SUBSTANCES GENERALLY RECOGNIZED AS SAFE:
NOTIFICATION PROCEDURE
OMB No. 0910-0342

SUPPORTING STATEMENT

A. JUSTIFICATION

1. Circumstances Necessitating Information Collection

Section 701 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 371) sets forth authority to issue regulations for the efficient enforcement of the act (Attachment 1). Section 201(f) of the act (21 U.S.C. 321(f); Attachment 2) defines “food” to mean “(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.”

Section 409 of the act (21 U.S.C. 348; Attachment 3) establishes a premarket approval requirement for "food additives." Under section 409 of the act, a producer must demonstrate the safety of a new additive (such as a preservative, antioxidant or emulsifier) to FDA before it can be used in food processing. However, in enacting section 409 of the act, Congress recognized that many substances intentionally added to food do not require formal premarket review by FDA to assure their safety. Congress thus adopted, in section 201(s) of the act (21 U.S.C. 321(s); Attachment 2), 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, which under section 201(f) includes animal food. The second step, however, excludes from the definition of food additive substances that are generally recognized as safe (GRAS) by qualified experts. It is on the basis of the GRAS provision that many ingredients are lawfully marketed today without a food additive regulation.

Congress' approach to defining food additive means, however, that a company developing a new food substance (i.e., a substance that will be added directly to food or that will indirectly migrate to food because it is a component of a food-contact article), a new version of an established food substance, or a new process for producing a food substance must make a judgment about whether the resulting substance is a food additive requiring premarket approval by FDA. Under section 409 of the act, manufacturers can determine that use of a food substance is not subject to the statutory premarket approval requirements because it is GRAS and may market such substances without requesting agency concurrence with their determination. However, when a use of a substance does not qualify for the GRAS provision or other exceptions 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.

In 1959-1961, FDA clarified the regulatory status of a multitude of ingredients that were used in food prior to 1958 by amending its regulations to include a list (now 21 CFR parts 182 and 582) of food ingredients whose conditions of use are GRAS. However, many substances

that were considered GRAS by the food and feed industry were not included in the agency GRAS list. In 1972, FDA established a voluntary process (21 CFR 170.35(c) and 570.35(c)) whereby manufacturers could petition FDA to affirm that a use of a substance is GRAS (GRAS affirmation process). The GRAS affirmation petition process requires that FDA initiate rulemaking by announcing that the agency has filed a petition proposing that a use of a substance is GRAS, conduct a comprehensive review of the submitted data and information and promulgate a regulation affirming that the petitioned use of the substance is GRAS. In practice, FDA has taken years to bring the GRAS affirmation petition process to closure and publish a final rule that describes the basis for the agency's conclusion; manufacturers who submit a GRAS affirmation petition frequently market that substance while the petition is under review.

In April 1997, FDA proposed to eliminate the current voluntary GRAS affirmation petition process and to replace it with a voluntary GRAS notification procedure that would allow FDA to direct its resources to questions about GRAS status that are a priority with respect to public health protection rather than to scrutinizing data and issuing rules (62 FR 18937; Attachment 4). Under the proposal, manufacturers would notify FDA about a view that a particular use (or uses) of a substance is not subject to the statutory premarket approval requirements based on a conclusion that such use is GRAS. The notice would include a detailed summary of the basis for the manufacturer's conclusion of GRAS status. FDA would, within a period of ninety days, respond to the notifier in writing and could advise the notifier that the agency has identified a problem with the notice.

FDA proposed procedural regulations (proposed 21 CFR 170.36 (§ 170.36) and 21 CFR 570.36 (§ 570.36) that would provide a standard format for the voluntary submission of a notice. FDA would not, however, establish a regulation listing the individual substances that the agency is notified about under proposed § 170.36 or § 570.36.

