DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Substances Generally Recognized as Safe

Docket No. FDA-2025-N-3262

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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Executive Summary

This proposed rule would revise the procedures by which a person introducing a human or animal food substance into interstate commerce notifies FDA of a conclusion that the use of such substance is generally recognized as safe (GRAS). Specifically, the proposed rule would require the submission of GRAS notices to FDA for certain uses of food substances. A substance that is GRAS under the conditions of its intended use is not subject to FDA premarket review and approval as a food additive for that particular use (see sections 201(s) and 409 of the FD&C Act). Under our current regulations, a person who concludes that the use of a substance is GRAS under the conditions of its intended use may, but is not required to, notify FDA of this conclusion. The submission of a GRAS notice is therefore currently voluntary. If the proposed rule is finalized, GRAS notices will be required for certain uses of substances in human and animal food.

The primary benefits of the proposed rule, if finalized, would come from increased information being made available to FDA and the public regarding substances used in human and animal foods. This information would enable us to more effectively determine if the use of a substance constitutes a food additive use that is subject to premarket review and approval under the FD&C Act. This information is also expected to provide FDA with information to help identify the use of potentially unsafe substances in food, thereby enabling FDA to take action as appropriate and regulate the safety of food substances more effectively. A mandatory GRAS notification program would allow FDA to ensure that GRAS conclusions have a scientific basis and that appropriate documentation supporting those conclusions exists. The proposed rule, if finalized, is in part intended to help strengthen public confidence in FDA's ability to oversee the safety of the U.S. food supply. One-time costs of the proposed rule to persons who introduce a substance into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act include reading the rule and revising standard operating procedures (SOPs) regarding GRAS notices. Other one-time per manufacturer costs of the proposed rule are preparing and submitting streamlined submissions related to uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule, for firms that choose to submit this information during the window of availability for this time-limited option for such submissions. Costs associated with these activities may include translation costs for manufacturers in non-English speaking countries. Recurring costs to manufacturers would include preparing and submitting GRAS notices for new uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act after the effective date of a final rule that would otherwise have been the subject of an independent conclusion of GRAS status (i.e., a GRAS conclusion has been reached without submitting a GRAS notice).

Costs to FDA would include one-time costs of reviewing streamlined submissions related to uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule during the time-limited period for such submissions, and annual costs of evaluating ongoing submissions of GRAS notices regarding uses of substances that would otherwise have been the subject of an independent conclusion of GRAS status.

We estimate that the present value of the costs of the proposed rule would be approximately $89.6 million, with a lower bound of $34.9 million and an upper bound of $210.0 million, discounted at 3 percent at 10 years in 2024 dollars. At a 7 percent discount rate, the present value of costs would

be approximately $82.3 million, with a lower bound of $31.5 million and an upper bound of $195.9 million. We estimate that the annualized costs of the proposed rule would be approximately $10.5 million, with a lower bound of $4.1 million and an upper bound of $24.6 million, discounted at 3 percent over 10 years. At a 7 percent discount rate, annualized costs would be approximately $11.7 million, with a lower bound of $4.5 million and an upper bound of $27.9 million.

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I. **Introduction and Summary**

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 14192, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. No. 104-4).

Executive Orders 12866 and 13563 direct us to assess all benefits and costs of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. Rules are economically significant under Executive Order 12866 if they have an annual effect on the economy of $100 million or more; or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities. The Office of Information and Regulatory Affairs (OIRA) has determined that this proposed rule is an economically significant regulatory action under section 3(f)(1) of Executive Order 12866.

Executive Order 14192 requires that any new incremental costs associated with certain significant regulatory actions "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least 10 prior regulations." This proposed rule, if finalized as proposed, is expected to be an Executive Order 14192 regulatory action.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we estimate that the economic impact of this proposed rule is more than 3 percent of annual revenue for small entities, we find that the proposed rule would have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (Section 202(a)) requires us to prepare a written statement, which includes estimates of anticipated impacts, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $193 million, using the most current (2025) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would result in an expenditure in at least one year that meets or exceeds this amount.

B. Overview of Benefits, Costs, and Transfers

This proposed rule would revise the procedures by which a person introducing a human or animal food substance into interstate commerce notifies FDA of a conclusion that the use of such substance is GRAS under the conditions of its intended use pursuant to section 201(s) of the FD&C Act. Specifically, the proposed rule would require the submission of GRAS notices to FDA unless an exception applies. Under the GRAS provision of section 201(s) of the FD&C Act, a substance that is GRAS under the conditions of its intended use does not constitute a food additive that requires premarket review and approval by FDA under section 409 of the FD&C Act. Under FDA's current regulations, a person who concludes that the use of a substance is GRAS under the

conditions of its intended use may, but is not required to, notify FDA of this conclusion. If the proposed rule is finalized, a GRAS notice will be required for such uses of these substances in food.

The primary benefits of the proposed rule, if finalized, would come from increased information being made available to FDA and the public regarding substances used in human and animal foods. A mandatory GRAS notification program would allow FDA to ensure that GRAS conclusions have a scientific basis and that appropriate documentation supporting those conclusions exists. The proposed rule, if finalized, is in part intended to help strengthen public confidence in FDA's ability to oversee the safety of the U.S. food supply. One-time costs of the proposed rule to persons who introduce a substance into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act include reading the rule and revising standard operating procedures regarding GRAS notices. Other one-time costs of the proposed rule are preparing and submitting streamlined submissions related to uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule, for firms that choose to submit this information during the window of availability for this time-limited option for such submissions. Costs associated with these activities may include translation costs for manufacturers in non-English speaking countries. Recurring costs to manufacturers include preparing and submitting GRAS notices for new uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act after the effective date of a final rule that would otherwise have been the subject of an independent conclusion of GRAS status.

Costs to FDA would include one-time costs of reviewing streamlined submissions related to uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule during the time-limited period for such submissions and annual costs of evaluating ongoing submissions of GRAS notices regarding uses of substances that would otherwise have been the subject of an independent conclusion of GRAS status.

Other effects of the proposed rule may include transfers of market share and revenue between manufacturers of products with similar ingredients. For example, the submission of a GRAS notice may lead to a determination by FDA that there is an insufficient basis for concluding that a substance that happens to be used in only certain of the products was GRAS. We acknowledge the potential for such transfers if the rule is finalized. We do not estimate the magnitude of such effects because we cannot identify which substances may be the subject of an insufficient basis letter, which products they are in, or the market share of such products.

We estimate that the present value of the costs of the proposed rule would be approximately $89.6 million, with a lower bound of $34.9 million and an upper bound of $210.0 million, discounted at 3 percent at 10 years in 2024 dollars. At a 7 percent discount rate, the present value of costs would be approximately $82.3 million, with a lower bound of $31.5 million and an upper bound of $195.9 million. We estimate that the annualized costs of the proposed rule would be approximately $10.5 million, with a lower bound of $4.1 million and an upper bound of $24.6

million, discounted at 3 percent over 10 years. At a 7 percent discount rate, annualized costs would be approximately $11.7 million, with a lower bound of $4.5 million and an upper bound of $27.9 million. The estimated benefits and costs of the proposed rule are summarized in Table 1.

Table 1. Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule (millions of 2024 dollars)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($millions/year)					7%		
						3%		
	Annualized Quantified					7%		
						3%		
	Qualitative	Increased information regarding substances used in human and animal foods						
Costs	Annualized Monetized ($millions/year)	$11.7	$4.5	$27.9	2024	7%	10 years	
		$10.5	$4.1	$24.6	2024	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized ($millions/year)					7%		
						3%		
		From:			To:			
	Other Annualized Monetized ($millions/year)					7%		
						3%		
		From:			To:			
Effects	State, Local or Tribal Government: None Small Business: Costs of approximately $7,800 to $53,100 per affected small entity Wages: None Growth: None							

Note: Benefits encompass positive and negative benefits. Costs encompass costs and cost savings.

In line with Executive Order 14192, we estimate present and annualized values of costs, cost savings, and net costs over an infinite time horizon in Table 2. The net present value of the costs of the proposed rule are approximately $86.0 million, with a lower bound of $37.8 million and an upper bound of $189.7 million, discounted at 7 percent over an infinite time horizon in 2024 dollars. The annualized costs of the proposed rule would be approximately $6.0 million, with a lower bound of $2.6 million with an upper bound of $13.3 million.

Table 2. EO 14192 Summary Table (millions of 2024 dollars, discounted over an infinite time horizon at a 7 percent discount rate)

	Primary Estimate	Low Estimate	High Estimate
Present Value of Costs	$86.0	$37.8	$189.7
Present Value of Cost Savings	$0	$0	$0
Present Value of Net Costs	$86.0	$37.8	$189.7
Annualized Costs	$6.0	$2.6	$13.3
Annualized Cost Savings	$0	$0	$0
Annualized Net Costs	$6.0	$2.6	$13.3

II. **Preliminary Economic Analysis of Impacts**

A. Background

In 1958, Congress enacted the Food Additives Amendment to the FD&C Act (the 1958 amendment) (Pub. L. No. 85-929, 72 Stat. 1784). Under the 1958 amendment, certain substances intentionally added to or used in connection with food constitute food additives that are subject to premarket review and approval by FDA (sections 201(s) and 409 of the FD&C Act). However, if a substance is GRAS under the conditions of its intended use (or otherwise excepted from the definition of food additive (e.g., color additives)), a person is not required to obtain premarket authorization under section 409 of the FD&C Act.

Since the 1958 amendment, we have provided oversight of GRAS substances used in food through various mechanisms. During this approximately 60-year period, we have revised our regulations several times to adapt our approach to the GRAS provision of section 201(s) of the FD&C Act to the nation's changing food supply. Currently, FDA administers a voluntary GRAS notification program. Under the voluntary GRAS notification program, any person may (but is not required to) notify FDA of a view that a substance is not subject to the premarket review and approval requirements for food additives under section 409 of the FD&C Act based on the conclusion that the substance is GRAS under the conditions of its intended use.

When FDA evaluates a GRAS notice, we consider whether we have questions about the data and information the notifier uses to conclude that the substance is safe under the conditions of its intended use and that the criteria for general recognition of safety are satisfied. For the use of a substance to be considered GRAS, all data necessary to establish safety must be publicly available, and the substance's safe use must be generally recognized by qualified experts. In addition, GRAS uses must meet the same safety standard as for food additives—a reasonable certainty of no harm under the conditions of its intended use—and have the same quantity and quality of information that would support the safety of a food additive.

B. Need for Federal Regulatory Action

Based on our experience administering the voluntary GRAS notification program, and in particular our experience administering the program since it was finalized in the rule "Substances Generally Recognized as Safe" (81 FR 54960, August 17, 2016), we have observed that the voluntary nature of these regulations has created the potential for informational asymmetries that may lead to institutional and market failures.[1] Consumers rely on food producers to provide them with accurate information about the substances in their food and assume that these substances are safe. When foods with substances that are purported to be GRAS under the conditions of their intended use, but do not in fact meet the criteria for GRAS and have not been approved by FDA as food additives, are marketed, it creates an informational asymmetry, as the consumer's

[1] Informational asymmetries occur when there is an imbalance of information between parties in a transaction. This imbalance can lead to inefficient market outcomes, particularly when a less-informed party must make decisions based on incomplete or uncertain information.

assumption about the safety of the substances in their food may be incorrect. This leads to market failure, which the establishment of a mandatory GRAS notification program would help to address.

The potential for institutional failures can also result from the voluntary nature of our current GRAS notification program. Because firms can conclude that the use of a substance is GRAS without notifying FDA (i.e., an independent conclusion of GRAS status), and can market a substance without premarket review and approval by FDA based on that conclusion, FDA does not have a complete picture of all the food substances being introduced into interstate commerce. This is another form of informational asymmetry. FDA may have little or no knowledge about uses of substances that are the subject of an independent conclusion of GRAS status and may become aware of the need to take action regarding unsafe food additives in food only after a public health concern emerges. There have been adverse events involving purported GRAS uses of substances, which have resulted in FDA making post-market determinations that the use of a substance is not GRAS under the conditions of its intended use (Ref. 1). Under a mandatory GRAS notification program, FDA would have greater access to information about purported uses of substances in the food supply, which would enable us to more effectively determine whether these uses constitute food additive uses that require premarket review and approval under section 409 of the FD&C Act. A mandatory GRAS notification program would also allow FDA to ensure that GRAS conclusions have a scientific basis and that appropriate documentation supporting those conclusions exist. We may therefore be able to identify and address safety concerns associated with the use of these substances before adverse events occur. The establishment of a mandatory GRAS notification program would thus help to prevent these potential institutional failures and help us to carry out the underlying purpose of the food additive provisions of the FD&C Act: preventing the use of unsafe additives in food.

C. Purpose of the Proposed Rule

The proposed rule, if finalized, would amend our GRAS regulations in parts 170 and 570 to replace the voluntary GRAS notification program with a mandatory GRAS notification program.

D. Baseline Conditions

1. GRAS Notices

After the voluntary GRAS notification program was proposed in 1997, FDA's Center for Food Safety and Applied Nutrition (now part of FDA's Human Foods Program) filed its first GRAS notice in 1998 under an interim pilot program. As of March 2025, HFP has filed 1,234 GRAS notices for human food substance uses (Ref. 2). Human food substances include substances added to food directly (i.e., ingredients) and indirectly (i.e., substances used in contact with food). It is rare for a food contact substance to be the subject of a GRAS notice, as firms generally prefer the food contact notification program as it offers market exclusivity. FDA's Center for Veterinary Medicine established its interim pilot program and filed its first GRAS notice more recently (both in 2010) and, since then, has filed 75 GRAS notices for animal food substance uses (Ref. 3). In

total, since 1998, there have been 1,309 GRAS notices filed by FDA. The distribution of GRAS notices by type (animal or human food) is presented in Table 3.

