Recommendations for Chemistry Data for Indirect Food Additive Petitions'' (1995).

GRAS exemption merely because it was used in food before January 1, 1958, if such use were not sufficiently widespread.[5]

The fact that GRAS status is determined through experience based on common use in food does not preclude, in addition to information documenting that a substance has a substantial history of consumption for food use by a significant number of consumers, a discussion of relevant data or information that bears on the safety of the substance under its intended conditions of use. Thus, the notice summary may also include a comprehensive discussion of scientific data or information that, in the notifier's view, corroborates the common use GRAS determination. With respect to toxicological studies that are viewed as corroborative, the comprehensive discussion should fully describe the studies, identify the conclusions drawn from such studies, and explain how these conclusions are relevant to the GRAS determination.

As discussed in section I.A of this document, it is the use of a substance, rather than the substance itself, that is eligible for the GRAS exemption. In addition, section 201(s) of the act makes a clear distinction between qualifying for the GRAS exemption through scientific procedures and qualifying for the GRAS exemption through common use in food. Many substances that are GRAS for a specific use through a common use GRAS determination could become the subject of GRAS determinations for additional uses. It is important to note, however, that an evaluation of whether an additional use of a substance that is GRAS through experience based on common use in food is also GRAS requires a scientific procedures GRAS determination when the use in question was not common prior to January 1, 1958.

b. *General availability.* As discussed for notifiers of a scientific procedures GRAS determination, notifiers of a common use GRAS determination should limit citations to published information to those that the notifier discusses and relies on to support a GRAS determination or that are appropriately discussed and explained because they appear to be inconsistent with the GRAS determination.

c. *Unfavorable information.* Proposed § 170.36(c)(3)(ii)(B) requires that the notice summary of a common use GRAS determination include a comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with the GRAS determination. The legislative history of the 1958 amendment demonstrates that Congress believed that there was no reason to conduct specific tests to establish the safety of substances commonly used in food because their history of common use established a presumption of such safety (Ref. 1). However, nothing in the legislative history suggests that Congress intended that subsequent reports of adverse effects associated with the use of a substance in food be ignored in the safety evaluation. A notice summary of a common use GRAS determination should also address whether use was/is sufficiently widespread that any substance-related adverse effects would be observed and recorded. Where a substance has been used by a limited population,[6] for a limited period of time, or under circumstances that do not lend themselves to the observation and recording of adverse effects, the lack of reported adverse effects may not be meaningful.

d. *Basis for concluding expert consensus.* Proposed § 170.36(c)(4)(ii)(C) requires that the notice summary of a common use GRAS determination include the basis for concluding, in light of the data and information described in the notice, that there is a consensus among qualified experts and that there is reasonable certainty that the substance is not harmful under the intended conditions of use. Thus, the notice summary must consider the totality of the publicly available and corroborative evidence about the safety of the substance for its intended use, including both favorable information and potentially unfavorable information.

FDA has previously discussed the common knowledge element as it applies to a common use GRAS determination which reads as follows:

> For a substance to be GRAS on the basis of a history of common use in food, there must be a consensus among the community of qualified experts that the use of the substance is safe. For such a consensus to be possible, information about the use of the substance must be generally available. General availability is the result of documentation of the information, usually by publication.

(50 FR 27294 at 27295, July 2, 1985)

In addition, under § 170.30(c)(2), when the common use in food occurred exclusively or primarily outside of the United States, a common use GRAS determination requires that such use be documented by published or other information and be corroborated by information from a second, independent, source that confirms the history and circumstances of use of the substance. Such information must be widely available in the country in which the use occurred and readily accessible to interested qualified experts in the United States.

C. Agency Response

1. Acknowledgment of Receipt

Proposed § 170.36(d) requires that, within 30 days of receipt of a notice, FDA acknowledge receipt of the notice by informing the notifier in writing of the date on which the notice was received. This acknowledgment would serve as a means to establish the date of receipt, which FDA is proposing to couple with certain aspects of the agency response (see discussion of proposed § 170.36 (d), (e), and (f) of this document).

2. 90-Day Response Letter

Under the proposed notification procedure, FDA would not receive the detailed data and information that support a GRAS determination. Therefore, FDA would not be in a position to affirm a notifier's conclusion that a use of a substance is GRAS, and the rulemaking part of the GRAS affirmation process would not be necessary or appropriate. Rather, FDA would evaluate whether the notice provides a sufficient basis for the notifier's GRAS determination. For example, FDA may question the GRAS status of use of a substance if the information provided in a notice: (1) Does not adequately establish technical evidence of safety; (2) is not generally available; (3) does not convince the agency that there is the requisite expert consensus about the safety of the substance for its intended use; or (4) is so poorly presented that the basis for the GRAS determination is not clear. FDA also may be aware of information that is not included in the notice but raises important public health issues that lead the agency to question GRAS status of use of the substance.

FDA believes that this narrow agency evaluation would not have a negative impact on public health because the agency is replacing a voluntary

[5] For example, subsequent to the 1958 amendment, FDA required that food additive petitions be submitted for several substances, such as polysorbates (25 FR 1727, February 27, 1960), even though those substances had been used in food prior to January 1, 1958, because the pre-1958 consumption alone was not sufficient to establish safety (24 FR 11079, December 31, 1959).

[6] An exception is the use of a food substance in a limited population such as infants, where such limited use may be part of a demonstration of the safety of the substance for use by the limited population (e.g., as an ingredient in an infant formula).

administrative process that was developed to provide official recognition of a lawfully made GRAS determination with a different voluntary administrative procedure. From a legal and regulatory perspective, this substitution is neutral.

This narrow evaluation would facilitate FDA's rapid response to the notifier. Accordingly, under proposed § 170.36(e), FDA would respond to the notifier in writing within 90 days of receipt of the notice. In some circumstances, the agency's response would not question the GRAS determination. This response, however, would not be equivalent to an agency affirmation of GRAS status because FDA would neither receive nor review the detailed data and information that support the GRAS determination. In addition, consistent with proposed § 170.36(a)(2), any response from FDA would not constitute compliance with § 101.14(b)(3)(ii) or with the requirements that the agency has proposed (61 FR 36154) for new infant formula submissions.

In other circumstances, the agency's response could include identification of a problem with the notice. However, whether FDA chooses to advise a notifier that the agency has identified a problem with the notice, where the notice raises no important public health issues, is a matter committed to the agency's discretion.

FDA is proposing to respond in writing to a notifier in all circumstances for the following reasons. First, a written response would make clear that the agency's evaluation of a notice has come to closure. Second, as discussed more fully in section X of this document, FDA believes that a written response would facilitate international trade. Third, as discussed more fully in section VI.F of this document, FDA believes that a written response would be a useful element of any file that the agency makes publicly accessible or any inventory that the agency prepares of notices received under proposed § 170.36.

However, under a notification procedure, an agency response is not imperative in those circumstances in which the agency chooses to raise no question about the GRAS status of the intended use of the substance. As discussed in sections I.A and II of this document, a manufacturer may market a substance that the manufacturer determines is GRAS without informing the agency or, if the agency were so informed, while the agency is reviewing that information. Thus, FDA's proposal to respond to a notifier in all circumstances does not alter a notifier's prerogative under the statute to market a GRAS substance. Nonetheless, as an alternative approach, the notification program could be structured so that FDA responds to the notifier only when the agency questions the GRAS status of the intended use of the substance. FDA specifically requests comment on whether the agency should, in all cases, provide a notifier with a letter at the conclusion of the agency's evaluation of a notice. Such comments may result in a modification to proposed § 170.36(e).

FDA has also considered whether the time for the agency's response should be longer than 90 days, and specifically requests comment on whether the proposed 90-day timeframe for an agency response should be lengthened, e.g., to 120 days or 150 days. FDA's proposal to respond within 90 days reflects both a commitment to operational efficiency and a belief that the agency's evaluation of whether a notice provides a sufficient basis for a GRAS determination could likely be accomplished in such a period. However, FDA's expectation that it could respond within 90 days is in part predicated on its estimate, which is discussed more fully in the agency's analysis of the information collection requirements of this document, that the agency would receive approximately 50 notices per year. Accordingly, although comments on the information collection requirements of this document are submitted directly to the Office of Information and Regulatory Affairs, OMB, the agency also requests comment directly to FDA on the number of notices that manufacturers anticipate submitting on an annual basis. Such information may result in a modified timeframe for the agency's response.