This is a request for OMB approval of the information collection requirements in the following proposed regulations:

21 CFR 170.36 and 21 CFR 570.36

Reporting - specifies the content of a notice that provides the basis for a conclusion of GRAS status

Recordkeeping - specifies that the information that provides the basis for a conclusion of GRAS status must be available for FDA review and copying or be sent to FDA upon request

2. How, by whom, and for what purpose information used

Under the proposed notification procedure, FDA does not routinely conduct its own detailed safety evaluation or affirm that a substance is GRAS for its intended use. Rather, the agency evaluates whether the notice provides a sufficient basis for a conclusion of GRAS status and whether information in the notice or otherwise available to FDA raises issues of public health significance that lead the agency to question whether use of the substance is GRAS. Although FDA proposed to respond in writing within 90 days of receipt of the notice, FDA requested comment on that time frame.

Between February 1998 and December 31, 2005, FDA received 188 GRAS notices and

responded to 173 of those notices. As of December 31, 2005, the response letters issued by FDA fall into three general categories: (1) FDA does not question the notifier's conclusion of GRAS status (76%); (2) FDA informs the notifier that the notice does not provide a basis for a conclusion of GRAS status (9%); and (3) FDA brings the process to closure by acknowledging that the notifier has requested that FDA cease to evaluate the notice (15%). The average response time during this period was 162 days; the median response time was 163 days.

FDA believed 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 the proposed regulations. Therefore, FDA proposed to make readily accessible to the public the information in a section of the notice called the "GRAS exemption claim" and the agency's response to the notice. At this time, FDA is making this information accessible through an electronic inventory of GRAS notices [http://www.cfsan.fda.gov/~rdb/opa-gras.html]. The entire GRAS notice is publicly available consistent with the Freedom of Information Act and other federal disclosure statutes.

3. Consideration of Information Technology

The information in the notice will be narrative text that the agency would read rather than data that the agency would either analyze or store in a database format. FDA would print and copy any notice submitted electronically. Therefore, for efficient enforcement of the act, FDA is requiring the submission of paper copies of the notice. However, FDA is aware that there is an increasing interest in submitting an electronic copy of information prepared for regulatory purposes. Therefore, in the proposed rule FDA requested 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 the proposed regulation, of the information in the notice. FDA also specifically requested comment on the narrower question of whether it would be appropriate to require or recommend that the notifier include an electronic copy of the notice's "GRAS exemption claim," which would include succinct descriptions of the notified substance and applicable conditions of use, to maximize the agency's flexibility in making such claims publicly accessible. Most of the comments to the proposed rule encouraged FDA to recommend, but not require, submission of an electronic copy of the GRAS notice. In the first few months of the program, FDA asked a few notifiers to voluntarily submit an additional, electronic copy of their GRAS notices. FDA found that some notifiers were willing to do so. However, some notifiers were reluctant to provide such copies because the electronic copy would be available for public disclosure. In addition, comments to the proposed rule expressed concern about the potential for public disclosure, in response to requests under the Freedom of Information Act (FOIA), of information identified in an electronic copy as confidential.

4. Identification of duplication and similar information already available

Under the Meat and Poultry Inspection Acts, the United States Department of Agriculture's Food Safety and Inspection Service (USDA/FSIS) has regulatory authority for meat and poultry. Recently, USDA/FSIS (64 FR 72167; December 23, 1999) and FDA (65 FR 51758; August 25, 2000) amended their regulations to harmonize and improve the efficiency of the procedures used

by USDA/FSIS and FDA with respect to reviewing and approving the use of substances in meat and poultry. In general, USDA/FSIS evaluates food substances as to their suitability for specified uses in meat or poultry products. When USDA/FSIS receives a request to evaluate the suitability of a substance for use in meat or poultry products, USDA/FSIS consults with FDA about the regulatory status of the substance. When FDA receives a GRAS notice that includes a use in meat or poultry products, FDA consults with USDA/FSIS and provides to the notifier feedback from USDA/FSIS about the suitability of the substance for use in meat or poultry products. If USDA/FSIS informs FDA that the use of the substance in meat or poultry products requires rulemaking under the statutes that FSIS implements, FDA provides that information to the notifier. FDA and USDA have now signed a Memorandum of Understanding regarding these procedures [http://www.fsis.usda.gov/OA/topics/mou_fda.htm].