Table 3. GRAS Notices Filed for Human and Animal Food Substance Uses

	GRAS Notices Filed	Notifiers
Animal Food Substance Uses	75 (5.73%)	36 (5.35%)
Human Food Substance Uses	1,234 (94.27%)	637 (94.65%)
Totals	1,309	673

After FDA files a GRAS notice, we respond in one of at least three ways: (1) a no questions letter (indicating that FDA does not have questions at this time regarding the notifier's conclusion that the notified substance is GRAS under the conditions of its intended use); (2) an insufficient basis letter (indicating that FDA concludes that the notice does not provide a sufficient basis for the conclusion that the notified substance is GRAS under the conditions of its intended use); or (3) a cease to evaluate letter (a letter from FDA granting a request from a notifier that FDA cease to evaluate their GRAS notice). FDA also publicly reports the number of GRAS notices that are pending evaluation. The distribution of outcomes for filed GRAS notices (no questions letter, pending, cease to evaluate letter, or insufficient basis letter) is presented in Table 4. As of March 2025, 94 filed GRAS notices are pending evaluation. Of the 1,215 filed GRAS notices that are not pending evaluation, 961 notices have received a no questions letter response. For 231 of the filed GRAS notices, FDA has granted requests from notifiers that we cease to evaluate their GRAS notice. For 23 of the filed GRAS notices, FDA has determined that the notice does not provide a sufficient basis for a conclusion that the notified substance is GRAS under the conditions of its intended use.

Table 4. Distribution of Outcomes for Filed GRAS Notices

	Animal Food	Human Food	Total
GRAS Notices Filed[1]	75	1,234	1,309
No Questions Letter Issued[2]	37 (49.33%)	924 (74.88%)	961 (73.41%)
Pending[3]	4 (5.33%)	90 (7.29%)	94 (7.18%)
Cease to Evaluate Letter Issued[4]	28 (37.33%)	203 (16.45%)	231 (17.65%)
Insufficient Basis Letter Issued[5]	6 (8%)	17 (1.38%)	23 (1.76%)

Notes: [1] The data in the table includes GRAS notice submissions filed between February 1998 and March 2025; [2] FDA has no questions at this time regarding the notifier's conclusion that the notified substance is GRAS under the conditions of its intended use; [3] Currently under FDA evaluation; [4] FDA has granted a request from a notifier that we cease to evaluate their GRAS notice; [5] FDA determines that the notice does not provide a sufficient basis for the conclusion that the notified substance is GRAS under the conditions of its intended use.

Overall, 617 filed GRAS notices (47.1 percent) were submitted by foreign firms and 503 of these filed GRAS notices (38.4 percent of all notifiers) were submitted by foreign firms located in countries where English is not the primary language. The distribution of filed GRAS notices submitted by foreign firms and foreign firms located in countries where English is not the primary language is presented in Table 5.

Table 5. Distribution of Filed GRAS Notices Submitted by Firms Located in Foreign and Non-English-Speaking Countries

	Animal Food	Human Food	Total
Domestic Notifier	49	643	692 (52.9%)
Foreign Notifier	26	591	617 (47.1%)
English speaking	55	751	806 (61.6%)
Non-English speaking	20	483	503 (38.4%)

2. Independent Conclusions of GRAS Status

Although the exact number of purported GRAS substances currently being used in human and animal foods is unknown, a 2011 study estimated that there were 1,000 substances being used in human food that were the subject of an independent conclusion of GRAS status (Ref. 4).[2] These are substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act. For this analysis, we take the 2011 study as a lower bound and assume that there are between 1,000 and 3,000 human and animal food substances purported to be GRAS for some use based on an independent conclusion of GRAS status. We take the midpoint of that range as our primary estimate. We assume the same distribution between human and animal food uses for substances on the market purported to be GRAS for some use based on an independent conclusion of GRAS status as for GRAS notices filed for human and animal food substances (see Table 3).[3] We assume that the characteristics of substances purported to be GRAS for some use based on an independent conclusion of GRAS status are similar to the characteristics of substances in the GRAS notice inventories (i.e., the GRAS Notice Inventory and the Animal Food GRAS Notice Inventory). Likewise, we assume the characteristics of firms manufacturing substances purported to be GRAS for some use based on an independent conclusion of GRAS status are similar to the characteristics of firms that have filed voluntary GRAS notices with FDA. These distributions are summarized in Table 6. We request comment on these assumptions. We additionally request

[2] This estimate was based on authors' interviews with food industry in conjunction with review of publicly available GRAS notices and reports. The estimate does not include food ingredients that were commonly used in food before 1958 or drugs in animal feed. The study intended to estimate the number of substances currently used in food based on an independent conclusion of GRAS status as of January 2011, including food contact substances and excluding food flavors included in the FEMA GRAS Library (see https://www.femaflavor.org/flavor-library).

[3] There may be fewer independent conclusions of GRAS status for substances used in animal food, as some state feed regulatory agencies do not recognize independent conclusions of GRAS status.

comment on the number of firms and substances currently using the GRAS process for food contact substances.

Table 6. Assumed Distribution of Substances Purported to be GRAS for Some Use Based on an Independent Conclusion of GRAS Status and Currently Introduced into Interstate Commerce

	Primary	Low	High
	2,000	1,000	3,000
Food Type			
Animal	114.6	57.3	171.9
Human	1,885.4	942.7	2,828.1
Firm Location			
Domestic	1,057.3	528.6	1,585.9
Foreign	942.7	471.4	1,414.1
Language			
English	1,231.5	615.7	1,847.2
Non-English	768.5	384.3	1,152.8

3. Association Expert Panel-Concluded GRAS Substances

A significant number of flavors and extracts purported to be GRAS under the conditions of their intended use have been evaluated by the Flavor and Extract Manufacturers Association (FEMA). Currently, FDA identifies 2,714 substances that have been evaluated by FEMA in the FDA Substances Added to Food Inventory (Ref. 14). FEMA publications have identified an additional 302 substances purported to be GRAS under the conditions of their intended use, for a total of 3,016 (Ref. 15). Of these purportedly GRAS substances evaluated by FEMA, 1,256 are authorized by FDA for use as a flavor in existing regulations, and 20 are prohibited for use as a flavor by existing regulations. The remaining 1,740 FEMA evaluated substances are substances introduced into interstate commerce under section 201(s) of the FD&C Act; in this analysis, we refer to these substances as "association expert panel-concluded GRAS substances." While this category currently includes only substances evaluated by FEMA, we generalize to potentially include other expert panels selected and convened by associations to evaluate potential GRAS substances that have been submitted by manufacturers seeking approval. This category would not, however, include other governmental organizations or foreign entities as the GRAS criteria is unique to the U.S. We request data and other information about additional expert panels that should be included in our analysis.

4. Affected Entities

Entities that would be affected by the proposed rule, if finalized, include all firms making GRAS conclusions. This includes firms that currently submit voluntary GRAS notices to FDA, as well as firms that make independent conclusions of GRAS status. As we do not know exactly how many firms are currently making independent conclusions of GRAS status, we estimate this figure by assuming that the number of firms that are making such conclusions is proportionate to the percentage of substances that are purported to be GRAS for some use based on an independent conclusion of GRAS status. We estimate that there are approximately 1,028 firms making independent conclusions of GRAS status, with a lower bound of 514 firms and an upper bound of 1,542 firms.[4] In addition to firms producing substances purported to be GRAS for some use based on an independent conclusion of GRAS status, there are food manufacturers that are using these substances in food products currently in interstate commerce. We estimate the number of food manufacturers that would be affected by this proposed rule using U.S. Census Bureau Economic Survey data (Ref. 5).[5] These numbers are summarized in Table 7.

Table 7. Number of Affected Entities

	Primary	Low	High
Unique Firms in GRAS Notice Database	673	673	673
GRAS Notice Filings	1,309	1,309	1,309
Estimated Independent Conclusions of GRAS Status for Some Use	2,000	1,000	3,000
Estimated Unique Firms with Independent Conclusions of GRAS Status	1,028	514	1,542
Total Estimated Affected GRAS Substance Producers	1,701.3	1,187	2,215
Estimated Affected Food Manufacturers	10,665.4	7,110	14,221
Total Estimated Affected Entities[1]	**12,366.7**	**8,297**	**16,436**

Notes:[1]We estimate that 839 of the affected entities are from the animal foods industry.

[4] We estimate the number of firms manufacturing substances based on an independent conclusion of GRAS status, that have not submitted a GRAS notice to FDA, by assuming that the distribution of all firms (firms that have filed GRAS notices with FDA plus firms that do not submit) is proportional to the distribution of all GRAS notices. For the primary estimate, we assume that there are 2,000 substances already introduced into interstate commerce based on an independent conclusion of GRAS status that have not been submitted to FDA's voluntary GRAS notification program. As discussed in section II.D.1 of this document, there have been 1,309 GRAS notices filed. Under the assumption that 2,000 substances have already been introduced into interstate commerce based on an independent conclusion of GRAS status that have not been submitted to FDA's voluntary GRAS notification program, around 40 percent of total substances purported to be GRAS for some use are the subject of a filed GRAS notice (1,309 / (2,000 + 1,309) = 0.395). As discussed above, 673 notifiers have filed GRAS notices. Therefore, the estimated number of firms that have already introduced substances into interstate commerce based on an independent conclusion of GRAS status and have not filed a GRAS notice with FDA is approximately 1,028 (= 673 / (1,309 / (1,309 + 2,000)) - 673). We request comment on this assumption.

[5] The total number of firms organized as C-corporations in Food Manufacturing (NAICS 311) and Soft Drink and Ice Manufacturing (NAICS 31211), less Animal Slaughtering and Processing (NAICS 3116).

The total number of affected firms includes the number of firms that have filed GRAS notices with FDA, the estimated number of firms that have made independent conclusions that a substance is GRAS under the conditions of its intended use, and the number of firms in the U.S. in NAICS 311 category (Food Manufacturing) organized as C corporations. We request comment on the methods, assumptions, and data sources utilized to estimate the affected entities.

E. Benefits of the Proposed Rule

Although we lack sufficient data to quantify the benefits of the proposed rule, we include a qualitative discussion of expected benefits. We request comment on sources of information pertaining to morbidity and mortality risks associated with unapproved food additives and uses of substances that are inappropriately purported to be GRAS. Mandating the submission of GRAS notices would provide FDA with information on the uses of substances that have been introduced into interstate commerce based on an independent conclusion of GRAS status. This would increase the level of knowledge and transparency about substances in the U.S. food supply that are purported to be GRAS under their conditions of intended use, giving FDA, consumers, industry, and consumer advocacy groups more information about the substances that are being added to human and animal food. This increase in knowledge and transparency could lead to a reduction in search costs for consumers. However, we do not monetize the impact associated with such costs, as we lack data on the number of consumers currently searching for this information, nor do we have estimates of the costs typically associated with searching for this information. We request comment on data sources, methods, and assumptions for identifying any impacts on consumer search costs associated with this proposed rule. A mandatory GRAS notification program would allow FDA to ensure that GRAS conclusions have a scientific basis and that appropriate documentation supporting those conclusions exists.

F. Costs of the Proposed Rule

The proposed rule, if finalized, amends certain of our existing regulations related to the GRAS provision of section 201(s) of the FD&C Act and replaces the voluntary GRAS notification program with a mandatory GRAS notification program. The proposed rule does not change the criteria under our regulations to reach the conclusion that a substance is GRAS under the conditions of its intended use. However, affected entities would be required to notify FDA of their conclusion that a substance is GRAS under the conditions of its intended use through the submission of a GRAS notice. Because the proposed rule would require the submission of GRAS notices for certain uses of substances, we estimate incremental annual costs for affected entities to notify FDA of the conclusion that a substance is GRAS under the conditions of its intended use. In addition, for substances that were introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule, our cost estimates take into account that affected entities may take advantage of the time-limited option provided under the proposed rule to submit a streamlined set of information about the uses of these

substances. GRAS notifiers and those who make these streamlined submissions would also incur one-time costs to read and understand the rule and to revise their standard operating procedures.

Although we quantify the administrative costs associated with resubmission of GRAS notices, we do not fully quantify potential additional costs associated with cases in which FDA may disagree with notifiers on their interpretation of the data and information described in their notice. We are unable to quantify costs associated with generating data as we do not have information on these costs. Also, it is uncertain whether firms producing substances purported to be GRAS for some use based on an independent conclusion of GRAS status are more or less likely to need additional data if they choose to submit a GRAS notice.[6] In addition, the need for additional data may vary for the type of substance or substance use. We request comment on data sources, methods, and assumptions associated with these potential costs.

Additional costs might result from FDA being able to identify the use of potentially unsafe substances in food or additives that require premarket review and approval prior to introduction into the food supply. In cases where FDA can more quickly identify as unsafe purported GRAS uses of substances, only the timing of costs would change. However, a mandatory GRAS notification program could also result in FDA identifying as unsafe purported GRAS uses of substances that may otherwise have gone undetected. We do not quantify costs incurred by FDA associated with increased volume of compliance actions, such as warning letters, and enforcement actions, such as seizure of adulterated products, as we lack data on the change in speed or likelihood that substances purported to be GRAS based on an independent conclusion of GRAS status will be identified by FDA. We request comment on data sources, methods, and assumptions associated with these potential costs.

1. <u>One-time Costs</u>

a. Cost of Reading and Understanding the Rule

We expect that all affected entities will spend time reading and understanding a final rule and revising SOPs for preparing and submitting GRAS notices. Based on the length of the proposed rule (approximately 45,000 words) and using the average reading speed ranging from 200 to 250 words per minute as recommended by the Department of Health and Human Services (Ref. 7), it will take approximately 3.11 hours for 1 person to read and understand the rule, with a lower bound of 2.8 hours and an upper bound of 3.5 hours. Due to the number of provisions in the proposed rule, we anticipate that 2 employees will perform this task. Drawing on Bureau of Labor Statistics (BLS) data for food manufacturing (Ref. 9) and basic chemical manufacturing (Ref. 10), we update the composite hourly wage rate from the 2016 GRAS Final Regulatory Impact Analysis (Ref. 8) by including food manufacturing manager wages and double for benefits and overhead. This yields a fully-loaded hourly wage rate for food and chemical product manufacturers of

[6] Under the proposed rule, rather than submitting a GRAS notice, notifiers may take advantage of the time-limited opportunity to submit certain information to FDA for a substance that was introduced into interstate commerce before the effective date of any final rule resulting from this rulemaking based on an independent conclusion of GRAS status (see proposed 21 CFR 170.205(b)(7) and 170.305, and proposed 21 CFR 570.205(b)(7) and 570.305).

approximately $215.82 in 2024 dollars.[7] Each affected notifier will incur a one-time cost to read and understand the rule of approximately $1,438.80 (= $215.82 x 2 x 3.33 hours), with a lower bound of $1,294.92 (= $215.82 x 2 x 3 hours) and an upper bound of $1,618.65 (= $215.82x 2 x 3.75 hours).[8] We estimate that the total costs of reading and understanding the rule are approximately $17.8 million (= 12,367 x $215.82 x 2 x 3.33 hours) in 2024 dollars, with a lower bound of $10.7 million (= 8,297 x $215.82 x 2 x 3 hours) and an upper bound of $26.6 million (= 16,436 x $215.82 x 2 x 3.75 hours). These costs are summarized in Table 8.