3. Subsequent Agency Action

FDA is continuously evaluating the safety of substances in the food supply. In some cases, FDA may consider whether an emerging body of scientific knowledge raises questions about the continued safe use of a food additive or of a substance whose use was listed as GRAS, affirmed as GRAS, or commonly considered to be GRAS by the food industry. Likewise, FDA may consider whether specific information brought to the agency's attention (e.g., through routine correspondence from interested parties or through a citizen petition) raises such safety questions. In most cases, the information that comes to FDA's attention does not demonstrate a health hazard, and the scientific issues are resolved upon consideration by the agency. Thus, the agency does not routinely publicize safety issues that it is considering, or reconsidering, concerning the safety of a substance or class of substances that is used in food unless action by the agency is necessary for public health protection.

Similarly, FDA may direct resources to exploring issues raised by a GRAS notice even though such issues do not, on their face, appear to be significant public health issues. Alternatively, FDA may, at some point after its 90-day response to the notifier, receive additional information about a notified substance that raises questions about the safety of that substance. If, after issuing a 90-day response letter, questions develop for the agency regarding the GRAS status of a use of a substance, FDA may subsequently advise the notifier and other interested parties of those questions.

In such circumstances, FDA ordinarily expects to advise a notifier by letter that the agency has subsequently identified a problem with the notice. As discussed more fully in section VI.F of this document, such a letter would be placed in a publicly accessible file so that other interested parties would become aware of the agency's position. Alternatively, FDA may, in accordance with §§ 170.35(b)(4) and 170.38, publish a notice in the **Federal Register** determining that use of a substance is not GRAS and is a food additive subject to section 409 of the act. Importantly, however, when faced with a public health hazard, the existence of such rulemaking authority would not preclude other agency action, including seizure and injunction, to remove from the market a product that is an unapproved food additive.

As discussed in section VI.A of this document, FDA has recently proposed that a ''new infant formula'' submission required under section 412 (c) and (d) of the act include the basis on which each ingredient is determined to be safe and suitable under the food safety provisions of the act (proposed § 106.120(b)(6)(ii); 61 FR 36154 at 36217). The agency could receive a notice under proposed § 170.36 concerning a GRAS determination for a broad use of a substance in foods and subsequently receive a new infant formula submission that lists the substance as an ingredient in a new infant formula and asserts that the use of the substance in infant formula is GRAS. In such circumstances, FDA could choose to reexamine the notice previously received under proposed § 170.36. If, following such reexamination, the agency questions whether use of the substance in infant formula is GRAS, the agency could so inform the person who submitted the GRAS notice under proposed § 170.36.

D. Appeals

FDA recognizes that in some cases a notifier may disagree with the agency if the notifier receives a response advising that FDA has identified a problem with the notice. FDA has recently reviewed the vehicles, provided in part 10 (21 CFR part 10) of its regulations, that any person or firm may use to appeal an agency employee's decision (61 FR 9181 at 9184, March 7, 1996). Although an agency response to a notice under proposed § 170.36 does not constitute an agency decision on the GRAS status of a substance, FDA is advising that it will consider any of the existing appeals processes that are described below as an appropriate vehicle to engage the agency in cases where a notifier disagrees with a response received under proposed § 170.36.

Under § 10.75, an interested person may request internal agency review of an agency decision made by anyone other than the Commissioner. Such review ordinarily would be by the employee's supervisor, but may move up the management ranks to the Center Director or to the Office of the Commissioner if the issue cannot be resolved, important policy matters are present, or it would be in the public interest. Sections 10.25 and 10.33 permit an interested person to petition the Commissioner to review any administrative action. The regulations also include less formal methods of appeal. For example, under § 10.65, an interested person may correspond or meet with FDA about any matter under FDA's jurisdiction. Finally, any person with concerns about an agency response to a notice received under proposed § 170.36 may contact FDA's Office of the Chief Mediator and Ombudsman (the Ombudsman's Office). The Ombudsman's Office, which reports directly to the Commissioner, works on resolving issues and conflicts that arise in any FDA component. The Ombudsman's staff is available to discuss options, explain FDA's practices and procedures, and suggest approaches for resolution. When appropriate, the staff of the Ombudsman's Office may contact FDA's staff involved in the issue and mediate a dispute.

E. Public Disclosure and Accessibility

1. Public Disclosure

Proposed § 170.36(f)(1) provides that any GRAS exemption claim submitted under proposed § 170.36(c)(1) of this section be immediately available for public disclosure on the date the notice is received. As discussed in section VI.B.1 of this document, any person who makes a GRAS determination is responsible for ensuring that the determination complies with the provisions of § 170.30, regardless of whether that person notifies the agency about the determination. Further, the common knowledge element of a GRAS determination signifies that neither the common or usual name of the substance, the intended use of the substance, nor the basis for the GRAS determination can be confidential.

Proposed § 170.36(f)(1) further provides that all remaining data and information in a notice be available for public disclosure, in accordance with part 20 (21 CFR part 20), on the date the notice is received. The common knowledge element of a GRAS determination signifies that neither the detailed information about the identity of the substance nor the information needed to establish technical evidence of safety can be confidential. Therefore, FDA assumes that a notice will not contain any information that is protected from public disclosure. Moreover, because a GRAS substance may be marketed without prior approval, FDA assumes that, in most cases, submission of a notice will not reflect the notifier's plans about the timing of commercialization, which is arguably confidential commercial information (§ 20.61(b)).

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 FDA consideration. FDA will review the identified information, determine whether that information is exempt from public disclosure under part 20, and release or protect the information in accordance with that determination. FDA advises that, in most cases, the agency is likely to determine that all information submitted to support a GRAS determination is available for public disclosure.

2. Public Accessibility

The food industry's basic need to know whether a food substance is in compliance with applicable provisions of the act originally persuaded the agency to clarify the regulatory status of a multitude of food substances by publishing the GRAS list. Under this proposal, the current GRAS list (i.e., current part 182) and the regulations listing uses of a substance that FDA has affirmed as GRAS (i.e., current parts 184 and 186 (21 CFR parts 184 and 186)) would remain in the agency's codified regulations. In addition, FDA is retaining the process whereby the agency may, on its initiative, review the GRAS status of a substance and, if appropriate, establish a regulation in part 184 or part 186 affirming such use as GRAS. However, if this proposal becomes final, the existing process whereby an interested person may petition FDA to affirm the GRAS status of use of a substance and list such affirmed uses in part 184 or part 186 would be eliminated.

FDA believes that there would be considerable interest, from a broad segment of the public, including members of the regulated industry, other Federal, State, and local government agencies, international government agencies, and public interest groups, in notices received under proposed § 170.36. Such groups likely would want to know whether FDA is aware that a substance is being used in food on the basis of the GRAS exemption and whether FDA has advised the notifier that it has identified a problem with the notice. Therefore, FDA is proposing to establish a procedure whereby all members of the public could readily access such information. Moreover, such a procedure would be in keeping with the agency's goals in meeting the Reinventing Food Regulations.

All GRAS petitions are currently on public display at the Dockets Management Branch (DMB) because the petition process includes informal rulemaking and DMB is the usual repository for information that is publicly available during informal rulemaking. However, FDA sees no need to place the entire GRAS notice on public display at DMB because, under the proposed notification procedure, the agency will no longer be engaged in rulemaking. Moreover, a process of maintaining a copy of all notices at DMB would require that an additional copy be submitted and that an administrative copy be maintained at two locations (i.e., CFSAN as well as DMB). Such a process would be administratively inefficient.

Nonetheless, FDA has considered the best way to make the information from the proposed notification procedure readily accessible to the public. FDA has tentatively concluded that making both the GRAS exemption claim provided under proposed § 170.36(c)(1) and all letters issued by the agency relevant to each claim easily accessible to the public is the most direct and administratively efficient way of meeting the needs of the public. Accordingly, under proposed § 170.36(f)(2), the following information would be readily accessible for public review and copying: (1) A copy of all GRAS exemption claims received under proposed § 170.36(c)(1); (2) a copy of all

letters issued by the agency under proposed § 170.36(e); and (3) a copy of any subsequent letter issued by the agency.

FDA considered whether the agency should only make a GRAS exemption claim readily accessible if the agency has not advised a notifier that it has identified a problem with the notice. The agency decided to make all claims and responses readily accessible because such a system will properly underscore the notifier's acceptance of responsibility for the determination. Proposed § 170.36(f)(2) makes explicit to notifiers that their notice to the agency about a GRAS determination is a public claim.