In the preamble to the proposal to replace the current voluntary GRAS affirmation petition process with a voluntary GRAS notification procedure, FDA explicitly stated that the act permits the marketing of a GRAS substance without prior approval from FDA and that any person who determines that a particular use (or uses) of a substance is not subject to the statutory premarket approval requirements on the basis that such use is GRAS is responsible for establishing that the determination meets the statutory requirements for GRAS status, regardless of whether FDA is notified about the conclusion of GRAS status. FDA interprets the "general recognition" standard to mean that the information that forms the basis for the conclusion of GRAS status must be widely available and ordinarily is published. FDA proposed that notifiers who voluntarily notify FDA of their conclusion of GRAS status summarize, rather than copy and submit this widely available information to show its relevance to their conclusion of GRAS status. Submission of a bibliography or copies of published articles contained in a bibliography, without an analysis of the relevance of the cited literature, is inadequate as a basis for a conclusion of GRAS status because it would require FDA, rather than the notifier, to evaluate the information. Such FDA review is inconsistent with one of the objectives of the proposed procedure - i.e., to direct the agency's resources to questions about GRAS status that are a priority with respect to public health protection rather than to scrutinizing data and issuing rules.

5. Small business

Many firms, large and small, market food substances on the basis of an independent conclusion that a use of a substance is GRAS. Most of the GRAS affirmation petitions voluntarily submitted under the existing process, however, are submitted by large chemical manufacturers. FDA believes that the simple format of the notification procedure and rapid agency response conceivably would provide incentive for manufacturers, including small businesses, who independently conclude that use of a substance is GRAS to inform FDA of that conclusion. Thus, FDA expects that the number of notices submitted under the proposed procedure would be greater than the number of petitions submitted under the current process and that a small business is more likely to submit a notice than a petition.

The proposed notification procedure would minimize the burden on all businesses, including small businesses, by providing that the notifier submit a detailed summary of the data and information, rather than the data and information itself, that are the basis for the conclusion of GRAS status. The notifier would include a signed statement that the data and information that are the basis for the conclusion of GRAS status are available for FDA review and copying at

reasonable times or will be sent to FDA upon request. There is no burden to the notifier for developing the data and information that provide the basis for a conclusion of GRAS status because such data and information must already be generally available to meet the GRAS standard. Additionally, any person who concludes that the use of a substance is GRAS ought to have assembled and evaluated the evidence that forms the basis of such a conclusion, regardless of whether the person subsequently notifies the agency about the conclusion. Therefore, the recordkeeping burden on the notifier is the minimal burden of (1) establishing an administrative file that contains the pertinent information and (2) maintaining that file.

6. Consequences of less frequent information collection and technical or legal obstacles

FDA now has more than forty-five years experience in processing food additive petitions and more than thirty years experience in processing GRAS affirmation petitions. As a result of that experience, FDA believes that the petition process, which is the statutorily mandated process for the agency to establish the conditions of safe use for a food additive, should not be applied to GRAS substances, where the conditions of safe use have already been recognized by qualified experts. FDA believes that the lengthy rulemaking associated with the GRAS affirmation petition process deters many persons who independently conclude that use of a substance is GRAS from informing the agency of such conclusions. Moreover, FDA believes that the current commitment of its resources to the GRAS affirmation petition process provides limited public health benefit because manufacturers who submit an affirmation petition frequently market the substance of issue before FDA reaches a decision on the GRAS status of its intended use.

Therefore, FDA proposed to replace the current voluntary GRAS affirmation petition process with a voluntary GRAS notification procedure. 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 a manufacturer to inform FDA of a conclusion of GRAS status. This would result in increased agency awareness of the composition of the nation's food supply and the cumulative dietary exposure to GRAS substances. 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.

A decision by FDA to not replace the current GRAS affirmation petition process with a notification procedure would cause FDA to utilize more resources answering questions about the regulatory status of substances that are not explicitly authorized by the agency's regulations, particularly for food products offered for import that may be refused entry under section 801 of the act (21 U.S.C. 381) on the grounds that they appear to contain an unapproved food additive. Although FDA does not intend to codify a list of substances that have been the subject of a notice to the agency, FDA has prepared an inventory of such substances, because the agency can most efficiently carry out its responsibilities by having basic information relevant to GRAS notices accessible in a streamlined format.