Table 8. Total Costs of Reading and Understanding the Rule (2024 dollars)

	Primary	Low	High
Number of affected entities[1]	12,367	8,297	16,436
Composite hourly wage of managers[2]	$215.82	$215.82	$215.82
Number of employees	2	2	2
Approximate number of words in rule	45,000	45,000	45,000
Number of words read per minute	225	250	200
Reading time burden (hours)	3.33	3.0	3.75
Reading cost per entity	$1,438.80	$1,294.92	$1,618.65
Total cost of reading and understanding the rule	**$17,793,212**	**$10,744,501**	**$26,2604,101**

Notes: [1] Number of entities that have filed GRAS notices with FDA, the estimated number of firms that have made independent conclusions that a substance is GRAS under the conditions of its intended use, and the number of entities in the U.S. in NAICS 311 organized as C corporations. [2] Composite wage rate is drawn from the 2016 GRAS Final Regulatory Impact Analysis (FRIA) (Ref. 8) and is the mean fully-loaded wage rate of compliance officers and business and financial operations employees in Food Manufacturing (NAICS 311000), Basic Chemical Manufacturing (NAICS 325100), and Other Chemical Manufacturing and Preparation (NAICS 329500), plus the average hourly wage for general and operations managers in Food Manufacturing.

b. Cost of Revising Standard Operating Procedures

We anticipate that affected entities will revise their SOPs to conform to the requirements of a final rule. Drawing on estimates from the 2016 GRAS Final Regulatory Impact Analysis (Ref. 8), we estimate that notifiers will spend approximately 35 hours performing this task, with a lower bound of 10 hours and an upper bound of 60 hours. Because revising and writing SOPs require effort from both clerical workers and managers, we use a weighted average hourly wage of approximately $74.49 (25 percent of the hourly wage for 1 clerical worker and 75 percent of the hourly wage for 1 manager).[9] Each notifier will incur a one-time cost to revise and write SOPs of

[7] The 2016 GRAS FRIA estimates an average hourly wage for food and chemical product manufacturing by averaging the BLS hourly mean wages for compliance officers and business and financial operations employees in Food Manufacturing (NAICS 311000), Basic Chemical Manufacturing (NAICS 325100), and Other Chemical Product and Preparation Manufacturing. We add the average hourly wage for general and operations managers in Food Manufacturing to this average to yield an updated composite wage rate.

[8] Throughout our analysis, discrepancies between calculations in the text and corresponding values in tables may arise due to rounding.

[9] The composite wage is drawn from BLS wage data and estimates in the 2016 GRAS FRIA, including the wage rate

approximately $2,606.98 (= $74.49 x 35 hours), with a lower bound of $744.85 (= $74.49 x 10 hours) and an upper bound of $4,469.10 (= $74.49 x 60 hours). The total cost associated with revising SOPs also depends on the number of affected entities that currently conclude that their use of substances is GRAS and have not voluntarily submitted a notice to FDA for substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act. We estimate that approximately 1,028 affected entities are currently reaching such independent conclusions of GRAS status, with a lower bound of 514 affected entities and an upper bound of 1,542 affected entities. We estimate the total costs to revise standard operating procedures are approximately $2.7 million (= 1,028.266 x $74.485 x 35 hours) in 2024 dollars, with a lower bound of $383.0 thousand (= 514.133 x $74.485 x 10) and an upper bound of $6.9 million (= 1,542.399 x $74.485 x 60 hours). These costs are summarized in Table 9.

Table 9. Cost of Revising Standard Operating Procedures (2024 dollars)

	Primary	Low	High
Number of affected entities (currently reaching independent conclusions of GRAS status but not voluntarily submitting a GRAS notice to FDA)	1,028	514	1,542
Composite hourly wage of food industry clerical and management workers	$74.49	$74.49	$74.49
Hours to revise standard operating procedures	35	10	60
Cost per entity to revise standard operating procedures	$2,606.98	$744.85	$4,469.10
Cost to Revise Standard Operating Procedures	**$2,680,663**	**$382,952**	**$6,893,134**

Notes: Number of affected entities is drawn from Table 7 (Number of Affected Entities). Composite wage rate is drawn from the 2016 GRAS FRIA (Ref. 8) and is the weighted sum of the manager composite wage ($83.38, 75% weight) and clerical worker composite wage ($47.80, 25% weight). Time burden to revise SOPs is drawn from the 2016 GRAS FRIA (Ref. 8).

c. Cost of Preparing and Submitting Streamlined Submissions Regarding Substances Already Introduced into Interstate Commerce Before the Effective Date of a Final Rule

The proposed rule, if finalized, would provide a time-limited option for affected entities to submit streamlined submissions to FDA for certain intended uses of substances already in interstate commerce under the GRAS provision of section 201(s) of the FD&C Act instead of initially submitting a GRAS notice. Although these submissions are not expected to require expenditures equivalent to that of a GRAS notice, affected entities would incur costs associated with this activity. We assume that these streamlined submissions would require between 10 percent and 25 percent of the time expenditure of a GRAS notice, with a central estimate of 17.5 percent. We request comment on our assumption of the time burden associated with the streamlined submissions.

for food and chemical product manufacturers ($83.38) and the average hourly wage for office clerk employees in Food Manufacturing (NAICS 311000), Basic Chemical Manufacturing (NAICS 325100), and Other Chemical Product and Preparation (NAICE 325900).

Because firms are responsible for the food substances they introduce or deliver for introduction into interstate commerce, we assume that, in addition to the firms that manufacture substances purported to be GRAS for some use based on an independent conclusion of GRAS status, some firms that manufacture human and animal foods that utilize substances purported to be GRAS for some use based on an independent conclusion will submit this information to FDA, while some firms will rely on others' submissions. If a substance purported to be GRAS for some use based on an independent conclusion is sourced from a supplier that sells to multiple food manufacturers, this could lead to multiple submissions for some substances. We assume that on average, each substance purported to be GRAS for some use based on an independent conclusion will be submitted 1 to 4 times, with a central estimate of 2.5 submissions. We request comment on this assumption. As mentioned in section II.D.2 of this document, we assume that there are currently in use between 1,000 and 3,000 substances that are the subject of an independent GRAS conclusion with a central estimate of 2,000 substances. As mentioned in section II.D.3 of this document, there are 1,740 flavors currently included in the FEMA GRAS Library which are not authorized by existing regulations. We combine the estimated number of substances purported to be GRAS for some use based on an independent conclusion with the association expert panel-concluded GRAS substances (i.e., FEMA GRAS Library) to estimate the number of streamlined submissions. Unlike other streamlined submissions, we assume that the association expert panel-concluded GRAS substances will only be submitted once; this assumption represents an approach to estimating the number of affected association expert panel-concluded GRAS substances.

The proposed rule requires that any material submitted in or referenced by a GRAS notice that is in a foreign language must be accompanied by an accurate and complete English translation. We therefore anticipate that some foreign manufacturers of substances purported to be GRAS for some use will need to translate their submissions into English. We estimate that approximately 38.4 percent of submissions are not initially in English, and that the average number of words in a GRAS submission is approximately 30,000 words. We assume that the time burden of translation is approximately 15 times that of the time burden of reading and understanding the rule, with a lower bound of 10 times and an upper bound of 20 times the time burden of reading. We request comment on this assumption. We use the fully-loaded BLS wage rate for technical writers ($88.78) to estimate the hourly cost of English translation (Ref. 11).

To estimate the cost to food manufacturers of preparing and submitting streamlined submissions for substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule, which we define as including independent conclusions of GRAS status and association expert panel-concluded GRAS substances, we multiply the number of substances introduced into interstate commerce based on an independent conclusion of GRAS status (2,000, with a lower bound of 1,000 and an upper bound of 3,000) by the number of submissions per affected entity preparing and submitting streamlined submissions for substances that were already introduced into interstate commerce before the effective date of a final rule based on an independent conclusion of GRAS status (2.5, with a lower bound of 1 and an upper bound of 4), the time burden of submitting the streamlined

submission (31.5 hours, with a lower bound of 17 hours and an upper bound of 47.5 hours), and the fully-loaded composite hourly wage for food industry clerical/management workers ($65.59). We estimate that the one-time costs of preparing and submitting streamlined submissions for substances introduced into interstate commerce based on an independent conclusion of GRAS status is approximately $10.3 million (= 2,000 x 2.5 x 31.5 hours x $65.59), with a lower bound of approximately $1.1 million (= 1,000 x 1 x 17 hours x $65.59) and an upper bound of approximately $37.4 million (= 3,000 x 4 x 47.5 hours x $65.59). We also expect to receive streamlined submissions for association expert panel-concluded GRAS substances that are not authorized by existing regulations. We expect to receive one submission for each of these 1,740 substances and multiply that by the time burden of submitting the streamlined submission (31.5 hours, with a lower bound of 17 hours and an upper bound of 47.5 hours), and the fully-loaded composite hourly wage for food industry clerical/management workers ($65.59). We estimate that the one-time costs of preparing and submitting streamlined submissions for association expert panel-concluded GRAS substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule is approximately $3.6 million (= 1,740 x 31.5 hours x $65.59), with a lower bound of approximately $1.9 million (= 1,740 x 17 hours x $65.59) and an upper bound of approximately $5.4 million (= 1,740 x 47.5 hours x $65.59). The total one-time costs of preparing and submitting streamlined submissions are approximately $13.9 million (= $10.3 million + $3.6 million), with a lower bound of approximately $3.06 million (= $1.12 million + $1.94 million) and an upper bound of approximately $42.8 million (= $37.4 million + $5.4 million).

We expect that some streamlined submissions may not be complete or may otherwise be inadequate. We estimate that approximately 11.6 percent, or approximately 781.8 submissions (= (5,000 + 1,740) x 11.6%) would be resubmitted, with a lower bound of approximately 63 submissions (= (1,000 + 1,740) x 2.3%) and an upper bound of approximately 2,871 submissions (= (12,000 x 1,740) x 20.9%). We estimate that the costs of resubmitting streamlined submissions are approximately $1.6 million (= 781.84 x $65.59 x 31.5 hours), with a lower bound of $70.27 thousand (= 63.0 x $65.59 x 17 hours) and an upper bound of $8.9 million (= 2,871.7 x $65.59 x 47.5 hours).

To estimate the additional cost of translation for some foreign manufacturers, we multiply the number of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act by the percentage of GRAS notices submitted by affected entities operating in non-English speaking countries (38.4 percent), the time burden of translation (33.3 hours, with a lower bound of 20 hours and an upper bound of 50 hours), and the hourly wage of technical writers ($88.14). We estimate that the one-time costs of translation for preparing and submitting streamlined submissions for substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule is approximately $4.3 million (= (2,000 + 1,740) x 38.43% x 33.33 hours x $88.78), with a lower bound of $1.9 million (= (1,000 + 1,740) x 38.43% x 20 hours x $88.78) and an upper bound of

$8.1 million (= (3,000 + 1,740) x 38.43% x 50 hours x $88.78). The total costs are summarized in Table 10.

Table 10. Total Costs of Preparing and Submitting Streamlined Submissions for Substances That Were Already Introduced into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule (2024 dollars)

	Primary	Low	High
Estimated number of substances that were already introduced into interstate commerce based on an independent conclusion of GRAS status	2,000	1,000	3,000
Number of submissions per affected entity preparing and submitting streamlined submissions for substances that were already introduced into interstate commerce before the effective date of a final rule based on an independent conclusion of GRAS status	2.5	1	4
Number of association expert panel-concluded GRAS substances	1,740	1,740	1,740
Time burden of submitting streamlined submissions relative to a GRAS notice	17.5%	10%	25%
Time burden of GRAS notice submission (hours)	180	170	190
Time burden of preparing and submitting streamlined submissions for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule	31.5	17	47.5
Composite hourly wage of food industry clerical and management workers	$65.59	$65.59	$65.59
Cost of preparing and submitting streamlined submissions for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule	$10,330,425.00	$1,115,030.00	$37,386,300.00
Percent that will require resubmission	11.6%	2.3%	20.9%
Number of resubmissions	781.8	63.0	2,871.7
Cost of resubmission	$1,615,347.90	$70,269.19	$8,946,728.52
Percent of submissions not in English	38.43%	38.43%	38.43%
Approximate number of words in typical GRAS notice submission	30,000	30,000	30,000
Time burden of reading (hours)	2.22	2.00	2.50
Reading/translation multiplier	15	10	20
Time burden of translating streamlined submissions for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule	33.33	20	50
Hourly wage of technical writer	$88.78	$88.78	$88.78
Cost of translation per streamlined submission for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule	$2,959.33	$1,775.60	$4,4393.00
Total cost of translation	$4,253,396.53	$1,869,674.84	$8,086,002.50
Total cost of preparing and submitting streamlined submissions for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule	**$19,794,157**	**$4,995,126**	**$59,840,045**

Notes: Time burden of GRAS notice submission is drawn from the 2016 GRAS FRIA (Ref. 8).