Initially, FDA intends to prepare a file containing the information specified by proposed § 170.36(f)(2) and to place that file on public display at DMB. FDA is planning this approach because DMB is a common repository for publicly available files. Alternatively, FDA could make the file accessible for inspection at the agency's Freedom of Information Office or, in keeping with the current procedures for public inspection of the information FDA considered and relied on to reach a decision on an FAP, at CFSAN. Although FDA has tentatively concluded that it would be best to provide for public accessibility at DMB because the public is already accustomed to obtaining information relating to GRAS substances at that location, the agency requests comment on this matter.

FDA is not proposing to codify how or where the information prescribed by proposed § 170.36(f)(2) would be made accessible because any mechanism that appears in the agency's regulations will bind the agency to its provisions. In keeping with the agency's goals in meeting the Reinventing Food Regulations, FDA wishes to maintain flexibility to improve the process for public accessibility, particularly as the agency gains experience with electronic modes of information dissemination. FDA is aware that the public review of hard copy (i.e., paper) files in a public reading room may become obsolete as electronic technology for public dissemination of information advances.

FDA requests comment on whether proposed § 170.36(f)(2) is an effective and efficient means to provide the public with ready access to information from the proposed notification procedure.

F. Inventory

Proposed § 170.36(f)(2) would not require that FDA maintain an inventory of the information retained in the publicly accessible file. Consequently, such an inventory would be a new record within the meaning of § 20.24 and FDA would not be required to prepare such an inventory in response to a FOIA request. However, FDA recognizes the utility and importance of an inventory of notices received under proposed § 170.36 and of the agency's response to those notices, particularly for persons without ready access to the agency's DMB. FDA also recognizes that many members of the public would prefer to access basic information relevant to GRAS notices in a streamlined format. FDA further recognizes that the agency itself can most efficiently carry out its own responsibilities (e.g., with respect to monitoring imports of food products) by having basic information relevant to GRAS notices available in such a format.

Therefore, FDA intends to maintain an inventory of notices received, the agency's response, and any subsequent relevant agency correspondence. Such an inventory would be an administratively efficient mechanism of accounting for the information residing in the publicly accessible file. Such an inventory also would complement the current agency regulations tabulating substances that are listed (part 182) or affirmed (parts 184 and 186) as GRAS.

FDA has tentatively concluded that any inventory of notices received should be an adjunct to proposed § 170.36(f)(2), rather than the sole means of distributing the information available from the notification procedure, because the agency could place the GRAS exemption claims and the letters issued by the agency in the publicly accessible file faster than it could amend an inventory. However, FDA is not proposing to codify the inventory as an adjunct to proposed § 170.36(f)(2) because such an inventory would require continuous amendment and the administrative procedures required to amend a codified inventory would be too cumbersome to meet the needs of the public and the agency efficiently.

FDA is also not proposing to mention the availability of the inventory in its codified regulations. In keeping with the agency's goals in meeting Reinventing Food Regulations, FDA believes that refraining from codifying any aspect of the inventory will provide the agency with maximum flexibility to improve the process by which the inventory is updated and maintained.

Initially, FDA intends that such an inventory would be publicly accessible in any file maintained in accordance with proposed § 170.36(f)(2), e.g., at DMB. FDA could also make such an inventory available through prevailing publicly accessible electronic modes, such as the agency's home page on the contemporary World Wide Web. FDA requests comment on making any inventory prepared by the agency available through such electronic modes.

VII. Effect of the Proposed Notification Procedure on Existing GRAS Petitions

Under the current GRAS affirmation process, the agency conducts a preliminary examination of the data and information submitted in the petition. If FDA finds that the submitted information conforms to the requirements established under §§ 170.30 and 170.35, FDA makes an administrative decision to file the petition and publishes a notice in the **Federal Register** to that effect.

At this time, approximately 60 filed GRAS affirmation petitions are pending at FDA. These petitions were filed with the agency under an administrative process that the agency is proposing to remove. Therefore, if this proposal becomes final, the administrative process that FDA would use to bring these petitions to closure will no longer be operative. Moreover, FDA is proposing to eliminate the GRAS affirmation process in order to increase effectiveness and efficiency. The continued commitment of agency resources to complete the GRAS petition process for pending petitions would be contrary to one of the agency's goals in this rulemaking.

FDA recognizes that persons who have a pending GRAS affirmation petition have invested time and resources in those petitions. Therefore, proposed § 170.36(g)(1) stipulates that any GRAS affirmation petition filed under § 170.35 prior to the date that a final rule based on this proposal becomes effective, and still pending as of such effective date, will be presumptively converted to a GRAS notice under proposed § 170.36. This conversion will allow the agency to bring filed GRAS affirmation petitions to closure, albeit under a different process than the one to which they were submitted.

However, the proposed notification procedure has certain requirements that have no specific counterpart in the petition process. In particular, under the notification procedure a notifier explicitly accepts full responsibility for the GRAS determination by signing a GRAS exemption claim (under proposed § 170.36(c)(1)). In contrast, under the petition process a petitioner requests that FDA attest to a GRAS determination. Thus, FDA cannot assume that all persons who submitted

a GRAS petition would in fact be willing to accept full responsibility for the determination.

Moreover, the GRAS exemption claim in proposed § 170.36(c)(1) would be a complete and separate section of a GRAS notice that could stand alone and would contain basic information in a consistent format. As discussed, under proposed § 170.36(f)(2) the agency would use the GRAS exemption claim to effectively and efficiently inform the public about received notices. Thus, logic compels that a GRAS exemption claim filed under proposed § 170.36(g) include all elements of the claim required under proposed § 170.36(c)(1), rather than only those elements that have no counterpart in the GRAS affirmation petition process.

Accordingly, proposed § 170.36(g)(2) provides that any person who submitted a GRAS affirmation petition that is converted to a notice under the provisions of proposed § 170.36(g)(1) may amend such converted petition to satisfy the requirements of proposed § 170.36 by submitting to the agency a claim, dated and signed by the notifier (i.e., the former petitioner), that a particular use of a substance is exempt from the premarket approval requirements of the act because the notifier has determined that such use is GRAS. Proposed § 170.36 (g)(2)(i) through (g)(2)(vi) describe the format of the GRAS exemption claim that would amend a converted GRAS affirmation petition to satisfy the requirements of a notice under proposed § 170.36. This claim format is similar to that required under proposed § 170.36(c)(1) but has been modified in two particulars (i.e., proposed § 170.36 (g)(2)(ii) and (g)(2)(vi)) to take into account the fact that the data and information to support the GRAS determination have already been submitted to the agency in the applicable GRAS petition.

Proposed § 170.36(g)(2)(i) requires that the GRAS exemption claim include the name and address of the notifier. As with proposed § 170.36(c)(1)(i), this is necessary for full identification of the person who accepts responsibility for the claim. This also is necessary so that the agency can administer the amendment to the converted petition according to the provisions of proposed § 170.36 (d) and (e) (see proposed § 170.36(g)(3)(i)).

Proposed § 170.36(g)(2)(ii) requires that the GRAS exemption claim include the applicable GRAS affirmation petition number. The petition number is the simplest way to identify the converted petition that is being amended.

Proposed § 170.36(g)(2)(iii) requires that the GRAS exemption claim include the common or usual name of the substance that was the subject of the converted GRAS affirmation petition (i.e., the notified substance). As with proposed § 170.36(c)(1)(ii), this is necessary to identify the notified substance as well as to identify whether there are any labeling issues that need to be addressed. FDA is satisfied that detailed identity information, such as that described in proposed § 170.36(c)(2), will be present in the referenced petition because, under current § 170.35(c)(1)(i), FDA requires that a GRAS petition contain such information as a prerequisite to filing the petition.

Proposed § 170.36(g)(2)(iv) requires that the GRAS exemption claim include the applicable conditions of use that are supported by data and information in the referenced GRAS petition, including the foods in which the notified substance is to be used, levels of use in such foods, and the purposes for which the notified substance is used, including, when appropriate, a description of the population expected to consume the substance. As with proposed § 170.36(c)(1)(iii), this information describing the conditions of use is necessary to delineate the boundaries of the GRAS exemption claim consistent with section 201(s) of the act, which states that a GRAS substance must be generally recognized as safe ''under the conditions of its intended use.'' Importantly, a petitioner who amends a converted GRAS affirmation petition to satisfy the requirements of a notice may do so only for the intended use that was the subject of the GRAS affirmation petition. Any additional use(s) would be the subject of a separate notice under proposed § 170.36(c).