7. Special circumstances

The proposed GRAS notification program, like the GRAS affirmation petition process that it would replace, is voluntary. Any person who responds to the agency would do so one time only for any particular use of a substance.

FDA proposed to require that the notifier retain the information that forms the basis for the conclusion of GRAS status and sign a statement that such information is available for FDA review and copying at reasonable times or will be sent to FDA upon request because, under the proposal, notifiers would supply a detailed summary of the information that provides the basis for a conclusion of GRAS status rather than the information itself.

8. Outside consultation

In accordance with 5 CFR 1320.8(d), in the **Federal Register** of December 8, 2005 (70 FR 73009), FDA published a 60-day notice requesting public comment on the proposed extension of this collection of information (Attachment 5). FDA received one letter in response.

(Comment) The comment states that obtaining the entire GRAS notice through the provisions of the FOIA is not a practical means for interested persons to learn about the safety of a substance. The comment suggests that, to enhance the quality, utility, and clarity of the information to be collected, FDA should make publicly available a summary of data and information that supports the GRAS notice and also contains a discussion of any negative or inconsistent data.

(Response) FDA does not agree that obtaining information through the provisions of FOIA is impractical for interested persons. FDA also disagrees with the comment's suggestion that the agency make publicly available in the GRAS notification process a summary of data and information that supports the GRAS notice and also contains a discussion of any negative or inconsistent data because such a summary would be duplicative of information available through FOIA procedures. This information collection is associated with the proposed rule entitled, "Substances Generally Recognized as Safe" (the proposed rule) (62 FR 18938). In that proposed rule, proposed § 170.36 (entitled "Notice of a Claim for Exemption Based on a GRAS Determination") proposed to establish requirements for a submission to FDA to support a conclusion of GRAS status. Proposed Sec. 170.36(c)(4) describes requirements for the submission in the GRAS notice of a "detailed summary." This section states that notifiers shall submit 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. Proposed Sec. 170.36(c)(4)(i)(B) and Sec. 170.36(c)(4)(ii)(B) state that this detailed summary shall contain a comprehensive discussion of any reports of investigations or other information that may appear to be inconsistent with the GRAS determination. Proposed Sec. 170.36(f)(1) states that all remaining data and information in the GRAS notice shall be available for public disclosure, in accordance with 21 CFR part 20, on the date the notice is received. This would include the detailed summary of the basis for the notifier's GRAS determination.

To the extent that the comment suggests a change to the requirements of the proposed rule, FDA responds that such a request is outside the scope of the four collection of information topics on which the notice solicits comments and, thus, will not be addressed here. In response to the request for comments in that proposed rule, the commenter timely filed a similar comment. This

comment will be considered in the development of the final rule.

9. Payment to respondents

FDA is not proposing any payment or gift to respondents.

10. Confidentiality of information

FDA proposed that a particular section (i.e., the "GRAS exemption claim") of a notice be immediately available for public disclosure on the date the notice is received. FDA also proposed that all remaining data and information in a notice will become available for public disclosure, in accordance with 21 CFR part 20, on the date of receipt of the notice. The general recognition standard signifies that neither the proposed use of the substance nor the critical information needed to establish its safety are confidential. Therefore, FDA presumes 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 presumes 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 (21 CFR 20.61(b)), because a notifier may market a substance at any time before or after notifying FDA.

FDA is recommending that a notifier who considers that certain information that is contained in the submission should not be available for public disclosure 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 21 CFR part 20, and release or protect the information in accordance with that determination.

11. Sensitive questions

There are no questions of a sensitive nature in a GRAS notice.

12. Burden hours and explanation

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

ESTIMATED ANNUAL REPORTING BURDEN					
21 CFR Section	No. of respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
170.36	50	1	50	150	7,500

570.36	10	1	10	150	1,500
Total					9,000

There are no operating and maintenance costs nor capital costs associated with this collection.