In total, the estimated costs of preparing and submitting streamlined submissions for substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule are approximately $19.8 million (= $15.5 million + $4.3 million) in 2024 dollars, with a lower bound of $5.0 million (= $3.1 million + $1.9 million) and an upper bound of $59.8 million (= $51.75 million + $8.09 million).

d. FDA Costs of Reviewing Streamlined Submissions for Substances That Were Already Introduced into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule

The proposed rule, if finalized, would require FDA to post in a publicly available list the information we receive about the uses of substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule. The posting of this information does not mean that we have reviewed the GRAS status of substances' conditions of intended use. We estimate that FDA will receive approximately 6,740 submissions (= (2,000 substances already introduced into interstate commerce based on an independent conclusion of GRAS status before the effective date of a final rule x 2.5 submissions per affected entity submitting streamlined submissions per substance) + 1,740 association expert panel-concluded GRAS substances), with a lower bound of 2,740 submissions (= (1,000 substances x 1 submitting entity) + 1,740 association expert panel-concluded GRAS substances) and an upper bound of 13,740 submissions (= (3,000 substances x 4 submitting entities) + 1,740 association expert panel-concluded GRAS substances). We assume that a submission will be reviewed for posting by the appropriate FDA staff and estimate a composite hourly wage rate using U.S. Office of Personnel Management (OPM) General Schedule (GS) data for 1 GS13-5 level employee of $124.35 (= $129,759 / 2,087 x 2) and 1 GS14-5 level employee of $151.40 (= $157,982 / 2,087 x 2) in the Washington-Baltimore-Arlington metropolitan area, doubled for benefits and overhead (Ref. 12). We estimate that the average time burden of reviewing a streamlined submission for posting is approximately 35 percent of the time burden of preparing and submitting streamlined submissions for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act, yielding a per submission FDA time burden of approximately 11.03 hours (= 31.5 hours x 35%), with a lower bound of 5.95 hours (= 17 hours x 35%) and an upper bound of 16.63 hours (= 47.5 hours x 35%). We multiply the number of submissions by the composite hourly wage of FDA reviewers and the time burden of review to yield a cost of initial review for posting of streamlined submissions for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule of approximately $20.5 million (= (5,000 + 1,740) x $275.746 x 11.03 hours), with a lower bound of $4.5 million (= (1,000 + 1,740) x $275.746 x 5.95 hours) and an upper bound of $63.0 million (= (12,000 + 1,740) x $275.746 x 16.63 hours).

We expect that some streamlined submissions may not be complete or may otherwise be inadequate. We estimate that approximately 11.6 percent, or 781.84 submissions (= (5,000 + 1,740) x 11.6%) would be resubmitted, with a lower bound of approximately 63.0 submissions (=

(1,000 + 1,740) x 2.3%) and an upper bound of approximately 2,871.7 submissions (= (12,000 + 1,740) x 20.9%). We estimate that the costs of reviewing resubmissions (re-reviewing) for posting are approximately $2.4 million (= 781.8 x $276.67 x 11.03 hours), with a lower bound of $103.4 thousand (= 63.0 x $276.67 x 5.95 hours) and an upper bound of $13.2 million (= 2,871.7 x $276.67 x 16.63 hours).

The total costs of reviewing for posting streamlined submissions for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule are approximately $22.9 million (= $20.5 million + $2.4 million), with a lower bound of $4.6 million (= $4.5 million + $103.4 thousand) and an upper bound of $76.2 million (= $63.0 million + $13.2 million). These costs are summarized in Table 11.

Table 11. Total Cost of Reviewing for Posting Streamlined Submissions for Substances That Were Already Introduced into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule (2024 dollars)

	Primary	Low	High
Potential number of submissions	6,740	2,740	13,740
Composite hourly wage of FDA reviewers	$275.75	$275.75	$275.75
Time burden of review (hours)	11.03	5.95	16.63
Cost of initial review	$20,490,275.13	$4,495,487.80	$62,987,980.14
Percent that will resubmit	11.6%	2.3%	20.9%
Number of resubmissions	781.84	63.0	2,871.7
Cost of FDA re-review	$2,376,871.92	$013,396.22	$13,164,487.85
Total costs of FDA review	**$22,867,147**	**$4,598,884**	**$76,152,468**

The total one-time costs of preparing, submitting, and reviewing for posting streamlined submissions for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule are approximately $42.7 million (= $19.8 million + $22.9 million) in 2024 dollars, with a lower bound of approximately $9.6 million (= $5.0 million + $4.6 million) and an upper bound of approximately $136.0 million (= $59.8 million + $76.2 million). Table 12 summarizes these costs.

Table 12. Total Costs of Preparing, Submitting, and Reviewing for Posting Streamlined Submissions for Substances That Were Already Introduced into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule (2024 dollars)

	Primary	Low	High
Cost of preparing/submitting streamlined submissions (industry)	$19,794,157	$4,995,126	$59,840,045
Cost of reviewing streamlined submissions (FDA)	$22,867,147	$4,598,884	$76,152,468
Total cost of streamlined submissions for substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule	**$42,661,304**	**$9,594,010**	**$135,992,513**

e. Total One-time Costs

We estimate that the total one-time costs of the proposed rule are approximately $63.1 million (= $17.79 million + $2.68 million + $19.79 million + $22.86 million), with a lower bound of $20.7 million (= $10.7 million + $382.95 thousand + $5.0 million + $4.6 million) and an upper bound of $169.5 million (= $26.6 million + $6.89 million + $59.8 million + $76.2 million). Table 13 summarizes these costs.

Table 13. Total One-time Costs of the Proposed Rule (2024 dollars)

	Primary	Low	High
Cost of reading and understanding the rule (industry)	$17,793,212	$10,744,501	$26,604,101
Cost of revising standard operating procedures (industry)	$2,680,663	$382,952	$6,893,134
Cost of preparing and submitting streamlined submissions (industry)	$19,794,157	$4,995,126	$59,840,045
Cost of reviewing streamlined submissions (FDA)	$22,867,147	$4,598,884	$76,152,468
Total one-time costs of the proposed rule	**$63,135,180**	**$20,721,463**	**$169,489,748**

2. Annual Costs

a. Costs of Preparing and Submitting GRAS Notices for Uses of Substances That Would Otherwise Have Been the Subject of an Independent Conclusion of GRAS Status or an Association Expert Panel GRAS Conclusion

If the proposed rule is finalized, food manufacturers would be required to submit to FDA GRAS notices for uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act after the effective date of a final rule. Some such uses of substances would not otherwise be the subject of a GRAS notice voluntarily submitted to FDA, as they would have been purported to be GRAS based on an independent conclusion. However, if the proposed rule is finalized, GRAS notices would be required for all such GRAS uses of substance unless an exception applies. We estimate that the average annual number of GRAS notice submissions filed between 1998 and 2025 is approximately 50.3 (= 1,309 GRAS notices / 26 years) and that the estimated percentage of GRAS uses of substances that are not submitted is approximately 60.44 percent (= 2,000 self-affirmed GRAS substances / (1,309 GRAS notices + 2,000 self-affirmed GRAS substances). We use the average annual number of GRAS submissions (50.3), and the estimated percent of GRAS uses of substances that are not submitted (60.44 percent), to estimate the annual number of substances purported to be GRAS for some use based on an independent conclusion of GRAS status, yielding an estimate of approximately 77

GRAS uses of substances (= (50.3 / (1 - 60.44%)) - 50.3) annually that would require submission of a GRAS notice under a final rule, with a lower bound of 38 (= (50.3 / (1 - 43.31%)) - 50.3) uses of substances and an upper bound of 115 (= (50.3 / (1 - 69.62%)) - 50.3) uses of substances.[10]

We also expect GRAS notices to be submitted for substances that would otherwise be submitted to an association expert panel (e.g., FEMA) (Ref. 4). Since 2011, 302 substances have been added to the FEMA GRAS Library (Ref. 15). On average, 21.57 (= 302 / 14) substances have been added to the FEMA GRAS Library annually. We add this annual average to our estimates of the annual number of substances purported to be GRAS for some use based on an independent conclusion of GRAS status, yielding an estimate of approximately 60 to 137 additional GRAS notice submissions with a primary estimate of 98.5.

We assume that the time burden to manufacturers of preparing a GRAS notice is approximately 180 hours, with a lower bound of 170 hours and an upper bound of 190 hours, and that submissions will be prepared by management and clerical staff. We request comment on this assumption. Drawing on BLS wage data (Ref. 9; Ref. 10), we estimate a fully-loaded composite wage rate for food manufacturing and chemical manufacturing managers and clerical staff of approximately $65.59. We request comment on these estimates. To estimate the annual cost of preparing and submitting such GRAS notices, we multiply the average annual number of uses of substances in food introduced into interstate commerce that would require a GRAS notice by the time burden of preparing a GRAS notice and the composite hourly wage rate, to yield an annual cost of submitting future GRAS notices of approximately $1.2 million (= 98.5 x 180 hours x $65.59), with a lower bound of $669.4 thousand (= 60.03 x 170 hours x $65.59) and an upper bound of $1.7 million (= 137.0 x 190 hours x $65.59).

We expect that some GRAS notice submissions may not be complete or may be inadequate such that FDA cannot file the submission as a GRAS notice or cannot issue a no questions letter after evaluating the GRAS notice. In such cases, we anticipate that some notifiers would submit revised GRAS submissions for FDA review. We estimate that approximately 11.6 percent, or 11.4 GRAS notices (= 98.5 x 11.6%) would be resubmitted, with a lower bound of 1.4 GRAS notices (= 60.0 x 2.3%) and an upper bound of 28.6 GRAS notices (= 137.0 x 20.9%). We multiply the number of resubmissions by the time burden of preparing the GRAS notices and the composite hourly wage rate to yield an annual resubmission cost of approximately $134.9 thousand (= 11.43 x 180 hours x $65.59), with a lower bound of $15.4 thousand (= 1.38 x 170 hours x $65.59) and an upper bound of $356.7 thousand (= 28.62 x 190 hours x $65.59).

To estimate the additional cost of translation for some foreign manufacturers, we multiply the estimated number of uses of substances introduced into interstate commerce based on an independent conclusion of GRAS status by the percent of GRAS notices submitted by notifiers in

[10] We assume that the estimate from Neltner et al. (Ref. 4) represents the low estimate of substances currently on the market. This includes independent conclusions of GRAS status not submitted to FDA and GRAS notices submitted to FDA. Given the time since publication and current uncertainty around GRAS substances on the market, we estimate 3,000 GRAS substances currently on the market as a high estimate. Our primary estimate is the midpoint between the two.

non-English speaking countries (38.4 percent), the time burden of translation (33.3 hours, with a lower bound of 20 hours and an upper bound of 50 hours), and the hourly wage of technical writers ($88.78). We estimate that the one-time costs of translation for such GRAS notices is approximately $112.0 thousand (= 98.5 x 38.43% x 33.33 hours x $88.78), with a lower bound of $41.0 thousand (= 60.0 x 38.43% x 20 hours x $88.78) and an upper bound of $233.6 thousand (= 136.96 x 38.43% x 50 hours x $88.78).

The total annual costs of preparing and submitting GRAS notices for uses of substances that otherwise would have been the subject of an independent conclusion of GRAS status is approximately $1.4 million (= $1.16 million + $134.9 thousand + $112.0 thousand) in 2024 dollars, with a lower bound of $725.7 thousand (= $669.4 thousand + $15.4 thousand + $41.0 thousand) and an upper bound of $2.3 million (= $1.71 million + $356.7 thousand + $233.6 thousand) in 2024 dollars. These costs are summarized at Table 14.

Table 14. Total Annual Costs of Preparing and Submitting GRAS Notices for Uses of Substances That Would Otherwise Have Been the Subject of an Independent Conclusion of GRAS Status or an Association Expert Panel GRAS Conclusion (2024 dollars)

	Primary	Low	High
Estimated Independent Conclusions of GRAS Status for Some Use	2,000	1,000	3,000
Number of GRAS notices	1,309	1,309	1,309
Average annual number of GRAS submissions submitted 1998-2024	50.3	50.3	50.3
Estimated percent of all GRAS substances that are not submitted	60.44%	43.31%	69.62%
Annual number of independent conclusions of GRAS status not submitted to FDA	76.9	38.5	115.4
Average annual number of association expert panel-concluded GRAS substances since 2011	21.57	21.57	21.57
Estimated increase in GRAS notice submissions	98.5	60	137
Time burden of GRAS notice (hours)	180	170	190
Hourly wage rate	$65.59	$65.59	$65.59
Cost to prepare and submit GRAS notices for uses of substances that otherwise would have been the subject of an independent conclusion of GRAS status	$1,162,845.83	$669,385.59	$1,706,759.92
Percent that will resubmit	11.6%	2.3%	20.9%
Number of resubmissions	11.43	1.38	28.62
Cost of resubmissions	$134,890.12	$15,395.87	$356,712.82
Percent of submissions not in English	38.43%	38.43%	38.43%
Approximate number of words in GRAS notice submission	30,000	30,000	30,000
Time burden of reading (hours)	2.22	2.00	2.50
Reading/translation multiplier	15	10	20
Time burden of translating GRAS notice submission (hours)	33.33	20	50
Hourly wage of technical writers	$88.78	$88.78	$88.78
Cost of translation per GRAS notice	$2,959.33	$1,775.60	$4,439.00
Total cost of translation	$112,015.02	$40,964.28	$233,634.37
Total cost of preparing and submitting GRAS notices for uses of substances that otherwise would have been the subject of an independent conclusion of GRAS status	**$1,409,751**	**$725,746**	**$2,297,107**

Note: Time burden of GRAS notice is drawn from the 2016 GRAS FRIA (Ref. 8).

In the Uncertainty and Sensitivity Analysis section of this document (section II.G), we consider additional costs related to product removal and reformulation for future GRAS notice

submissions where FDA issues a "cease to evaluate" or "insufficient basis" letter following the filing of the GRAS notice.

b. Cost of Reviewing GRAS Notices for Uses of Substances That Would Otherwise Have Been the Subject of an Independent Conclusion of GRAS Status

Under the proposed mandatory GRAS notification program, GRAS submissions would come from a variety of notifiers, including from manufacturers of substances introduced into interstate commerce for the first time after the effective date of a final rule. Submissions could also concern existing uses of substances introduced into interstate commerce based on an independent conclusion of GRAS status. We also expect GRAS notices to be submitted for substances that would otherwise be submitted to an association expert panel (e.g., FEMA). We estimate that under the mandatory GRAS notification program, FDA will receive approximately 99 additional GRAS submissions (= 77 GRAS substances + 22 association expert panel-concluded GRAS substances) annually, with a lower bound of 60 submissions (= 38 GRAS substances + 22 association expert panel-concluded GRAS substances) and an upper bound of 137 submissions (= 115 GRAS substances + 22 association expert panel-concluded GRAS substances). We assume that these submissions will be reviewed by the appropriate FDA staff and estimate a composite wage rate for one GS13-5 level employee of $124.35 (= $129,759 / 2,087 * 2) and one GS14-5 level employee of $151.40 (= $157,982 / 2,087 * 2) in the Washington-Baltimore-Arlington metropolitan area, doubled for benefits and overhead (Ref. 12). We estimate that the time burden of reviewing a GRAS notice submission is approximately 35 percent of the time burden of preparing and submitting a GRAS notice, yielding a per submission FDA time burden of approximately 63 hours (= 180 hours x 35%), with a lower bound of approximately 59.5 hours (= 170 hours x 35%) and an upper bound of approximately 66.5 hours (= 190 hours x 35%).