Proposed § 170.36(g)(2)(v) requires that the GRAS exemption claim identify the basis for the GRAS determination as scientific procedures or experience based on common use in food. As discussed in section I.B.4 of this document, under § 170.30, the requirements for a scientific procedures GRAS determination are different from those for a common use GRAS determination. The basis for a GRAS determination is thus fundamental to the GRAS exemption claim.

Proposed § 170.36(g)(2)(vi) requires that the GRAS exemption claim include either a statement that the complete record that supports the GRAS determination has already been submitted to the agency in the relevant GRAS petition (proposed § 170.36(g)(2)(vi)(A)) or a statement that all data and information that are the basis for the GRAS determination are available for FDA review and copying or will be sent to FDA upon request (proposed § 170.36(g)(2)(vi)(B)). Proposed § 170.36(g)(2)(vi) takes into account the fact that, in many cases, a petitioner has already submitted the complete record that supports the GRAS determination. Alternatively, proposed § 170.36(g)(2)(vi) provides to the person who submitted a GRAS petition the option of agreeing to provide upon request any additional information that supports the GRAS determination but was not included in the GRAS petition. As discussed with respect to proposed § 170.36(c)(1)(v), FDA might conduct random audits of such data and information or 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.

FDA requests comment on proposed § 170.36(g) as a mechanism for administering pending GRAS affirmation petitions if the proposed notification procedure becomes final. Proposed § 170.36(g) would not preclude any person who had a filed GRAS petition prior to the effective date of a final GRAS notification rule from submitting a notice of a claim for exemption according to the provisions of proposed § 170.36(c) or from submitting an FAP under § 171.1 and requesting that FDA cross reference the information contained in the filed GRAS petition in accordance with § 171.1(b).

VIII. Interim Policy

Between the time of publication of this proposal and any final rule based on this proposal, FDA invites interested persons who determine that a use of a substance is GRAS to notify FDA of such GRAS determinations as described in proposed § 170.36 (b) and (c). In general, the agency would administer the notices as described in proposed § 170.36 (d) through (f) (i.e., FDA would acknowledge receipt of the notice, respond in writing to the notifier, and make publicly accessible a copy of all GRAS exemption claims and the agency's response). However, although FDA would make a good faith effort to respond within the proposed 90-day timeframe, the agency would not be bound by such a timeframe. FDA will determine whether its experience in administering such notices suggests modifications to the proposed procedure.

FDA realizes that some individuals who have a filed GRAS affirmation petition pending at the agency may be interested in converting such petition to a notice under proposed § 170.36(g) or

in submitting a complete notice for the petitioned use under proposed § 170.36 (b) and (c). FDA invites such petitioners to submit an amendment in accordance with proposed § 170.36(g)(2) or to submit a complete notice for the petitioned use in accordance with proposed § 170.36 (b) and (c). FDA would administer such notice or amendment as described in proposed § 170.36 (d) through (f). However, during the interim period FDA would not continue to commit resources to review of a GRAS affirmation petition if the agency receives an amendment in accordance with proposed § 170.36(g)(2) or receives a complete notice concerning the petitioned use.

FDA will consult upon request with interested persons who seek additional guidance in preparing a notice because such consultation may identify sections of the proposed procedure that may require clarification in any final rule based on the proposal.

IX. Conforming Amendments

This proposal would eliminate the GRAS petition process set out in § 170.35(c). Therefore, FDA is proposing conforming amendments to revise current §§ 184.1(b)(1) and 186.1(b)(1) by removing the last sentence of each paragraph. These sentences provide that persons seeking FDA approval of an independent determination that a use of a food substance is GRAS may submit a petition in accordance with § 170.35.

Consistent with the proposed elimination of the GRAS petition process set out in § 170.35(c), FDA is also proposing a conforming amendment to revise current § 170.38(a) to: (1) Remove the provision that the Commissioner may, in accordance with § 170.35(c)(5), publish a notice in the **Federal Register** determining that a substance is not GRAS and is a food additive subject to section 409 of the act and (2) retain the provision in § 170.38(a) that the Commissioner may, in accordance with § 170.35(b)(4) (i.e., on his/her own initiative), publish such a notice in the **Federal Register**. Importantly, however, when faced with a public health hazard, the existence of such rulemaking authority would not preclude other agency action, including seizure and injunction, to remove from the market a product that is an unapproved food additive.

X. International Harmonization

FDA is committed to international harmonization of regulatory requirements and guidelines that preserve and enhance the agency's ability to accomplish its public health mission, enhance regulatory effectiveness by providing more consumer protection with scarce government resources, and increase worldwide access to safe and high quality food products (60 FR 53078, October 11, 1995). FDA is not aware of a provision in the laws of any other country that is equivalent to the GRAS exemption. On the other hand, the laws of other countries provide exemptions (e.g., for ''natural'' products) that have no equivalent under the act. Thus, the international community is already accustomed to operating in accordance with a variety of regulatory approaches for substances added to food. FDA's proposed substitution of a GRAS notification procedure for the current GRAS petition process would not impose any new requirements that would affect imported food products.

Under the current petition process, FDA makes a public announcement that a petition has been filed and incorporates an affirmed use of a substance into a codified list. Under the proposed notification procedure, FDA would make readily accessible to the public, including international agencies and firms, the notice's ''GRAS exemption claim,'' which would include a succinct description of the notified substance, the applicable conditions of use, and the basis for the GRAS determination (i.e., through scientific procedures or through experience based on common use in food). FDA would also make readily accessible to the public the agency's response to the notice. Further, under the act, a variety of substances that must be declared on the food label are exempt from premarket approval on the basis of the GRAS exemption and are not included on any government list or inventory of substances that are used lawfully in the U.S. food supply. Operation of either the petition process or the proposed notification procedure does not change that fact.

FDA recognizes that interested persons may want to know the official regulatory status of a food substance in the United States prior to using that substance in foods that will enter international commerce. FDA also recognizes that the proposed agency response to a GRAS notice may have less weight in the international community than the agency's affirmation of GRAS status. However, as a practical matter, FDA has announced only approximately 30 GRAS affirmations in the 10 years preceding this proposed rule. This small number of GRAS affirmations has a minimal impact on considerations of international trade.

For these reasons, FDA does not anticipate that the proposed substitution of a GRAS notification procedure for the GRAS petition process will have any impact on international trade. Nevertheless, the agency invites comment on this matter from the international community and from firms who import food products into the United States or who export U.S. made food products.

XI. Food Substances Used in Animal Feed

FDA's regulations regarding the eligibility of substances used in animal food or feeds for classification as GRAS, and the procedures for affirmation of GRAS status for such substances, are codified at §§ 570.30 and 570.35, respectively. The requirements described in these regulations are parallel to the requirements for GRAS substances that are used in human food, although some requirements of § 170.30 have no corresponding requirement in § 570.30. As an example relevant to this rulemaking, the requirements of § 570.30(c) are identical to the requirements of § 170.30(c)(1), but § 570.30(c) has not been amended to describe the requirements for a common use GRAS determination based on history of use when that history of use occurred primarily or exclusively outside the United States. In addition, the agency's GRAS review did not extend to the use of food substances in animal food or feeds. Thus, § 570.30 does not contain provisions analogous to § 170.30 (e) and (f).

The general provisions in subpart A of part 184 were issued under the auspices of the agency's comprehensive review of GRAS substances. Because this agency review did not extend to the use of food substances in animal food or feeds, the agency did not issue a corresponding subpart A in part 584 (21 CFR part 584). Therefore, any proposed rule to modify §§ 570.30 and 570.35 would require no conforming amendments in part 584.

FDA is also proposing to amend the provisions of § 570.30 that are parallel to the provisions of current § 170.30 (i.e., § 570.30 (a) and (b)) because §§ 170.30 and 570.30 implement the same statutory provisions. Therefore, it is important for the agency's standards concerning GRAS substances to be consistent with respect to substances used in human food and substances used in animal food or feeds.

FDA is also proposing to eliminate the GRAS affirmation petition process provided for in § 570.35 (a) and (c) because the corresponding process for substances used in human food is being eliminated. Although the GRAS

affirmation process has rarely been employed for substances used in animal food or feeds, FDA believes that it is appropriate to provide the option of a GRAS notification procedure for animal food or feeds that would be parallel to proposed § 170.36. Therefore, in proposed § 570.36 the agency is proposing a GRAS notification procedure for substances used in animal food or feeds. Finally, FDA is proposing to revise current § 570.38(a) as a conforming amendment required by removing the current GRAS affirmation petition process for substances used in animal food or feeds.