ESTIMATED ANNUAL RECORDKEEPING BURDEN					
21 CFR Section	No. of record-keepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
170.36(c)(v)	50	1	50	15	750
570.36(c)(v)	10	1	10	15	150
Total					900

There are no operating and maintenance costs nor capital costs associated with this collection.

In the proposed rule, FDA estimated that CFSAN would receive approximately 50 GRAS notices per year and that CVM would receive approximately 10 GRAS notices per year. Although FDA requested comment on this estimate, the comments did not provide useful information regarding this issue. Therefore, FDA evaluated the number of notices received by CFSAN during the interim period. CFSAN received 12 GRAS notices during calendar year 1998, 23 notices during 1999, 30 notices during 2000, 28 notices during 2001, 26 notices during 2002, 23 notices during 2003, 20 notices during 2004, and 26 notices in 2005. Based on this experience, FDA continues to operate on the assumption that the annual number of GRAS notices submitted to CFSAN will be 50 or less.

Due to resource limitations, CVM did not receive any GRAS notices during the interim period between the proposed and final rules. Because we are making no changes to our assumptions about the annual number of GRAS notices received by CFSAN, we continue to assume that the annual number of GRAS notices submitted to CVM will be 10 or less.

The reporting requirement was previously published in the *Federal Register* as a proposed rule. FDA received no comments on the agency's estimate of the hourly reporting requirements to prepare and submit three paper copies of a GRAS notice. Therefore, the agency's original estimate of the hourly reporting requirements to prepare and submit three paper copies of a GRAS notice is unchanged (§ 170.36(b); § 570.36(b)).

There are no costs associated with generating the information because a conclusion of GRAS status must be supported by data and information that are generally available and accepted. Thus, this information exists prior to making, or notifying FDA about, a conclusion of GRAS status. However, under the proposal, manufacturers who notify FDA about a conclusion of GRAS status must establish and maintain an administrative file that contains the data and information that provides the basis for the conclusion of GRAS status. FDA estimates that the

one-time process of establishing that file would absorb approximately 10% of the hourly burden already estimated for preparing a GRAS notice (i.e., approximately 15 hours) and that preparation of the submission itself would absorb the remaining 90% of the estimated hourly burden (i.e., approximately 150 hours).

Prior to issuing the proposed rule, FDA consulted with three members of the food industry to estimate the hourly cost to prepare a GRAS notice and received an estimate of $70 per hour from one of the consulted members. FDA received no comments on this estimate. Therefore, the agency's original estimate is unchanged. Due to inflation since publication of the proposed rule, the estimated hourly cost is now $84 per hour. FDA therefore estimates that the cost of submitting a GRAS notice would be the estimated hourly burden (i.e., 165 hours) multiplied by the estimated hourly cost (i.e., $84), or $13,860 per submission. The estimated yearly cost, based on the submission of 50 human food notices per year at a cost of $13,860 each would therefore be $693,000. The predicted cost for 10 animal food notices would be $138,600. Total yearly cost for both human and animal foods is expected to be $831,600.

13. Capital costs (maintenance of capital costs)

There are no capital costs and/or maintenance costs associated with this collection of information.

14. Annual cost to government

FDA is estimating that the agency will direct approximately 4 full time equivalent positions (FTE's) to the GRAS notification procedure for human foods. Due to the smaller number of notices anticipated for animal food, only 1 FTE is expected to be devoted to processing the notices submitted to CVM. Based on an average cost of $149,564 per fully supported position, the cost of processing GRAS notifications would be $747,820 per year.

15. Explanation of change in items 13 and 14

There are no changes.

16. Statistical reporting

The information obtained from this data collection will not be published.

17. Expiration date on form

There are no reasons why display of the expiration date for OMB approval of the information collection would be inappropriate.

18. Exception to Certification Statement

No exceptions to the certification statement identified in item 19 of the instructions for completing OMB Form 83i have been identified.

B. COLLECTIONS OF INFORMATION EMPLOYING STATISTICAL METHODS

There are no plans to publish the information collected under the provisions of this proposed regulation for statistical use.