We multiply the number of GRAS notice submissions by the composite hourly wage of FDA reviewers and the time burden of review to yield a cost of initial GRAS notice review of approximately $1.7 million (= 98.5 x $275.75 x 63 hours), with a lower bound of $985.0 thousand (= 60.03 x $275.75 x 59.5 hours) and an upper bound of $2.5 million (= 137.0 x $275.75 x 66.5 hours).

We expect that some GRAS notice submissions may not be complete or may be inadequate such that FDA cannot file the submission as a GRAS notice or cannot issue a no questions letter after evaluating the GRAS notice. In such cases, we anticipate that some notifiers would submit revised GRAS submissions for FDA review. We estimate that approximately 7.5 percent, or approximately 11.4 GRAS notices (= 98.5 x 11.6%) would be resubmitted, with a lower bound of approximately 1.4 GRAS notices (= 60.0 x 2.3%) and an upper bound of approximately 28.6 GRAS notices (= 137.0 x 20.9%). We multiply the number of resubmissions by the time burden of reviewing GRAS notices and the FDA composite wage rate to yield an annual re-review cost of approximately $198.5 thousand (= 11.425 x 63 hours x $275.746), with a lower bound of $22.7 thousand (= 1.381 x $275.746 x 59.5 hours) and an upper bound of $524.9 thousand (= 28.624 x 66.5 hours x $275.746). The estimated annual costs of reviewing GRAS notices for uses of

substances that otherwise would have been the subject of an independent conclusion of GRAS status is approximately $1.9 million (= (98.49 x $275.746 x 63 hours) + (11.425 x $275.746 x 63 hours)) in 2024 dollars, with a lower bound of $1.0 million (= (60.0 x $275.746 x 59.5 hours) + (1.38 x $275.746 x 59.5 hours)) and an upper bound of $3.0 million (= (137.0 x $275.746 x 66.5 hours) + (28.62 x $275.746 x 66.5 hours)). These costs are summarized in Table 15.

Table 15. Total Annual Costs of Reviewing GRAS Notices for Uses of Substances that Otherwise Would Have Been the Subject of an Independent Conclusion of GRAS Status or an Association Expert Panel GRAS Conclusion (2024 dollars)

	Primary	Low	High
Increase in GRAS notice submissions[1]	98.5	60.0	137.0
Composite hourly wage of FDA reviewers	$275.75	$275.75	$275.75
Time burden to reviewers (hours)	63.0	59.5	66.5
Cost of initial review	$1,711,046.64	$984,954.27	$2,511,378.33
Percent that will be resubmitted	11.6%	2.3%	20.9%
Number of resubmissions	11.425	1.381	28.624
Cost of FDA re-review	$198,481.41	$22,653.95	$524,878.07
Total annual cost of reviewing GRAS notices for uses of substances that otherwise would have been the subject of an independent conclusion of GRAS status or association expert panel GRAS conclusion	**$1,909,528.05**	**$1,007,608.22**	**$3,036,256.41**

Notes: [1]We estimate that on average, this increase in GRAS notice submissions will include 4.4 GRAS notices submitted for animal foods and 94.1 submitted for human foods.

3. Total Costs

One-time costs incurred in the year after the rule is finalized include reading and understanding the rule and revising SOPs. Other one-time costs include preparing and submitting streamlined submissions for uses of substances that were already introduced into interstate commerce before the effective date of a final rule, for affected entities that choose to submit this information during the window of availability for this time-limited option, and the cost of FDA's review of these submissions. We estimate that total one-time costs of the proposed rule are approximately $63.1 million (= $17.8 million + $2.68 million + $19.79 million + $22.8 million) in 2024 dollars, with a lower bound of $20.7 million (= $10.74 million + $382.95 thousand + $5.0 million + $4.6 million) and an upper bound of $169.5 million (= $26.6 million + $6.89 million + $59.8 million + $76.2 million). Annually recurring costs include costs associated with affected entities preparing and submitting GRAS notices for new and existing uses of substances, and FDA's ongoing review of GRAS notices for new uses of substances. We estimate that total recurring costs of the proposed rule are approximately $3.3 million (= $1.4 million + $1.9 million), with a lower bound of $1.7 million (= $725.7 thousand + $1.0 million) and an upper bound of $5.3 million (= $2.3 million + $3.0 million). These costs are summarized in Table 16.

Table 16. Total Costs of the Proposed Rule (2024 dollars)

	Primary	Low	High
Reading and understanding the rule (one-time)	$17,793,212.07	$10,744,500.62	$26,604,101.37
Revising standard operating procedures (one-time)	$2,680,663.37	$382,951.91	$6,893,134.38
Preparing and submitting streamlined submissions for substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule, for affected entities that choose to submit this information during the limited time for such submission (one-time)	$19,794,157.33	$4,995,126.23	$59,840,044.52
Reviewing streamlined submissions for substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule, for affected entities that choose to submit this information during the limited time for such submission (one-time)	$22,867,147.05	$4,598,884.02	$76,152,467.99
Preparing and submitting GRAS notices for uses of substances that otherwise would have been the subject of an independent conclusion of GRAS status or an association expert panel GRAS conclusion (annual)	$1,409,750.97	$725,745.74	$2,297,107.11
Reviewing GRAS notices for uses of substances that otherwise would have been the subject of an independent conclusion of GRAS status or an association expert panel GRAS conclusion (annual)	$1,909,528.05	$1,007,608.22	$3,036,256.41
Total one-time costs of the proposed rule	**$63,135,180**	**$20,721,463**	**$169,489,748**
Total recurring costs of the proposed rule	**$3,319,279**	**$1,733,354**	**$5,333,364**

Table 17 presents the 10-year stream of estimated costs of the proposed rule, as well as the present value and annualized value of costs, discounted at 3 and 7 percent over 10 years in 2024 dollars.

Table 17. 10-year Stream, Present Value, and Annualized Costs of the Proposed Rule (2024 dollars)

	Primary	Low	High
Year 1	$66,454,458.84	$22,454,816.75	$174,823,111.77
Year 2	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 3	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 4	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 5	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 6	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 7	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 8	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 9	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 10	$3,319,279.03	$1,733,353.96	$5,333,363.51
Present Value of Costs (3%)	$89,610,414	$34,903,786	$210,047,826
Present Value of Costs (7%)	$82,318,068	$31,540,206	$195,860,947
Annualized Costs (10 years, 3%)	**$10,505,074**	**$4,091,789**	**$24,624,013**
Annualized Costs (10 years, 7%)	**$11,720,241**	**$4,490,616**	**$27,886,193**

We estimate that the present value of the costs of the proposed rule is approximately $89.6 million, with a lower bound of $34.9 million and an upper bound of $210.0 million, discounted at a 3 percent in 2024 dollars. At a 7 percent discount rate, the present value of costs is approximately $82.3 million, with a lower bound of $31.5 million and an upper bound of $195.9 million. The annualized costs of the proposed rule are approximately $10.5 million, with a lower bound of $4.1 million and an upper bound of $24.6 million, discounted at 3 percent. At a 7 percent discount rate, annualized costs are approximately $11.7 million, with a lower bound of $4.5 million and an upper bound of $27.9 million.

G. Analysis of Regulatory Alternatives to the Proposed Rule

1. Extend Submission Period for Streamlined Submissions for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule

With this alternative to the proposed rule, manufacturers of substances that are already in interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule would have up to 3 years (rather than the proposed 1 year) after the publication of the final rule to submit this streamlined submission to FDA. The additional flexibility of this alternative would decrease costs to manufacturers of purported GRAS substances. We equally divide the one-time costs (i.e., those incurred only in the year after publication of the final rule) of the proposed rule to manufacturers across the 3 years after the effective date of a final rule. These estimates suggest that some manufacturers may submit when the rule becomes effective, while others may take advantage of the added flexibility and submit up to 3 years after the publication of the final rule.

Under this regulatory alternative, we estimate the annualized costs of the proposed rule are approximately $8.8 million, with a lower bound of approximately $3.2 million and an upper bound of approximately $22.1 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimated costs are approximately $9.5 million, with a lower bound of approximately $3.5 million and an upper bound of approximately $24.3 million. These estimates are summarized in Table 18.

Extending the submission period for streamlined submissions of substances that were already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule would lead to potential delays in the benefits discussed in Section E. That is, while the information would still be provided, the potential benefits of the information will be delayed.

Table 18. Regulatory Alternative to the Proposed Rule: Extended Submission Period (2024 dollars)

	Primary	Low	High
Primary annualized costs (10 years, 3%)	$10,505,074	$4,091,789	$24,624,013
Primary annualized costs, (10 years, 7%)	$11,720,241	$4,490,616	$27,886,193
Alternative annualized costs, (10 years, 3%)	**$8,811,520**	**$3,243,771**	**$22,136,293**
Alternative annualized costs, (10 years, 7%)	**$9,540,759**	**$3,452,529**	**$24,309,472**

2. Require Submission of a GRAS Notice for All Substances Already Introduced into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule

With this alternative to the proposed rule, manufacturers of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule would be required to submit a GRAS notice (i.e., they would not be able to submit a streamlined submission). We estimate that the time burden to manufacturers of submitting a GRAS notice for such substances would be equal to the time burden of submitting a GRAS notice for a new or existing use of a substance that was already in interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule. This alternative to the proposed rule would increase costs to manufacturers and increase costs to FDA to review additional submissions.

Under this regulatory alternative, we estimate the annualized costs of the proposed rule are approximately $31.1 million, with a lower bound of approximately $12.0 million and an upper bound of approximately $68.3 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimated costs are approximately $35.8 million, with a lower bound of approximately $13.7 million and an upper bound of approximately $78.9 million. These estimates are summarized in Table 19.

This alternative could lead to increases in potential benefits. A GRAS notice provides substantially more information than what the proposed rule is requesting from manufacturers of substances already introduced into interstate commerce before the effective date of a final rule based on an independent conclusion of GRAS status. As information asymmetries form the basis of the potential benefits associated with the proposed rule, this alternative could generate larger benefits.

Table 19. Regulatory Alternative to the Proposed Rule: GRAS Notice Requirement (2024 dollars)

	Primary	Low	High
Primary annualized costs (10 years, 3%)	$10,505,074	$4,091,789	$24,624,013
Primary annualized costs, (10 years, 7%)	$11,720,241	$4,490,616	$27,886,193
Alternative annualized costs, (10 years, 3%)	**$31,113,270**	**$12,004,167**	**$68,297,445**
Alternative annualized costs, (10 years, 7%)	**$35,813,422**	**$13,741,031**	**$78,945,098**

3. Require GRAS Notices but Extend Submission Period for Substances Already Introduced into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule

With this alternative to the proposed rule, manufacturers of substances already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule would be required to submit a GRAS notice to FDA (i.e., regulatory alternative 2). In addition, manufacturers of substances already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule would have 3 years to submit a GRAS notice to FDA (as in regulatory alternative

1). Because the decrease in costs from the extended submission period alternative is smaller than the increase in costs from the GRAS notice submission requirement alternative in absolute value, the combination of these alternatives would be a net cost increase to manufacturers.

Under this regulatory alternative, we estimate the annualized costs of the proposed rule are approximately $28.8 million, with a lower bound of approximately $10.9 million and an upper bound of approximately $64.6 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimate costs are approximately $32.1 million, with a lower bound of approximately $12.1 million and an upper bound of approximately $72.1 million. These estimates are summarized in Table 20.

This alternative would have an ambiguous effect on benefits over 10 years. Although the increased information provided could lead to an increase in benefits, the delayed provision of this information would similarly delay any potential benefits.

Table 20. Regulatory Alternative to the Proposed Rule: Extended Submission Period and GRAS Notice Requirement (2024 dollars)

	Primary	Low	High
Primary annualized costs (10 years, 3%)	$10,505,074	$4,091,789	$24,624,013
Primary annualized costs, (10 years, 7%)	$11,720,241	$4,490,616	$27,886,193
Alternative annualized costs, (10 years, 3%)	**$28.825.305**	**$10,927,930**	**$64,550,033**
Alternative annualized costs, (10 years, 7%)	**$32,092,122**	**$12,110,973**	**$72,100,917**

4. Permit Streamlined Submissions for All Substances Purported to be GRAS Under the Conditions of Their Intended Use Under Section 201(s) of the FD&C Act

With this alternative to the proposed rule, manufacturers of substances would be permitted to submit a streamlined submission (i.e., they would not be required to submit a GRAS notice) for uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act after the effective date of a final rule. The additional flexibility of this alternative would decrease costs to manufacturers of preparing submissions. We expect that the costs to FDA of reviewing submissions described in this analysis would also decrease, but we acknowledge that a proposal requiring only streamlined submissions may generate other costs to FDA that we are unable to quantify. Such costs may include the cost to FDA of obtaining safety information and data rather than such information residing with notifiers (in the case of GRAS notices) or manufacturers (in the case of streamlined submissions).

Under this regulatory alternative, we estimate the annualized costs of the proposed rule are approximately $7.9 million, with a lower bound of approximately $2.6 million and an upper bound of approximately $20.8 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimated costs are approximately $9.1 million, with a lower bound of approximately $3.0 million and an upper bound of approximately $24.1 million. These estimates are summarized in Table 21.

This alternative would have an ambiguous effect on net benefits. While this would reduce the cost to manufacturers of preparing submissions and costs to FDA to review submissions, a

GRAS notice that requires safety assessment information provides substantially more information than the streamlined submission. As information asymmetries form the basis of the potential benefits associated with the proposed rule, the cost savings of this alternative relative to the costs of the primary proposal may not be greater than the foregone benefits of the alternative.

Table 21. Regulatory Alternative to the Proposed Rule: Streamlined Submissions (2024 dollars)

	Primary	Low	High
Primary annualized costs (10 years, 3%)	$10,505,074	$4,091,789	$24,624,013
Primary annualized costs, (10 years, 7%)	$11,720,241	$4,490,616	$27,886,193
Alternative annualized costs, (10 years, 3%)	**$7,859,081**	**$2,568,638**	**$20,799,216**
Alternative annualized costs, (10 years, 7%)	**$9,074,248**	**$2,967,465**	**$24,061,396**

5. Permit Streamlined Submissions for All Substances Purported to be GRAS Under the Conditions of Their Intended Use Under Section 201(s) of the FD&C Act and Extend Submission Period for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule

With this alternative to the proposed rule, manufacturers of substances would be permitted to submit a streamlined submission (i.e., they would not be required to submit a GRAS notice) for uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act after the effective date of a final rule (as in regulatory alternative 4). In addition, manufacturers of substances already introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule would have 3 years to submit a streamlined submission to FDA (as in regulatory alternative 1). Because both proposed alternatives yield lower total costs individually, we estimate that the combination of these alternatives would be cost saving to manufacturers.