With regard to the notification procedure, FDA's proposal for substances that would be used in animal food or feeds is for practical purposes identical to FDA's proposal for substances that would be used in human food. As discussed in more detail throughout this document, FDA is specifically requesting comment on the following issues concerning the proposed regulations for substances that would be used in human food: (1) Whether it would be appropriate to require or recommend that the submission include an electronic copy, in addition to three paper copies, of some or all of the notice; (2) the proposed requirement that, in all cases, FDA respond to the notifier; (3) whether the agency should be permitted more than 90 days to respond to a GRAS notice; (4) the number of notices that notifiers anticipate submitting on an annual basis; (5) the agency's proposal to provide the public with ready access to information from the proposed notification procedure and the location for such information; (6) whether any inventory prepared by the agency should be available through electronic modes; (7) its proposal for administering pending GRAS affirmation petitions if the proposed notification procedure becomes final; and (8) whether the proposed substitution of a GRAS notification procedure for the GRAS petition process would have any impact on international trade. FDA specifically requests comments on these same issues for the proposed regulations concerning substances that would be used in animal foods or feed.

In the case of substances that would be used in animal feed, FDA is particularly concerned about the practical implications of a 90-day response period, because, to date, the agency has received fewer than 10 GRAS affirmation petitions for substances that would be used solely in animal food or feed. Should the number of notices received under a GRAS notification program exceed more than a few notices per year, agency resources devoted to the animal feed program likely would be insufficient to evaluate, within the proposed 90-day timeframe, whether the notice provides a sufficient basis for a GRAS determination. Thus, comments to the proposal may justify that the agency adopt, in a final rule, a longer timeframe for notifications concerning substances used in animal feed.

The agency recognizes that notifiers may have questions concerning the common or usual name for a substance that would be used in animal feeds. FDA advises that, in such circumstances, a notifier should consult with the Division of Animal Feeds in FDA's Center for Veterinary Medicine.

XII. Summary of the Proposal

FDA is proposing to clarify current § 170.30 regarding the eligibility of the use of a substance for exemption from the act's premarket approval requirements based on a GRAS determination. Specifically, FDA is proposing to amend current § 170.30(a) to clarify that general recognition of safety requires that there be common knowledge among the qualified expert community that there is reasonable certainty that the substance is not harmful under the intended conditions of use. This amendment would also clarify that a GRAS substance is neither more safe nor less safe than an approved food additive, and that the distinction between a GRAS substance and an approved food additive is in the common knowledge of, and expert consensus about, that safety.

In addition, FDA is proposing two changes to current § 170.30(b). First, FDA is proposing to clarify the types of technical evidence of safety that ordinarily would constitute common knowledge about a substance that is GRAS through scientific procedures. FDA is proposing this change because the quantity and quality of scientific evidence required to obtain approval of a substance as a food additive vary considerably depending upon the estimated dietary exposure to the substance and the chemical, physical, and physiological properties of the substance. Second, FDA is proposing to clarify the role of publication in satisfying the common knowledge element of the GRAS standard because publication is ordinarily required, but may not always be sufficient, to satisfy this element. For consistency with these proposed amendments, FDA is also proposing to amend the definition of ''scientific procedures'' in § 170.3(h).

In keeping with the Reinventing Food Regulations, FDA is proposing to replace the current voluntary GRAS affirmation process with a voluntary procedure whereby any person may notify FDA of a GRAS determination. The notice would include a ''GRAS exemption claim,'' dated and signed by the notifier, that would provide, in a consistent format, specific information about a GRAS determination. This claim would include a succinct description of the notified substance, the applicable conditions of use, and the basis for the GRAS determination. The GRAS exemption claim would also include a statement that the information supporting the GRAS determination was available for FDA review and copying or would be sent to FDA upon request. In addition to the GRAS exemption claim, the notice would include detailed information about the identity of the notified substance and a detailed discussion of the basis for the notifier's GRAS determination.

FDA would evaluate whether the notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to FDA raises issues that lead the agency to question whether use of the substance is GRAS. Within 90 days from the date of receipt of the notice, FDA would respond to the notifier in writing and could advise the notifier that the agency has identified a problem with the notice. A response that does not advise that the agency has identified a problem with the notice would not be equivalent to an affirmation of GRAS status by the agency.

For each notice received, FDA would make readily accessible to the public the GRAS exemption claim and the agency's response. Although FDA would maintain a readily accessible inventory of notices received and the agency's response to them, this inventory would be neither codified nor referenced in the agency's regulations.

Under the proposal, all GRAS affirmation petitions that were filed by FDA under § 170.35 prior to the effective date of a GRAS notification final rule and still pending as of that date would be presumptively converted to a notice on that date. Any person who had submitted a GRAS affirmation petition that is converted to a notice could: (1) Amend such converted petition to satisfy the requirements of the notification procedure by submitting to the agency a modified GRAS exemption claim; (2) submit an FAP for the substance and request that FDA cross reference the information in the GRAS affirmation petition; or (3) submit a complete notice in accordance with the notification procedure.

FDA's regulations in part 570 concerning GRAS substances for use in animal food or feeds implement the same statutory provisions as the regulations in part 170 concerning GRAS substances for use in human food. Accordingly, FDA is proposing: (1) To amend the provisions of § 570.30 that are parallel to the provisions of current § 170.30 (*i.e.*, § 570.30(a) and (b)); (2) to eliminate the GRAS affirmation petition process provided for in § 570.35(a) and (c); and (3) to provide the option of a GRAS notification procedure for substances used in animal food or feeds that would be parallel to proposed § 170.36.

FDA is also proposing several amendments to parts 170, 184, 186, and 570 of its regulations as conforming amendments.

XIII. Paperwork Reduction

This proposed rule contains information that is subject to review by OMB under the Paperwork Reduction Act of 1995 (Pub. L. 104–13). Therefore, in accordance with 44 U.S.C. 3506(c)(2)(B) and 5 CFR part 1320, FDA is providing below the title, description, and respondent descriptions for the information collections contained in this proposal, along with an estimate of the resulting annual information collection burden. Included in the estimate is the time needed to review instructions, to gather the required information, and to disclose the information.

FDA invites comments on the following: (1) Whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) the accuracy of the agency's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on those who are to respond, including through the use of automated collection techniques, where appropriate, or other forms of information technology.

Title: Notice of a Claim for GRAS Exemption Based on a GRAS Determination

Description: Section 409 of the act establishes a premarket approval requirement for ''food additives;'' section 201(s) of that act provides an exemption from the definition of ''food additive'' and thus from the premarket approval requirement, for uses of substances that are GRAS by qualified experts. FDA is proposing a voluntary procedure whereby members of the food industry who determine that use of a substance satisfies the statutory exemption may notify FDA of that determination. The notice would include a detailed summary of the data and information that support the GRAS determination, and the notifier would maintain a record of such data and information. FDA would make the information describing the GRAS claim, and the agency's response to the notice, available in a publicly accessible file; the entire GRAS notice would be publicly available consistent with the FOIA and other Federal disclosure statutes.

Description of Respondents: Manufacturers of Substances Used in Food and Feed

FDA estimates the total annual burden for this information collection to be 9,900 hours.

ESTIMATED ANNUAL REPORT BURDEN

21 CFR	Number of respondents	Annual frequency per response	Total annual response	Hours per response	Total hours
170.36	50	1	50	150	7,500
570.36	10	1	10	150	1,500

There are no operating or maintenance costs or capital costs associated with this collection.

ESTIMATED ANNUAL RECORDKEEPING BURDEN

21 CFR	Number of record-keepers	Annual frequency of record-keeping	Total annual records	Hours per record-keeper	Total hours
170.36(c)(v)	50	1	50	15	750
570.36(c)(v)	10	1	10	15	150

There are no operating or maintenance costs or capital costs associated with this collection.

FDA tentatively concludes that there are no anticipated capital costs or operating and maintenance costs associated with the proposed information collection requirements. However, the agency welcomes comments on any such anticipated costs.

The agency has submitted copies of the proposed rule to OMB for review of the portions of the proposal that are subject to the Paperwork Reduction Act of 1995. Interested persons are requested to send comments regarding information collection by May 19, 1997 to the Office of Information and Regulatory Affairs, OMB (address above).

XIV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select the regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects; other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. If a rule has a significant economic impact on a

substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize the economic impact of that rule on small entities.

FDA finds that this proposed rule is not a significant rule as defined by Executive Order 12866, and finds under the Regulatory Flexibility Act that this proposed rule will not have a significant impact on a substantial number of small entities. Finally, FDA, in conjunction with the Administrator of OMB, finds that this proposed rule is not a major rule for the purpose of congressional review (Pub. L. 104–121).