Under this regulatory alternative, we estimate the annualized costs of the proposed rule are approximately $6.2 million, with a lower bound of approximately $1.7 million and an upper bound of approximately $18.3 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimated costs are approximately $6.9 million, with a lower bound of approximately $1.9 million and an upper bound of approximately $20.5 million. These estimates are summarized in Table 22.

This alternative would have an ambiguous effect on net benefits. While we estimate in the previous regulatory alternative that streamlined submissions are likely to reduce costs to manufacturers and FDA, a GRAS notice provides substantially more information than the streamlined submission. As information asymmetries form the basis of the potential benefits associated with the proposed rule, the cost savings of this alternative may not be greater than the foregone benefits. The delayed provisions of this information would similarly delay any potential benefits.

Table 22. Regulatory Alternative to the Proposed Rule: Streamlined Submissions and Extended Submission Period (2024 dollars)

	Primary	Low	High
Primary annualized costs (10 years, 3%)	$10,505,074	$4,091,789	$24,624,013
Primary annualized costs, (10 years, 7%)	$11,720,241	$4,490,616	$27,886,193
Alternative annualized costs, (10 years, 3%)	**$6,165,528**	**$1,720,621**	**$18,311,496**
Alternative annualized costs, (10 years, 7%)	**$6,894,766**	**$1,929,378**	**$20,484,675**

H. International Effects

In our primary analysis, we estimate costs to affected foreign manufacturers of substances already introduced into interstate commerce before the effective date of a final rule based on an independent conclusion of GRAS status, as well as new uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the F&DC Act that would be required to be the subject of a GRAS notice after the effective date of a final rule. If the proposed rule is finalized, we expect foreign manufacturers to incur costs related to reading the rule, revising SOPs, and preparing and submitting GRAS notices for new uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act after the effective date of a final rule. For those foreign manufacturers that choose to submit streamlined submissions during the limited time for such submissions, they will also incur costs related to preparing and submitting streamlined submissions for substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of the final rule. We also expect some affected foreign firms to incur costs of translating streamlined submissions and GRAS notice documentation to English.

We estimate that 47.14 percent of GRAS-notifying entities are outside the U.S. and that 81.52 percent of foreign GRAS-notifying entities are in non-English speaking countries. To consider the effect of the proposed rule on foreign entities, we estimate the costs described in section II.F for 47.14 percent of affected entities. We additionally estimate translation costs for 81.52 percent of affected foreign entities.

The estimated present value of costs to affected foreign entities is approximately $44.7 million, with a lower bound of $18.2 million and an upper bound of $102.0 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, the estimated present value of costs is approximately $41.1 million, with a lower bound of $16.5 million and an upper bound of $95.0 million. The estimated annualized costs to affected foreign entities are approximately $5.2 million, with a lower bound of $2.1 million and an upper bound of $12.0 million, discounted at 3 percent over 10 years. At a 7 percent discount rate, estimated annualized costs are approximately $5.8 million, with a lower bound of $2.4 million and an upper bound of $13.5 million. These estimates, as well as the estimated 10-year stream of costs are presented in Table 23.

Table 23. Estimated Costs of the Proposed Rule to Affected Foreign Entities (2024 dollars)

	Primary	Low	High
Year 1	$33,382,819.18	$12,223,543.02	$84,487,195.15
Year 2	$1,623,919.79	$838,756.97	$2,637,647.77
Year 3	$1,623,919.79	$838,756.97	$2,637,647.77
Year 4	$1,623,919.79	$838,756.97	$2,637,647.77
Year 5	$1,623,919.79	$838,756.97	$2,637,647.77
Year 6	$1,623,919.79	$838,756.97	$2,637,647.77
Year 7	$1,623,919.79	$838,756.97	$2,637,647.77
Year 8	$1,623,919.79	$838,756.97	$2,637,647.77
Year 9	$1,623,919.79	$838,756.97	$2,637,647.77
Year 10	$1,623,919.79	$838,756.97	$2,637,647.77
Present value, 3% (10 years)	44,686,248.13	$18,207,957.40	$101,965,250.49
Present value, 7% (10 years)	$41,086,947.47	$16,531,064.91	$95,020,638.30
Annualized, 3% (10 years)	**$5,238,592**	**$2,134,528**	**$11,953,438**
Annualized, 7% (10 years)	**$5,849,857**	**$2,353,652**	**$13,528,801**

I. Uncertainty and Sensitivity Analysis

1. Producer Costs of Removing Products from Interstate Commerce and Potential Reformulation of Removed Products

As described in section F.3.a of this document, we expect future annual submissions of GRAS notices for substances that industry intends to incorporate into products already on the market once FDA evaluates and responds to a GRAS notice. In some cases, FDA may disagree with notifiers, at least temporarily, regarding whether a substance is GRAS under the conditions of its intended use. While there is no requirement that industry must wait for an FDA response, this disagreement could potentially delay the introduction of the substance into the market. Alternatively, some manufacturers may introduce the substance in their products after they meet the notification requirement, but before FDA has evaluated and responded to the GRAS notice. In those cases, a disagreement about a GRAS conclusion could lead to costs associated with temporarily removing the product from the market, reformulating, and then reintroducing the product. Below, we estimate the costs associated with these removals and potential reformulations, and qualitatively address the costs associated with delayed use of the purportedly GRAS substance.

Costs associated with the delayed use of a new purported GRAS substance are characterized by uncertainty, including as regards a food producer's tradeoff between running the risk of needing to remove a product from interstate commerce or instead forgoing profit on new or updated products until FDA's "no questions" conclusion is reached.[11] We request comments and data associated with the delayed use of GRAS substances in food products.

[11] Where the voluntary submissions data include both filing date and closure date, the average lag between them is 195 days. However, filing date has been unavailable in the online databases since 2017, and hence the 195-day estimate may no longer be representative.

To estimate the number of potential removals, we assume that between 2.3 and 20.9 percent (with primary estimate of 11.6 percent) of GRAS notices that, in the absence of the rule, would have been the subject of an independent conclusion of GRAS status will receive a "cease to evaluate" letter or receive an "insufficient basis" letter.[12] The range of ratios, from 2.3 to 20.9 percent, will be applied to the estimated increase in GRAS notice submissions from Table 14.

For the cost per instance of such removals, we draw on (ERG, 2022, Ref. 14), which was a key source cited in the regulatory impact analysis for "Requirements for Additional Traceability Records for Certain Foods" (RIN 0910-AI44). Used here are ERG's cost estimates for product destruction, product restocking, product storage, public relations and advertising, and labor, as experienced by producers/processors, shippers/distributors, restaurants and non-restaurant retailers. Because ERG's expert elicitation relates to *overly broad* recalls—characterized by, for example, lack of identification of firms that are the source of recall-prompting problems—the estimates would probably have a tendency toward overstatement of the costs attributable to this proposed rule. As a result, only low and most likely estimates, rather than high estimates, will be used in this analysis; the resulting cost range (adjusted to 2024 dollars) per product removal is $0.14 million to $4.85 million.

Instead of using ERG's estimates of costs of lost sales, we develop a quantitative approach that reflects the passage of time between submissions and associated resubmissions to the voluntary GRAS evaluation program. For GRAS substances that: (1) have received insufficient-basis responses or been associated with a notifier's request that FDA cease evaluating, and (2) have subsequently received a no-questions response from FDA, the average length of time between the original date of filing and the date of closure (for the no-questions response) has been 723 days, or 1.98 years (Ref. 2; 3).

The next source of inputs for this analysis is FDA's Reformulation Cost Model (Muth et al., 2015, Ref. 16). A common use of this model in regulatory impact analyses is quantification of the cost of reformulation that occurs in response to issuance of a new rulemaking; notably (for purposes of quantifying cost of reduced market access), regulated entities are willing to incur such costs to the extent they are exceeded by the profit that would flow from selling the relevant products.[13] As shown in Table 24, these estimates vary by complexity of ingredient and by size of the associated business entity.

[12] Under the existing voluntary GRAS program, cases in which FDA has communicated an insufficient basis for a GRAS determination represent 2.3 percent (= 23 / (961 + 23), per Table 4) of submissions for which FDA's position has established the closure outcome—that is, either communicating "FDA has no questions" or "notice does not provide a basis for a GRAS determination." This percentage estimate allows for a comparison of relatively concrete outcomes, which is an advantage but also a disadvantage in that it omits any accounting for the prevalent cases in which notifiers request that FDA cease to evaluate voluntary GRAS submissions. An upper-bound quantification of the removal consequences of this proposal might take the form of assuming that all cease-to-evaluate cases are characterized by insufficient evidence in the GRAS notices; the resulting ratio would be 20.9 percent, which equals (231 + 23) / (961 + 231 + 23), again per Table 4.

[13] This approach has a tendency toward underestimation due to its omission of surplus accruing to consumers.

Table 24. Reformulation Cost Model Estimates (2024$, millions)

Ingredient Complexity	Small Business Entity	Medium-sized Business Entity	Large Business Entity
Low Complexity	$0.018	$0.362	$0.922
Medium Complexity	$0.022	$0.440	$1.095
High Complexity	$0.032	$0.452	$1.126

Notes: Estimates reflect means as reported in the Model, equally-weighted across major, minor functional, and minor nonfunctional ingredients.

If the above estimates are applied in the proportions shown in Ref. 16 Table 3-1 (which lists food formulae by complexity and business size) and updated to 2024 dollars, the resulting average is approximately $0.53 million per reformulation. Moreover, Ref. 16's section 3.3.2 implies that a year of market access can, relative to cost estimates as primarily presented in that Model, be worth 75 percent (for small entities), 125 percent (for medium-sized entities), or 50 or 150 percent (for large entities, depending on when the year of market access occurs). Therefore, although there is uncertainty about the relationship between the $0.53 million estimate and the flow over time of market access value, it may be reasonable to assume that this estimate approximates 100 percent of the value of one year's market access. Table 25 presents the annual costs associated with removal of products from interstate commerce.

Table 25. Cost of Removing Products from Interstate Commerce and Potential Reformulation (millions of 2024 dollars)

	Primary	Low	High
Removal Percentage	7.5%	2.3%	20.9%
Percent of Removals that Reformulate	50%	0%	100%
Per-removal Cost Subtotal*	$1.00	$0.14	$4.85
Per-removal Cost Including 1.98 Years of Lost Market Access Valued at $0.53 million annually	$2.07	$1.20	$5.91
Per-reformulation Cost	$0.53	$0.53	$0.53
Substances Potentially Affected	98.5	60	137
Estimated Removals	7.39	3.00	13.7
Estimated Removals that Reformulate	3.695	0	13.7
Estimated Removal Cost	$7.40	$0.42	$66.48
Estimated Reformulation Cost	$1.96	$0.00	$7.26
Total Cost of Removing Products from Interstate Commerce and Potential Reformulation	**$9.36**	**$0.42**	**$73.74**

* Sources of primary, low, and high estimates are, respectively, the median (most likely), median (low), and average (low) columns of Tables 3-24 and 3-25 of ERG (2022, Ref. 14).

We estimate that between 60 and 137 additional GRAS notices are going to be submitted annually (see Table 14). Applying the range of ratios that we expect to receive a "cease to evaluate" or "insufficient basis" letter, we expect that between 3 and 13.7 (primary estimate of 7.4) GRAS notices will receive a "cease to evaluate" or "insufficient basis" letter. If all of these substances are in products which are currently on the market, we would thus expect between 3 and 13.7 (primary estimate of 7.4) product removals to take place following the receipt of a "cease to evaluate" or

"insufficient basis" letter. We assume that between 0% and 100% of the products removed from the market would then reformulate. This would result in an estimated range of between 0 and 13.7 product reformulations.

Applying the cost per removal and cost per reformulation to the estimated number of removals and reformulations, we estimate that it could cost between $0.42 million and $73.74 million (with a primary estimate of $9.36 million) annually to remove products from the market that contain a substance for which a "cease to evaluate" or an "insufficient basis" letter is issued by FDA. We request comment and data on the methods, assumptions, and sources associated with these estimates.

2. Qualitative Benefits Associated with Identifying and Removing Unsafe Substances

A mandatory GRAS notification program would also help to ensure that human food safety, as well as target animal safety in the case of animal food GRAS notices, is fully assessed as part of a notifier's GRAS conclusion. This information would help us to more efficiently determine whether the use of a substance meets the definition of a food additive use under the FD&C Act, and therefore whether the use of the substance requires premarket review and approval to be lawfully marketed. Under a mandatory GRAS notification program, FDA may identify unsafe uses of substances purported to be GRAS earlier; FDA may also identify unsafe uses more frequently. Because we lack data on the current number of unsafe uses of purported GRAS substances, we are unable to monetize benefits associated with earlier and more frequent identifications of unsafe use. The magnitude of benefits may also vary by the cost of illnesses prevented by a mandatory GRAS notification program. We request comment on data sources, methods, and assumptions for identifying potentially unsafe uses of substances purported to be GRAS.

III. **Initial Small Entity Analysis**

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we estimate that the economic impact of this proposed rule is more than three percent of annual revenue of small entities, we find that the proposed rule will have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document and the Preamble of the proposed rule, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act (5 U.S.C. 601–612).

A. Description and Number of Affected Small Entities

The data on affected entities comes from FDA's GRAS Notice Inventory, Animal Food GRAS Notice Inventory (Ref. 2) and Dun & Bradstreet (D&B) firm data. We merge the FDA GRAS Notice Inventories with D&B firm data to identify firm-level characteristics. As discussed in section II.D.2 of this document, we assume the characteristics of firms manufacturing substances based on an independent conclusion of GRAS status are similar to the firms that have submitted GRAS notices to FDA. Firms across a variety of industries are involved with the production of substances purported to be GRAS for some use and submission of GRAS notices. The most common industries of firms that have previously submitted GRAS notices are Pharmaceutical Preparations (NAICS 325412), Perishable Prepared Food Manufacturing (NAICS 311991), Dry, Condensed, and Evaporated Dairy Product Manufacturing (NAICS 311514), and Industrial Organic Chemicals (NAICS 325199). The Small Business Administration considers firms in these categories small if they do not exceed a certain number of employees: 1,300 employees for Pharmaceutical Preparations, 700 employees for Perishable Prepared Food Manufacturing, 1,000 employees for Dry, Condensed, and Evaporated Dairy Product Manufacturing, and 1,250 employees for Industrial Organic Chemicals Industry (Ref. 13). These small business thresholds are summarized in Table 26.

Table 26. Small Business Administration Size Standards for Industries Affected by the Proposed Rule

NAICS Code	Industry Description	SBA Small Business Threshold (number of employees)
311514	Dry, Condensed, and Evaporated Dairy Product Manufacturing	1,000
311991	Perishable Prepared Food Manufacturing	700
325199	Industrial Organic Chemical Manufacturing	1,250
325412	Pharmaceutical Preparation Manufacturing	1,300

Using FDA's GRAS Notice Inventory, Animal Food GRAS Notice Inventory and D&B data we estimate that approximately 40 percent of domestic GRAS notifiers are small entities, and that there are approximately 210 affected small entities.

In Table 27 we present additional data on firm size by receipts among the firms identified as small businesses in the D&B data. D&B had receipt data for small entities on 130 of the 132 domestic small entities. We assume that the receipts for the 2 firms missing receipt data would not significantly affect the distribution. We request comment on data sources, methods, and assumptions for identifying affected small entities.

Table 27. Domestic Small Entities by Annual Receipts

Annual Receipt Category	Average Receipts in Category	Receipts as Share of Industry	Firm Count	Percent of all Small Firms
Under $100,000	$65,858	0.05%	12	9.23%
$100,000 to $499,999	$256,037	0.21%	33	25.38%
$500,000 to $999,999	$750,232	0.61%	12	9.23%
$1,000,000 to $1,999,999	$1,439,362	1.17%	11	8.46%
$2,000,000 to $4,999,999	$3,156,816	2.56%	18	13.85%
$5,000,000 to $9,999,999	$7,477,742	6.07%	20	15.38%
$10,000,000 to $14,999,999	$11,900,000	9.66%	7	5.38%
More than $15,000,000	$98,200,000	79.68%	17	13.08%
Total	$123,246,047	100%	130	100%

B. Description of the Potential Impacts of the Rule on Small Entities

We assume that the costs associated with this proposed rule that are incurred by small entities are proportional to the size of the small-entity product market, and that the proportion of small entities is equal for foreign and domestic firms. We estimate that there are approximately 132 (= 210 firms x 62.9 percent) domestic affected small entities and approximately 78 (= 210 firms x 37.1 percent) foreign affected small entities. We request comments on these assumptions. We therefore estimate that the annualized costs of the proposed rule incurred by affected small entities are approximately $2.6 million (= $10.5 million x 62.86 percent x 40 percent), with a lower bound of $1.0 million (= $4.1 million x 62.86 percent x 40 percent) and an upper bound of $6.2 million (= $24.6 million x 62.86 percent x 40 percent), discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, annualized costs of the proposed rule incurred by affected small entities are approximately $2.9 million (= $11.7 million x 62.86 percent x 40 percent), with a lower bound of $1.1 million (= $4.5 million x 62.86 percent x 40 percent) and an upper bound of $7.0 million (= $27.9 million x 62.86 percent x 40 percent). We divide annualized costs to small entities by the estimated number of affected small entities (132) to yield per entity costs of approximately $20.0 thousand (= $2.64 million / 132), with a lower bound of $7.8 thousand (= $1.0 million / 132) and an upper bound of $46.9 thousand (= $6.2 million / 132),

discounted at 3 percent over 10 years. At a 7 percent discount rate, per entity costs are approximately $22.3 thousand (= $2.9 million / 132), with a lower bound of $8.6 thousand (= $1.1 million / 132) and an upper bound of $53.1 thousand (= $7.0 million / 132).

Using the mean ($17.2 million) and median ($1.2 million) annual revenue for small entities, we estimate the proportion of estimated costs to revenue, alternatively expressing estimated annual costs as a percentage of mean and median revenue. We estimate that costs of the rule as a percentage of mean annual revenue are approximately 0.12 percent (= $20,010 / $17.2 million, with a lower bound of 0.05 percent (= $67,794 / $17.2 million) and an upper bound of 0.27 percent (= $46,903 / $17.2 million), discounted at 3 percent over 10 years. At a 7 percent discount rate, costs as a percentage of mean annual revenue are approximately 0.13 percent (= $22,324 / $17.2 million), with a lower bound of 0.05 percent (= $8,554 / $17.2 million) and an upper bound of 0.31 percent (= $53,117 / $17.2 million). We estimate that costs of the rule as a percentage of median annual revenue are approximately 1.67 percent (= $20,010 / $1.2 million), with a lower bound of 0.65 percent (= $7,794 / $1.2 million) and an upper bound of 3.91 percent (= $46,903 / $1.2 million), discounted at 3 percent over 10 years. At a 7 percent discount rate, costs as a percentage of mean annual revenue are approximately 1.86 percent (= $22,324 / $1.2 million), with a lower bound of 0.71 percent (= $8,554 / $1.2 million) and an upper bound of 4.43 percent (= $53,117 / $1.2 million). The costs of the proposed rule for affected small entities are summarized in Table 28.

Table 28. Costs of the Proposed Rule for Affected Small Entities (2024 dollars)

	Primary	Low	High
Annualized costs of the proposed rule (3%)	$10,505,074.28	$4,091,788.51	$24,624,013.08
Annualized costs of the proposed rule (7%)	$11,720,240.93	$4,490,615.76	$27,886,192.57
Number of affected domestic small entities	132	132	132
Number of affected foreign small entities	78	78	78
Total number of affected small entities	210	210	210
Percent of small entities that are domestic	62.9%	62.9%	62.9%
Percent of affected entities considered small	40%	40%	40%
Annualized costs of the proposed rule to small entities (3%)	$2,641,275.82	$1,028,792.54	$6,191,180.43
Annualized costs of the proposed rule to small entities (7%)	$2,946,803.43	$1,129,069.11	$7,011,385.56
Annualized costs of the proposed rule per small entity (3%)	$20,009.67	$7,793.88	$46,902.88
Annualized costs of the proposed rule per small entity (7%)	$22,324.27	$8,553.55	$53,116.56
Mean annual revenue of small entities	$17,200,000	$17,200,000	$17,200,000
Median annual revenue of small entities	$1,200,000	$1,200,000	$1,200,000
Cost of the rule as a percentage of mean annual revenue (3%)	0.12%	0.05%	0.27%
Cost of the rule as a percentage of mean annual revenue (7%)	0.13%	0.05%	0.31%
Cost of the rule as a percentage of median annual revenue (3%)	1.67%	0.65%	3.91%
Cost of the rule as a percentage of median annual revenue (7%)	1.86%	0.71%	4.43%

Table 29 provides additional detail on the impact of the rule on domestic small entities broken down by annual receipts category. For the smallest entities (under $100,000 in annual receipts) the annualized burden of the rule exceeds 22 percent. The first-year costs associated with the rule exceed 119 percent of annualized receipts for the smallest entities. As mentioned above,

we assume that the receipts for the 2 firms missing receipt data would not significantly affect the distribution.

Table 29. Impacts on Domestic Small Entities by Annual Receipts

Annual Receipt Category	Firm Count	Average Receipts in Category	Primary Estimate of Annualized Cost at 7% (as a Percent of Receipts)	First Year Costs (as a Percent of Annual Receipts)
Under $100,000	12	$65,858	22.21%	119.67%
$100,000 to $499,999	33	$256,037	5.71%	30.78%
$500,000 to $999,999	12	$750,232	1.95%	10.51%
$1,000,000 to $1,999,999	11	$1,439,362	1.02%	5.48%
$2,000,000 to $4,999,999	18	$3,156,816	0.46%	2.50%
$5,000,000 to $9,999,999	20	$7,477,742	0.20%	1.05%
$10,000,000 to $14,999,999	7	$11,900,000	0.12%	0.66%
More than $15,000,000	17	$98,200,000	0.01%	0.08%
Total	130	$123,246,047	0.01%	0.06%

C. Alternatives to Minimize the Burden on Small Entities

Alternatives discussed in section II.G would apply to the entire industry. However, here, we quantify and discuss how the burden on small entities could be minimized.

1. Extend Submission Period to 3 Years for Streamlined Submissions for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule

With this alternative to the proposed rule, manufacturers of substances that are already in interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule would have up to 3 years (rather than the proposed 1 year) after the publication of the final rule to submit this streamlined submission to FDA. We have estimated the impact of this regulatory alternative (see II.G.1) for affected small entities.

Under this regulatory alternative, we estimate that the annualized costs of the proposed rule to affected small entities is approximately $2.2 million, with a lower bound of $815.6 thousand and an upper bound of $5.6 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimated costs are approximately $2.4 million, with a lower bound of approximately $868.1 thousand and an upper bound of approximately $6.1 million.

We divide annualized costs to small entities by the estimated number of affected small entities (132) to yield per entity costs of approximately $16.8 thousand (= $2.2 million / 132), with a lower bound of $6.2 thousand (= $815.6 thousand / 132) and an upper bound of $42.2 thousand (= $5.6 million / 132), discounted at 3 percent over 10 years. At a 7 percent discount rate, per entity costs are approximately $18.2 thousand (= $2.4 million / 132), with a lower bound of $6.6 thousand

(= $868.1 thousand / 132) and an upper bound of $46.3 thousand (= $6.1 million / 132). These estimates are summarized in Table 30.

Table 30. Regulatory Alternative to the Proposed Rule for Affected Small Entities: Extended Submission Period (2024 dollars)

	Primary	Low	High
Annualized costs of the alternative to all affected entities (3%)	$8,811,520.40	$3,243,771.45	$22,136,292.90
Annualized costs of the alternative to all affected entities (7%)	$9,540,758.66	$3,452,528.67	$24,309,472.28
Number of affected domestic small entities	132	132	132
Number of affected foreign small entities	78	78	78
Total number of affected small entities	210	210	210
Percent of small entities that are domestic	62.9%	62.9%	62.9%
Percent of affected entities considered small	40%	40%	40%
Annualized costs of the alternative to small entities (3%)	$2,215,467.99	$815,576.82	$5,565,696.50
Annualized costs of the alternative to small entities (7%)	$2,398,819.32	$868,064.35	$6,112,095.89
Annualized costs of the alternative per small entity (3%)	$16,783.85	$6,178.61	$42,164.37
Annualized costs of the alternative per small entity (7%)	$18,172.87	$6,576.25	$46,303.76
Mean annual revenue of small entities	$17,200,000	$17,200,000	$17,200,000
Median annual revenue of small entities	$1,200,000	$1,200,000	$1,200,000
Cost of the alternative as a percentage of mean annual revenue (3%)	0.10%	0.04%	0.25%
Cost of the alternative as a percentage of mean annual revenue (7%)	0.11%	0.04%	0.27%
Cost of the alternative as a percentage of median annual revenue (3%)	1.40%	0.51%	3.51%
Cost of the alternative as a percentage of median annual revenue (7%)	1.51%	0.55%	3.86%

2. Permit Streamlined Submissions for All Substances Purported to be GRAS Under the Conditions of Their Intended Use Under Section 201(s) of the FD&C Act

With this alternative to the proposed rule, affected small manufacturers of substances would be permitted to submit a streamlined submission (i.e., they would not be required to submit a GRAS notice) for uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act after the effective date of a final rule. The additional flexibility of this alternative would decrease costs to affected small entities of preparing submissions. We expect that costs to FDA of reviewing submissions described in this analysis would also decrease, but we acknowledge that a proposal requiring only streamlined submissions may generate other costs to FDA that we are unable to quantify. Only requiring streamlined submissions may undermine FDA's ability to meet its responsibilities under the FD&C Act to

ensure the safety of the food supply and protect public health. We have estimated the impact of this regulatory alternative (see II.G.4) for affected small entities.

Under this regulatory alternative, we estimate that the annualized costs of the proposed rule to affected small entities is approximately $2.0 million, with a lower bound of $645.8 thousand and an upper bound of $5.2 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimated costs are approximately $2.3 million, with a lower bound of approximately $746.1 thousand and an upper bound of approximately $6.0 million.

We divide annualized costs to small entities by the estimated number of affected small entities (132) to yield per entity costs of approximately $15.0 thousand (= $2.0 million / 132), with a lower bound of $4.9 thousand (= $645.8 thousand / 132) and an upper bound of $39.6 thousand (= $5.2 million / 132), discounted at 3 percent over 10 years. At a 7 percent discount rate, per entity costs are approximately $17.3 thousand (= $2.3 million / 132), with a lower bound of $5.7 thousand (= $746.1 thousand / 132) and an upper bound of $45.8 thousand (= $6.0 million / 132). These estimates are summarized in Table 31.

Table 31. Regulatory Alternative to the Proposed Rule for Affected Small Entities: Streamlined Submissions (2024 dollars)

	Primary	Low	High
Annualized costs of the alternative to all affected entities (3%)	$7,859,081.48	$2,568,637.79	$20,799,216.22
Annualized costs of the alternative to all affected entities (7%)	$9,074,248.13	$2,967,465.05	$24,061,395.72
Number of affected domestic small entities	132	132	132
Number of affected foreign small entities	78	78	78
Total number of affected small entities	210	210	210
Percent of small entities that are domestic	62.9%	62.9%	62.9%
Percent of affected entities considered small	40%	40%	40%
Annualized costs of the alternative to small entities (3%)	$1,975,997.63	$645,828.93	$5,229,517.22
Annualized costs of the alternative to small entities (7%)	$2,281,525.24	$746,105.50	$6,049,722.35
Annualized costs of the alternative per small entity (3%)	$14,969.68	$4,892.64	$39,617.55
Annualized costs of the alternative per small entity (7%)	$17,284.28	$5,652.31	$45,831.23
Mean annual revenue of small entities	$17,200,000	$17,200,000	$17,200,000
Median annual revenue of small entities	$1,200,000	$1,200,000	$1,200,000
Cost of the alternative as a percentage of mean annual revenue (3%)	0.09%	0.03%	0.23%
Cost of the alternative as a percentage of mean annual revenue (7%)	0.10%	0.03%	0.27%
Cost of the alternative as a percentage of median annual revenue (3%)	1.25%	0.41%	3.30%
Cost of the alternative as a percentage of median annual revenue (7%)	1.44%	0.47%	3.82%

3. Permit Streamlined Submissions for All Substances Purported to be GRAS Under the Conditions of Their Intended Use Under Section 201(s) of the FD&C Act and Extend Submission Period for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule

With this alternative to the proposed rule, affected small manufacturers of substances would be permitted to submit a streamlined submission (i.e., they would not be required to submit a GRAS notice) for uses of substances introduced into interstate commerce under the GRAS provision of section 201(s) of the FD&C Act after the effective date of a final rule (as in regulatory alternative 4). In addition, manufacturers of substances already introduced into interstate commerce before the effective date of a final rule based on an independent conclusion of GRAS status would have 3 years to submit a GRAS notice to FDA (as in regulatory alternative 1). Because both proposed alternatives yield lower total costs individually, we estimate that the combination of these alternatives would be cost saving to affected small entities. We have estimated the impact of this regulatory alternative (see II.G.5) for affected small entities.