A. Regulatory Options

FDA has the following primary options:

(1) Take no action;

(2) Adopt proposed GRAS notification procedure;

(3) Adopt a GRAS notification procedure allowing FDA feedback on independent GRAS determinations of either a higher or lower level of authoritativeness than the proposed notification system; and

(4) Eliminate agency participation in independent GRAS determinations.

B. Costs and Benefits

1. Option One: Take No Action

Neither costs nor benefits are associated with taking no action. This option is the baseline case in comparison with which the costs and benefits of the other options are determined.

The existing GRAS petition process is a government service provided to industry by which firms may voluntarily submit information to FDA for agency review and affirmation of the GRAS status of the use of a substance in food. Although FDA does not charge a fee to review material submitted under the GRAS petition process, participation in that process is not without cost because the required information must either be generated or gathered, and submitted to FDA. The fact that some firms participate in this voluntary process implies that for some firms, the benefit of participation must be greater than the cost of participation, and also that the net benefit of participation must be greater than the net benefit of existing alternatives, such as private third-party review of independent GRAS determinations. However, the fact that the cost of participation does not reflect the costs involved in actually administering the GRAS petition process means that participation in that process cannot support inferences regarding the net social benefits of the petition process.

The benefit firms receive from participation in the existing GRAS petition process appears to involve a reduction in the cost of marketing foods containing substances independently determined to be GRAS because FDA affirmation of GRAS status would likely facilitate marketing of such substances. Manufacturers of these foods and retail establishments buying these foods for subsequent resale to consumers may be reluctant to offer them for sale in the absence of assurance that FDA will not subsequently conclude that ingredients independently determined to be GRAS are unapproved food additives. If these substances were subsequently found not to be GRAS, any ensuing seizure of foods containing the unapproved food additive might damage the credibility of those manufacturers and retail establishments, and might lead to economic losses. If there were no process for agency GRAS affirmation, firms making independent GRAS determinations may attempt to substitute for GRAS affirmations by doing additional research, contracting with third party research organizations, or taking other steps to provide adequate assurances to other firms that FDA will probably not subsequently challenge their independent GRAS determinations.

In addition to providing a desired good or service, the GRAS petition process may result in some benefit in terms of reducing the health risks from substances independently determined to be GRAS if FDA review of the information supporting independent GRAS determinations uncovers an erroneous determination which, if undetected, could lead to health risks.

2. Option Two: Adopt Proposed GRAS Notification Procedure

The chief benefit of eliminating the existing GRAS petition process and replacing it with the proposed GRAS notification procedure is that the notification procedure will enable industry to obtain a limited degree of FDA feedback on independent GRAS determinations more quickly and at lower cost, to both industry and FDA, than the GRAS petition process. Under the proposed notification procedure, FDA will determine whether the notice provides a sufficient basis for a GRAS determination or whether information in the notice, or otherwise available to FDA, raises issues that lead the agency to question whether use of the substance is GRAS.

The proposed notification procedure will come to closure more quickly and generate less uncertainty than the GRAS petition process because the notification procedure is based on a 90-day review period rather than on the open-ended review period of the GRAS petition process. In some cases, the GRAS petition process involves a number of iterative steps in which FDA asks for and receives additional supporting information. Under the notification procedure, FDA will base its response on the notifier's initial submission.

In addition to the time advantage, the cost of participation in the proposed notification procedure will probably be less than the cost of participation in the GRAS petition process because the notification procedure will require the submission of only a summary of the information used to support the independent GRAS determination, rather than the full supporting information required under the GRAS petition process. For example, the notification procedure will not require the submission of references or material relating to methods of detection in foods, which are required under the GRAS petition process. Submissions under the notification procedure will probably be about 25 to 30 pages, while submissions under the current GRAS petition process can have hundreds or even thousands of pages.

On the other hand, the same underlying information will be required under the notification procedure as under the GRAS petition process, so the potential cost savings will be confined to the relatively modest costs of assembling, copying, and mailing information. The more significant cost of generating or locating the requisite underlying information will not be affected. In addition, the summary required under the proposed notification procedure may fairly be viewed as a step beyond simply providing the supporting information as required under the GRAS petition process. Therefore, although participation in the proposed notification procedure will probably be somewhat less costly than participation in the GRAS petition process, the cost reduction is likely to be relatively modest.

The primary cost of replacing the existing GRAS petition process with the proposed notification procedure is that it reduces the options available to industry for obtaining FDA feedback on independent GRAS determinations at a level of authoritativeness comparable to that currently offered under the GRAS petition process. Currently, feedback at this level of authoritativeness is available through both the GRAS petition process and the FAP process. The fact that FDA receives both GRAS petitions and FAP's suggests that some

firms find participation in the GRAS petition process less costly than participation in the FAP process. However, this difference in cost is probably relatively modest because the systems are quite similar. For example, substances that are GRAS may be marketed without prior agency approval and thus may be marketed during the period in which either a GRAS petition or an FAP on that substance is under review.

The net benefit or cost of the proposed notification procedure will depend largely on whether the value of participation in the proposed notification procedure is or is not comparable to that of participation in the GRAS petition process. If the value of participation in the two systems is roughly comparable, then the time and cost advantages of the proposed notification procedure will probably lead to modest net benefits. However, if participation in the proposed notification procedure is significantly less valuable than participation in the GRAS petition process because of the lower level of authoritativeness of FDA feedback available through the notification procedure, then the proposed procedure could lead to net costs because firms may submit relatively more costly FAP's or take other steps to compensate for the lack of more authoritative FDA feedback on independent GRAS determinations.

3. Option Three: Adopt a GRAS Notification Procedure Allowing FDA Feedback on Independent GRAS Determinations of Either a Higher or Lower Level of Authoritativeness Than the Proposed Notification System

The benefits and costs of replacing the existing GRAS petition process with notification procedures allowing FDA feedback on independent GRAS determinations at either higher or lower levels of authoritativeness than the proposed notification procedure are qualitatively similar to the benefits and costs of adopting the proposed notification procedure.

The net benefits or costs of notification procedures allowing more or less authoritative FDA feedback depend largely on the cost of participation in those systems and the value of the feedback provided to participating firms under those systems. The value of FDA feedback to participating firms involves the degree to which that feedback facilitates the marketing of substances that have been subject to independent GRAS determinations. A system providing more authoritative feedback than the proposed GRAS notification procedure would either require submission of more information or more detailed information, or would involve more detailed agency review of the same amount of information. Thus, participation in such a system would arguably provide more valuable feedback than participation in the proposed notification procedure but would also be more costly than participation in the proposed notification procedure. A system providing less authoritative feedback than the proposed GRAS notification procedure would either require submission of less information or less detailed information, or would involve less detailed agency review of the same amount of information. Thus, participation in such a system would arguably provide less valuable feedback than participation in the proposed notification procedure but would probably also be less costly than participation in the proposed notification procedure.

In both cases, it is difficult to determine whether the resulting changes in the value of FDA feedback available through the notification procedure would compensate firms for the resulting changes in the cost of participation in such procedures, or to compare the net social benefits of offering such procedures with the net benefits of the existing GRAS petition process.

4. Option Four: Eliminate Agency Participation in Independent GRAS Determinations

The costs and benefits of this option are qualitatively similar to those of adopting a notification procedure allowing FDA feedback of only a minimal level of authoritativeness. In general, the same results will occur if the value of participation in a notification procedure drops below the costs involved in participation, or if a notification procedure is not available. In both cases, industry will either submit relatively costly FAP's or take other steps to compensate for the lack of a GRAS notification procedure or petition process, or simply forgo government oversight of their independent GRAS determinations.

If FDA no longer participates in independent GRAS determinations, FDA will not be aware of substances that have been the subject of independent GRAS determinations unless firms choose to submit FAP's for those substances. Any public health benefits associated with FDA awareness of these substances will be lost. However, if firms take other steps to confirm independent GRAS determinations, then these other steps will be associated with countervailing public health benefits.

Again, it is difficult to determine whether this option would result in net social costs or benefits because of the difficulty of estimating the value of various levels of FDA and non FDA feedback on independent GRAS determinations. However, the distinctive role of FDA in GRAS issues suggests that FDA feedback may be more valuable to industry than other, equally costly, activity designed to confirm independent GRAS determinations. Therefore, it is likely that the availability of some type of notification procedure will lead to greater net benefits than no notification procedure.