Under this regulatory alternative, we estimate that the annualized costs of the proposed rule to affected small entities are approximately $1.6 million, with a lower bound of $432.6 thousand and an upper bound of $4.6 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimated costs are approximately $1.7 million, with a lower bound of approximately $485.1 thousand and an upper bound of approximately $5.2 million.

We divide annualized costs to small entities by the estimated number of affected small entities (132) to yield per entity costs of approximately $11.7 thousand (= $1.6 million / 132), with a lower bound of $3.3 thousand (= $432.6 thousand / 132) and an upper bound of $34.9 thousand (= $4.6 million / 132), discounted at 3 percent over 10 years. At a 7 percent discount rate, per entity costs are approximately $13.1 thousand (= $1.7 million / 132), with a lower bound of $3.7 thousand (= $485.1 thousand / 132) and an upper bound of $39.0 thousand (= $5.2 million / 132). These estimates are summarized in Table 32.

Table 32. Regulatory Alternative to the Proposed Rule for Affected Small Entities: Streamlined Submissions and Extended Submission Period (2024 dollars)

	Primary	Low	High
Annualized costs of the alternative to all affected entities (3%)	$6,165,527.60	$1,720,620.73	$18,311,496.05
Annualized costs of the alternative to all affected entities (7%)	$6,894,765.86	$1,929,377.96	$20,484,675.42
Number of affected domestic small entities	132	132	132
Number of affected foreign small entities	78	78	78
Total number of affected small entities	210	210	210
Percent of small entities that are domestic	62.9%	62.9%	62.9%
Percent of affected entities considered small	40%	40%	40%
Annualized costs of the alternative to small entities (3%)	$1,550,189.80	$432,613.21	$4,604,033.29
Annualized costs of the alternative to small entities (7%)	$1,733,541.13	$485,100.74	$5,150,432.68
Annualized costs of the alternative per small entity (3%)	$11,743.86	$3,277.37	$34,879.04
Annualized costs of the alternative per small entity (7%)	$13,132.89	$3,675.01	$39,018.43
Mean annual revenue of small entities	$17,200,000	$17,200,000	$17,200,000
Median annual revenue of small entities	$1,200,000	$1,200,000	$1,200,000
Cost of the alternative as a percentage of mean annual revenue (3%)	0.07%	0.02%	0.20%
Cost of the alternative as a percentage of mean annual revenue (7%)	0.08%	0.02%	0.23%
Cost of the alternative as a percentage of median annual revenue (3%)	0.98%	0.27%	2.91%
Cost of the alternative as a percentage of median annual revenue (7%)	1.09%	0.31%	3.25%

4. Extend Submission Period to 2 Years for Streamlined Submissions for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule

With this alternative to the proposed rule, manufacturers of substances that are already in interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule would have up to 2 years (rather than the proposed 1 year) after the publication of the final rule to submit this streamlined submission to FDA. The additional flexibility of this regulatory alternative would decrease costs to affected small manufacturers.

Table 33 summarizes the costs of the proposed rule with an extended submission period to 2 years for streamlined submissions for substances already in interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule for all affected entities. Under this regulatory alternative, we estimate that the annualized costs of the proposed rule are approximately $9.6 million, with a lower bound of approximately $3.7 million and an

upper bound of approximately $23.0 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimated costs are approximately $10.5 million, with a lower bound of approximately $4.0 million and an upper bound of approximately $25.3 million.

Table 33. 10-year Stream, Present Value, and Annualized Costs of the Proposed Rule with 2 Year Extended Submission Period (2024 dollars)

	Primary	Low	High
Year 1 (Reading Costs)	$17,793,212.07	$10,744,500.62	$26,604,101.37
Year 2 (Other One-time Costs)	$45,341,967.74	$ 9,976,962.16	$142,885,646.89
Year 3 (Recurring Costs)	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 4	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 5	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 6	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 7	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 8	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 9	$3,319,279.03	$1,733,353.96	$5,333,363.51
Year 10	$3,319,279.03	$1,733,353.96	$5,333,363.51
Present Value of Costs (3%)	$81,976,900.01	$31,304,938.34	$195,802,093.98
Net present value (7%)	$73,544,510.91	$27,796,271.96	$177,481,999.25
Annualized costs (3%)	**$9,610,194**	**$3,669,894**	**$22,953,979**
Annualized costs (7%)	**$10,471,084**	**$3,957,564**	**$25,269,444**

Table 34 summarizes the costs of the regulatory alternative of extending the submission period to 2 years for streamlined submissions for substances already in interstate commerce under the GRAS provision of section 201(s) of the FD&C Act before the effective date of a final rule for affected small entities. Under this regulatory alternative, we estimate that the annualized costs of the proposed rule to affected small entities is approximately $2.4 million, with a lower bound of approximately $0.9 million and an upper bound of approximately $5.8 million, discounted at 3 percent over 10 years in 2024 dollars. At a 7 percent discount rate, estimated costs are approximately $2.6 million, with a lower bound of approximately $1.0 million and an upper bound of approximately $6.4 million.

We divide annualized costs to small entities by the estimate number of affected small entities (132) to yield per entity costs of approximately $18.3 thousand (= $2.4 million / 132), with a lower bound of $7.0 thousand (= $922.7 thousand / 132) and an upper bound of $43.7 thousand (= $5.8 million / 132), discounted at 3 percent over 10 years. At a 7 percent discount rate, per entity costs are approximately $19.9 thousand (= $2.6 million / 132), with a lower bound of $7.5 thousand ($995.0 thousand / 132) and an upper bound of $48.1 thousand (= $6.4 million / 132).

Table 34. Regulatory Alternative to the Proposed Rule for Affected Small Entities: 2 Year Extended Submission Period (2024 dollars)

	Primary	Low	High
Annualized costs of the alternative to all affected entities (3%)	$9,610,194	$3,669,894	$2,953,979
Annualized costs of the alternative to all affected entities (7%)	$10,471,084	$3,957,564	$25,269,444
Number of affected domestic small entities	132	132	132
Number of affected foreign small entities	78	78	78
Total number of affected small entities	210	210	210
Percent of small entities that are domestic	62.9%	62.9%	62.9%
Percent of affected entities considered small	40%	40%	40%
Annualized costs of the alternative to small entities (3%)	$2,416,277.23	$922,716.15	$5,771,286.07
Annualized costs of the alternative to small entities (7%)	$2,632,729.64	$995,044.61	$6,353,460.16
Annualized costs of the alternative per small entity (3%)	$18,305.13	$6,990.27	$43,721.86
Annualized costs of the alternative per small entity (7%)	$19,944.92	$7,538.22	$48,132.27
Mean annual revenue of small entities	$17,200,000	$17,200,000	$17,200,000
Median annual revenue of small entities	$1,200,000	$1,200,000	$1,200,000
Cost of the alternative as a percentage of mean annual revenue (3%)	0.11%	0.04%	0.25%
Cost of the alternative as a percentage of mean annual revenue (7%)	0.12%	0.04%	0.28%
Cost of the alternative as a percentage of median annual revenue (3%)	1.53%	0.58%	3.64%
Cost of the alternative as a percentage of median annual revenue (7%)	1.66%	0.63%	4.01%

Finally, we estimate the cost savings of the regulatory alternatives to the proposed rule for affected small entities. We estimate the difference between the annualized costs of the proposed rule (Table 28) and each regulatory alternative to yield cost savings. The cost savings of regulatory alternatives to small entities are summarized in Table 35.

For the first regulatory alternative (Extend Submission Period to 3 Years for Streamlined Submissions for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule), estimated cost savings compared to the proposed rule are approximately $425.8 thousand (= $2.64 million - $2.22 million), with a lower bound of approximately $213.2 thousand (= $1.02 million - $815.6 thousand) and an upper bound of approximately $625.5 thousand (= $6.19 million - $5.6 million),

discounted at 3 percent. At a 7 percent discount rate, estimated cost savings are approximately $548.0 thousand (= $2.94 million - $2.4 million), with a lower bound of approximately $261.0 thousand (= $1.13 million - $868.1 thousand) and an upper bound of approximately $899.3 thousand (= $7.0 million - $6.1 million.)

For the second regulatory alternative (Permit Streamlined Submissions for All Substances Purported to be GRAS Under the Conditions of Their Intended Use Under Section 201(s) of the FD&C Act), estimated cost savings compared to the proposed rule are approximately $665.3 thousand (= $2.64 million - $2.0 million), with a lower bound of approximately $383.0 thousand (= $1.03 million - $645.8 thousand) and an upper bound of approximately $961.7 thousand (= $6.2 million - $5.2 million), discounted at 3 percent. At a 7 percent discount rate, estimated cost savings are approximately $665.3 thousand (= $2.64 million - $2.0 million), with a lower bound of approximately $383.0 thousand (= $1.1 million - $485.1 thousand) and an upper bound of approximately $961.7 thousand (= $7.0 million - $6.0 million.)

For the third regulatory alternative (Permit Streamlined Submissions for All Substances Purported to be GRAS Under the Conditions of Their Intended Use Under Section 201(s) of the FD&C Act and Extend Submission Period for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule), estimated cost savings compared to the proposed rule are approximately $1.1 million (= $2.64 million - $1.6 million), with a lower bound of approximately $596.2 thousand (= $1.02 million - $596.2 thousand) and an upper bound of approximately $1.6 million (= $7.0 million - $4.6 million), discounted at 3 percent. At a 7 percent discount rate, estimated cost savings are approximately $1.2 million (= $2.9 million - $1.7 million), with a lower bound of approximately $644.0 thousand (= $1.1 million - $644.0 thousand) and an upper bound of approximately $1.9 million (= $7.0 million - $5.2 million.)

For the fourth regulatory alternative (Extend Submission Period to 2 Years for Streamlined Submissions for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule), estimated cost savings compared to the proposed rule are approximately $225.0 thousand (= $2.64 million - $2.42 million), with a lower bound of approximately $106.1 thousand (= $1.03 million - $922.7 thousand) and an upper bound of approximately $420.0 thousand (= $6.2 million - $5.8 million), discounted at 3 percent. At a 7 percent discount rate, estimated cost savings are approximately $314.1 thousand (= $2.95 million - $2.63 million), with a lower bound of approximately $134.0 thousand (= $1.13 million - $995.0 thousand) and an upper bound of approximately $657.9 thousand (= $7.01 million - $6.35 million).

Table 35. Cost Savings of Regulatory Alternatives to the Proposed Rule for Affected Small Entities (2024 dollars)

	Primary	Low	High
Annualized costs of the proposed rule to small entities, 3%	$2,641,275.82	$1,028,792.54	$6,191,180.43
Annualized costs of the proposed rule to small entities, 7%	$2,946,803.43	$1,129,069.11	$7,011,385.56
Annualized costs of alternative 1, 3%[1]	$2,215,467.99	$815,576.82	$5,565,696.50
Annualized costs of alternative 1, 7%[1]	$2,398,819.32	$868,064.35	$6,112,095.89
Cost savings to small entities of alternative 1, 3%[1]	$425,807.83	$213,215.72	$625,483.93
Cost savings to small entities of alternative 2, 7%[1]	$547,984.11	$261,004.75	$899,289.67
Annualized costs of alternative 2, 3%[2]	$1,975,997.63	$645,828.93	$5,229,517.22
Annualized costs of alternative 2, 7%[2]	$2,281,525.24	$746,105.50	$6,049,722.35
Cost savings to small entities of alternative 2, 3%[2]	$665,278.19	$382,963.61	$961,663.21
Cost savings to small entities of alternative 2, 7%[2]	$665,278.19	$382,963.61	$961,663.21
Annualized costs of alternative 3, 3%[3]	$1,550,189.80	$432,613.21	$4,604,033.29
Annualized costs of alternative 3, 7%[3]	$1,733,541.13	$485,100.74	$5,150,321.68
Cost savings to small entities of alternative 3, 3%[3]	$1,091,086.02	$596,179.33	$1,587,147.14
Cost savings to small entities of alternative 3, 7%[3]	$1,213,262.30	$643,968.36	$1,860,952.88
Annualized costs of alternative 4, 3%[4]	$2,416,277.23	$922,716.15	$5,771,286.07
Annualized costs of alternative 4, 7%[4]	$2,632,729.64	$995,044.61	$6,353,460.16
Cost savings to small entities of alternative 4, 3%[4]	$224,998.59	$106,076.39	$419,894.37
Cost savings to small entities of alternative 4, 7%[4]	$314,073.79	$134,024.50	$657,925.40

Notes: Cost savings are calculated as the difference the baseline annualizes costs of the proposed rule to affected small entities and the annualized costs of regulatory alternatives. [1]Extend Submission Period to 3 Years for Streamlined Submissions for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule; [2]Permit Streamlined Submissions for All Substances Purported to be GRAS Under the Conditions of Their Intended Use Under Section 201(s) of the FD&C Act; [3]Permit Streamlined Submissions for All Substances Purported to be GRAS Under the Conditions of Their Intended Use Under Section 201(s) of the FD&C Act and Extend Submission Period for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule; [4]Extend Submission Period to 2 Years for Streamlined Submissions for Substances Already Introduced Into Interstate Commerce Under the GRAS Provision of Section 201(s) of the FD&C Act Before the Effective Date of a Final Rule .

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