C. Regulatory Flexibility Analysis

The proposed action will affect any firm that may have chosen to participate in the existing GRAS petition process or may choose to participate in the proposed GRAS notification process, including manufacturers of both human and animal food, food additives, and feed additives. The Dun's Market Identifiers database lists 27,989 firms in Standard Industry Code (SIC) 20, Food and Kindred Products. This includes dog and cat food, and prepared feeds not elsewhere classified. In addition, this database lists 113 firms in SIC 2869, Industrial Organic Chemicals, Not Elsewhere Classified, the SIC code that includes manufacturers of food additives. Therefore, a total of 28,102 firms will potentially be affected by this proposed rule.

The Small Business Administration (SBA) guidelines on the definition of a small business for SIC 20 identify a small business as being a business having no more than 1,000, 750, or 500 employees, depending on the more precise four-digit SIC code associated with the firm in question. However, there is no easy way to distribute the total number of firms in SIC 20 into the appropriate four-digit SIC categories because more than one primary four-digit SIC code may be associated with any given firm. To avoid missing any small firms, the least restrictive size definition of 1,000 or fewer employees was used for all firms. The SBA definition of a small business in SIC 2869 is a business with 1,000 or fewer employees. Based on these definitions, and assuming that the distribution of employment for firms for which no employee data are available is the same as the distribution for firms for which data are available, a total of 27,531 firms could potentially be affected by this proposed rule.

Although this proposal may affect a substantial number of firms that manufacture food or food additives, many of which are small firms, this proposal will not have a significant impact on these firms for two reasons. First, this proposal replaces one voluntary program with another voluntary program. Therefore, small firms will not be required to undertake any additional activity or bear any additional costs. Second, participation in the proposed GRAS notification procedure should be somewhat less costly than participation in the GRAS petition process. Therefore, small firms should be better able to participate in the notification procedure than the petition process.

D. Conclusions

In accordance with Executive Order 12866, FDA has analyzed this proposed rule and finds that this proposed rule is neither economically significant nor a significant action, as defined by that order. FDA has also analyzed this proposed rule in accordance with the Regulatory Flexibility Act and finds that this proposed rule will not have a significant impact on a substantial number of small businesses. Accordingly, under the Regulatory Flexibility Act, 5 U.S.C. 605(b), the Commissioner certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities.

The net costs and benefits of replacing the GRAS petition process with the proposed GRAS notification procedure are indeterminate. However, any increase in net costs or benefits relative to the current system will probably be modest. FDA requests comments on the costs and benefits of replacing the GRAS petition process with the proposed GRAS notification procedure.

XV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) 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.

XVI. References

The following references have been placed on display at DMB (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. House Report No. 2284, July 28, 1958.

2. Price, J. M., C. G. Biava, B. L. Oser, E. E. Vogin, J. Steinfeld, and H. L. Ley, ''Bladder Tumors in Rats Fed Cyclohexylamine or High Doses of a Mixture of Cyclamate and Saccharin,'' *Science*, 167:1131–1132, 1970.

3. New York Times, p. 22, October 31, 1969.

4. Sneath, P. H. A. et. al., *Bergey's Manual of Systematic Bacteriology*, Williams & Wilkins, Baltimore, 1984.

5. Subcommittee on the 10th Edition of the Recommended Dietary Allowances, Food and Nutrition Board, Commission on Life Sciences, National Research Council, *Recommended Dietary Allowances*, 10th ed., Washington, DC, National Academy Press, 1989.

6. ''Biotechnology and Food Safety,'' (Food and Agriculture Organization, Rome, 1996).

7. ''Strategies for Assessing the Safety of Foods Produced by Biotechnology'' (World Health Organization, Geneva, 1991).

8. ''Safety Evaluation of Foods Derived by Modern Biotechnology: Concepts and Principles'' (Organization for Economic Cooperation and Development, Paris, 1993).

9. ''Application of the Principles of Substantial Equivalence to the Safety Evaluation of Foods or Food Components from Plants Derived by Modern Biotechnology'' (World Health Organization, Geneva, 1995).

10. Kessler, D. A., M. R. Taylor, J. H. Maryanski, E. L. Flamm, and L. S. Kahl, ''The Safety of Foods Developed by Biotechnology,'' *Science*, 256:1747–1749 and 1832, 1992.

List of Subjects

21 CFR Part 170

Administrative practice and procedure, Food additives, Reporting and recordkeeping requirements.

21 CFR Part 184

Food ingredients.

21 CFR Part 186

Food ingredients, 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, it is proposed that 21 CFR parts 170, 184, 186, and 570 be amended as follows:

PART 170—FOOD ADDITIVES

1. The authority citation for 21 CFR part 170 is revised to read as follows:

Authority: Secs. 201, 401, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 341, 342, 348, and 371).

2. Section 170.3 is amended by revising paragraph (h) to read as follows:

§ 170.3 Definitions.

* * * * *

(h) *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.

* * * * *

3. Section 170.30 is amended by revising the last sentence of paragraphs (a), (b), and (c)(2); and by removing and reserving paragraph (f) to 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 intended conditions of use.

(b) * * * General recognition of safety through scientific procedures shall be 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.

(c)(1) * * *

(2) * * * 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 proposed § 170.36.

* * * * *

4. Section 170.35 is amended by revising paragraph (a) and by removing 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 the GRAS status of the use of a substance that directly or indirectly becomes a component of food.

* * * * *

5. New § 170.36 is added to subpart B to read as follows:

§ 170.36 Notice of a claim for exemption based on a GRAS determination.

(a)(1) 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).

(2) Notice to the agency of this section shall not constitute compliance with:

(i) Section 101.14(b)(3)(ii) of this chapter. Any person who submits a health claim petition under § 101.14 of this chapter shall comply in full with § 101.14(b)(3)(ii) regardless of whether

the agency has been notified under this section about a substance and regardless of the nature of the agency's response.

(ii) Section 106.120(b)(6)(ii) of this chapter. Any person who submits a new infant formula submission under proposed § 106.120 of this chapter shall comply in full with proposed § 106.120(b)(6)(ii) regardless of whether the agency has been notified under this section about a substance and regardless of the nature of the agency's response.

(b) A notice of a GRAS exemption claim shall be submitted in triplicate to the Office of Premarket Approval (HFS–200), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204.

(c) Notifiers shall submit the following information:

(1) A claim, 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, that a particular use of a substance is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the act) because the notifier has determined that such use is GRAS. Such GRAS exemption claim shall include:

(i) The name and address of the notifier;

(ii) The common or usual name of the substance that is the subject of the GRAS exemption claim (i.e., the ''notified substance'');

(iii) 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;

(iv) The basis for the GRAS determination (i.e., through scientific procedures or through experience based on common use in food); and

(v) A statement that the data and information that are the basis for the notifier's GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at reasonable times at a specific address set out in the notice or will be sent to FDA upon request.

(2) 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 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;

(3) Information on any self-limiting levels of use; and

(4) 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 act because such use is GRAS. Such determination may be based either on scientific procedures or on common use in food.

(i) For a GRAS determination through scientific procedures, such summary shall include:

(A) 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;

(B) A comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with the GRAS determination; and

(C) The basis for concluding, in light of the data and information described under paragraphs (c)(1), (c)(2), (c)(3), (c)(4)(i)(A), and (c)(4)(i)(B) of this section, 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.

(ii) For a GRAS determination through experience based on common use in food, such summary shall include:

(A) 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;

(B) A comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with the GRAS determination;

(C) The basis for concluding, in light of the data and information described under paragraphs (c)(1), (c)(2), (c)(3), (c)(4)(ii)(A), and (c)(4)(ii)(B) of this section, 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.

(d) Within 30 days of receipt of the notice, FDA shall acknowledge receipt of a notice by informing the notifier in writing of the date on which the notice was received.

(e) Within 90 days of receipt of the notice, FDA shall respond to the notifier in writing.

(f)(1) Any GRAS exemption claim submitted under paragraph (c)(1) of this section shall be immediately available for public disclosure on the date the notice is received. All remaining data and information in the notice shall be available for public disclosure, in accordance with part 20 of this chapter, on the date the notice is received.

(2) For each GRAS notice submitted under this section, the following information shall be readily accessible for public review and copying:

(i) A copy of the GRAS exemption claim submitted under paragraph (c)(1) of this section.

(ii) A copy of any letter issued by the agency under paragraph (e) of this section.

(iii) A copy of any subsequent letter issued by the agency regarding such notice.

(g)(1) Any GRAS affirmation petition that was filed by FDA under § 170.35 prior to (date the final rule becomes effective) and is still pending as of (date the final rule becomes effective) shall be presumptively converted to a notice under the provisions of this section on (date the final rule becomes effective).

(2) Any person who submitted a GRAS affirmation petition that is converted to a notice under paragraph (g)(1) of this section may amend such converted petition to meet the requirements of this section by submitting to the agency a claim, dated and signed by the notifier (i.e., the former petitioner), or by the notifier's attorney or agent, or (if the notifier is a corporation) by an authorized official, that a particular use of a substance is exempt from the premarket approval requirements of the act because the notifier has determined that such use is GRAS. Such GRAS exemption claim shall include:

(i) The name and address of the notifier;

(ii) The applicable GRAS affirmation petition number;

(iii) The common or usual name of the substance that was the subject of the converted GRAS affirmation petition (i.e., the notified substance);

(iv) The applicable conditions of use of the notified substance that are

supported by data and information in the referenced GRAS petition, 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;

(v) The basis for the GRAS determination (i.e., through scientific procedures or through experience based on common use in food); and

(vi)(A) A statement that the complete record that supports the GRAS determination has been submitted to the agency in the applicable GRAS petition; or

(B) A statement that the data and information that are the basis for the notifier's GRAS determination are available for FDA review and copying at reasonable times at a specific address set out in the claim or will be sent to FDA upon request.

(3)(i) A petition that is converted to a notice under the provisions of paragraph (g)(1) of this section and that is amended according to the provisions of paragraph (g)(2) of this section shall be reviewed and administered according to the provisions of paragraphs (d), (e), and (f) of this section. For the purposes of paragraphs (d), (e), and (f) of this section, the date of receipt of the amendment described in paragraph (g)(2) of this section shall be the date of receipt of the notice.

(3)(ii) After (date 90 days after date of publication of the final rule), FDA will inform any person who submitted a GRAS affirmation petition that is converted to a notice under the provisions of paragraph (g)(1) of this section, and who has not amended such petition according to the provisions of paragraph (g)(2) of this section, that the converted petition is inadequate as a notice under this section.

6. Section 170.38 is amended by revising 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 and is a food additive subject to section 409 of the act.

* * * * *

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

7. The authority citation for 21 CFR part 184 continues to read as follows:

Authority: Secs. 201, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 348, and 371).

§ 184.1 [Amended]

8. Section 184.1 *Substances added directly to human food affirmed as generally recognized as safe (GRAS)* is amended in paragraph (b)(1) by removing the last sentence.

PART 186—INDIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

9. The authority citation for 21 CFR part 186 continues to read as follows:

Authority: Secs. 201, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 348, and 371).

§ 186.1 [Amended]

10. Section 186.1 *Substances added indirectly to human food affirmed as generally recognized as safe (GRAS)* is amended in paragraph (b)(1) by removing the last sentence.

PART 570—FOOD ADDITIVES

11. The authority citation for 21 CFR part 570 is revised to read as follows:

Authority: Secs. 201, 401, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 341, 342, 348, and 371).

12. Section 570.3 is amended by revising paragraph (h) to read as follows:

§ 570.3 Definitions.

* * * * *

(h) *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.

* * * * *

13. Section 570.30 is amended by revising the last sentence of paragraphs (a) and (b) 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 under the intended conditions of use.

(b) * * * General recognition of safety through scientific procedures shall be 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.

* * * * *

14. Section 570.35 is amended by revising paragraph (a) and by removing 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 the GRAS status of the use of a substance that directly or indirectly becomes a component of food.

* * * * *

15. New § 570.36 is added to subpart B to read as follows:

§ 570.36 Notice of a claim for exemption based on a GRAS determination.

(a) 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).

(b) A notice of a GRAS exemption claim shall be submitted in triplicate to the Division of Animal Feeds (HFV–220), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

(c) Notifiers shall submit the following information:

(1) A claim, 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, that a particular use of a substance is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the act) because the notifier has determined that such use is GRAS. Such GRAS exemption claim shall include:

(i) The name and address of the notifier;

(ii) The common or usual name of the substance that is the subject of the GRAS exemption claim (i.e., the notified substance);

(iii) 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;

(iv) The basis for the GRAS determination (i.e., through scientific procedures or through experience based on common use in food); and

(v) A statement that the data and information that are the basis for the notifier's GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at reasonable times at a specific address set out in the notice or will be sent to FDA upon request.

(2) 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 substances of natural biological origin, source information such as genus and species), characteristic properties, any content of potential human or animal toxicants, and specifications for feed-grade material;

(3) Information on any self-limiting levels of use; and

(4) 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 act because such use is GRAS. Such determination may be based either on scientific procedures or on common use in food.

(i) For a GRAS determination through scientific procedures, such summary shall include:

(A) 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;

(B) A comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with the GRAS determination; and

(C) The basis for concluding, in light of the data and information described under paragraphs (c)(1), (c)(2), (c)(3), (c)(4)(i)(A), and (c)(4)(i)(B) of this section, 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.

(ii) For a GRAS determination through experience based on common use in food, such summary shall include:

(A) 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;

(B) A comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with the GRAS determination;

(C) The basis for concluding, in light of the data and information described under paragraphs (c)(1), (c)(2), (c)(3), (c)(4)(ii)(A), and (c)(4)(ii)(B) of this section, 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.

(d) Within 30 days of receipt of the notice, FDA shall acknowledge receipt of a notice by informing the notifier in writing of the date on which the notice was received.

(e) Within 90 days of receipt of the notice, FDA shall respond to the notifier in writing.

(f)(1) Any GRAS exemption claim submitted under paragraph (c)(1) of this section shall be immediately available for public disclosure on the date the notice is received. All remaining data and information in the notice shall be available for public disclosure, in accordance with part 20 of this chapter, on the date the notice is received.

(2) For each GRAS notice submitted under this section, the following information shall be readily accessible for public review and copying:

(i) A copy of the GRAS exemption claim submitted under paragraph (c)(1) of this section.

(ii) A copy of any letter issued by the agency under paragraph (e) of this section.

(iii) A copy of any subsequent letter issued by the agency regarding such notice.

(g)(1) Any GRAS affirmation petition that was filed by FDA under § 570.35 prior to (date the final rule becomes effective) and is still pending as of (date the final rule becomes effective) shall be presumptively converted to a notice under the provisions of this section on (date the final rule becomes effective).

(2) Any person who submitted a GRAS affirmation petition that is converted to a notice under paragraph (g)(1) of this section may amend such converted petition to meet the requirements of this section by submitting to the agency a claim, dated and signed by the notifier (i.e., the former petitioner), or by the notifier's attorney or agent, or (if the notifier is a corporation) by an authorized official, that a particular use of a substance is exempt from the premarket approval requirements of the act because the notifier has determined that such use is GRAS. Such GRAS exemption claim shall include:

(i) The name and address of the notifier;

(ii) The applicable GRAS affirmation petition number;

(iii) The common or usual name of the substance that was the subject of the converted GRAS affirmation petition (i.e., the notified substance);

(iv) The applicable conditions of use of the notified substance that are supported by data and information in the referenced GRAS petition, 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;

(v) The basis for the GRAS determination (i.e., through scientific procedures or through experience based on common use in food); and

(vi)(A) A statement that the complete record that supports the GRAS determination has been submitted to the agency in the applicable GRAS petition; or

(B) A statement that the data and information that are the basis for the GRAS determination are available for FDA's review and copying at reasonable times at a specific address set out in the claim or will be sent to FDA upon request.

(3)(i) A petition that is converted to a notice under the provisions of paragraph (g)(1) of this section and that is amended according to the provisions of paragraph (g)(2) of this section shall be reviewed and administered according to the provisions of paragraphs (d), (e), and (f) of this section. For the purposes of paragraphs (d), (e), and (f) of this section, the date of receipt of the amendment described in paragraph (g)(2) of this section shall be the date of receipt of the notice.

(ii) After (date 90 days after date of publication of the final rule), FDA will inform any person who submitted a GRAS affirmation petition that is converted to a notice under the provisions of paragraph (g)(1) of this section, and who has not amended such petition according to the provisions of paragraph (g)(2) of this section, that the converted petition is inadequate as a notice under this section.

§ 570.38 [Amended]

16. Section 570.38 *Determination of food additive status* is amended in paragraph (a) by removing ''or (c)(5)''.

Dated: April 8, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97–9706 Filed 4–16–97; 8:45 am]

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