DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use

Docket No. FDA-1975-N-0012 (formerly Docket No. 1975N-0183H)

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. OMB has determined that this final rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because many firms that will be affected by this rule are defined as small businesses, we find that the final rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The

current threshold after adjustment for inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule would result in an expenditure in any one one year that meets or exceeds this amount.

B. Summary of Costs and Benefits

As discussed in the preamble of the final rule, this rule establishes that 19 active ingredients, including triclosan and triclocarban, are not generally recognized as safe and effective and are misbranded for use in over-the-counter (OTC) consumer antiseptic washes. Regulatory action is being deferred on three active ingredients that were included in the consumer antiseptic wash proposed rule: benzalkonium chloride, benzethonium chloride, and chloroxylenol. The costs and benefits of the final rule are summarized in the table below, entitled *Economic Data: Costs and Benefits Statement*. As the table shows, the primary estimated benefits come from reduced exposure to antiseptic active ingredients by 2.2 million pounds per year. We note that triclosan and triclocarban, are the most widely used OTC consumer antiseptic wash active ingredients on the market, based on available data, thus, our analysis focuses on these two products. Using the primary estimates, the combined total benefit consists of a reduction in triclosan exposure by 799,426 pounds per year, and triclocarban exposure by 1.4 million pounds per year. Limitations in the available data characterizing the health effects resulting from widespread long-term exposure to such ingredients prevent us from translating the estimated reduced exposure into monetary equivalents of health effects.

The primary estimate of costs annualized over 10 years is approximately $23.6 million at a 3 percent discount rate and $27.6 million at a 7 percent discount rate. These costs consist of total one-time costs of relabeling and reformulation ranging from $106.3 to $402.8 million. Under the final rule, we estimate that each pound of reduced exposure to antiseptic active ingredients will cost $12.97 to $14.28 at a 3 percent discount rate and $16.36 to $18.02 at a 7 percent discount rate.

Economic Data: Costs and Benefits Statement							
				Units			
Category	Primary Estimate	Low Estimate	High Estimate	Year Dollars	Discount Rate	Period Covered	Notes
Benefits							
Annualized Monetized $millions/year					7%	Annual	
					3%	Annual	
Annualized Quantified	2,197,737	989,856	3,405,619		7%	Annual	Reduced antiseptic active ingredient exposure (in pounds)
	2,197,737	989,856	3,405,619		3%	Annual	
Qualitative							
Costs							
Annualized Monetized $millions/year	27.6	14.1	53.6	2014	7%	Annual	Annualized costs of relabeling and reformulation. Range of estimates captures uncertainty.
	23.6	12.1	45.8	2014	3%	Annual	
Annualized Quantified					7%		
					3%		
Qualitative							
Transfers							
Federal Annualized Monetized $millions/year					7%		None.
					3%		
From/To	From:			To:			
Other Annualized Monetized $millions/year					7%		
					3%		
From/To	From:			To:			
Effects							
State, Local, or Tribal Government: Not applicable							

Small Business	
Annual cost per affected small entity estimated as $0.11-$0.41 million, which will represent 0.28-1.10 percent of annual shipments.	
Wages: No estimated effect	
Growth: No estimated effect	

The full analysis of economic impacts is available in the docket for this final rule (Ref. [FDA-1975-N-0012]) and at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.

C. Comments on the Preliminary Regulatory Impact Analysis and Our Responses

FDA's proposed rule "Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record" was published on December 17, 2013 (78 FR 76444) (2013 Consumer Wash PR), and its comment period ended June 16, 2014. We had prepared a full "Preliminary Regulatory Impact Analysis" in connection with the 2013 Consumer Wash PR. In the following paragraphs, we describe and respond to comments we received on our analysis of the impacts presented in those sections. We received comments from only one commenter that touched on the preliminary regulatory impact analysis. We have numbered each comment from the commenter to help distinguish between the different comment themes. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value, or the order in which it was discussed by the commenter.

(Comment 1) One comment requested that two additional regulatory alternatives be considered in the Regulatory Flexibility Analysis: no action and differentiated requirements (i.e. different requirements for different sized companies, or different active ingredients).

(Response 1) By definition "no action" is simply the status quo or the baseline. Each regulatory option or alternative must be compared to the baseline in which there is no regulatory action. Hence, there would be no associated costs or benefits in the case of "no action." In the section called "Small Entity Effects," we do examine the effect of two regulatory alternatives that would reduce the burden for small businesses. Additionally, given that the majority of the costs are driven by one active ingredient, creating different requirements for different active ingredients would not provide much benefit for companies.

(Comment 2) One comment expressed concerns that there would be costs associated with increased illnesses if the affected products were to come off the market. Specifically, the comment used expert elicitation to estimate the cost to the health care system of non-avoided gastrointestinal illnesses if antibacterial consumer washes were to come off the market. The commenter's analysis estimated this potential cost at $38 billion.

(Response 2) We disagree that there would be an increase in illnesses associated with the implementation of this rule. Products containing triclosan and triclocarban have not been shown to be more effective than non-antibacterial soap in preventing illnesses. Therefore, removing them from the market should not cause an increase in illness. If there were sufficient evidence to demonstrate that such products were safe and more effective than non-antibacterial soaps, they would continue to stay on the market.

(Comment 3) One comment stated that the adjusted estimate of total Universal Product Codes (UPCs) to account for underrepresentation in the Nielsen data was too high and asserted that the regulatory impact analysis should have used the adjustment factor for the over-the-counter (OTC) drug market rather than the adjustment factor for the dietary supplement market.

(Response 3) The preliminary regulatory impact analysis uses an adjustment factor as a multiplier for the initial estimate of number of UPCs from the Nielsen data to estimate the total size of the consumer antiseptic washes market affected by the rule. Because we did not have access to an adjustment factor that was specific to this market, we used the adjustment factor for the dietary supplement market for reasons outlined in the analysis. The dietary supplement adjustment factor was used to estimate the number of total UPCs primarily because we expect that the ratio of total market sales to sales covered by Nielsen for dietary supplements was similar to that of consumer antiseptic hand wash products. Also, the two products are often sold in a similar range of retailers, making them closely comparable products in terms of their availability and market. Additionally, in the context of the RTI Labeling Cost Model, the distribution channels of products used to calculate the dietary supplement adjustment factor in the model are more similar to those used in consumer antiseptic wash products than those for the OTC adjustment factor. We believe that using the lower OTC adjustment factor may lead to an underestimation of the costs associated with relabeling and reformulating, and therefore we continue to use the dietary supplement adjustment factor.

(Comment 4) One comment stated that the analysis did not consider impacts to institutional sales.

(Response 4) It is true that the AC Nielsen data does not include institutional sales. However, it is the total number of distinct products and product-package combinations affected by the rule, whether they are sold to institutions or directly to consumers, that matters for determining the costs and benefits. When applying the same adjustment factor used to account for additional products sold outside of Nielsen retail channels (see Comment 2) to dollar sales value, we find that the total dollar sales matches other industry reports for the total size of the market, which includes institutional sales. Because the adjusted dollar sales figures are approximately as large as the total dollar sales for the total market size, the total number of UPCs should account for both household and institutional sales. Especially given that institutional sales, while perhaps accounting for a large proportion of total sales in the market, have fewer available products, leading to lower total costs for relabeling and reformulating, the main drivers of the costs of this rule.

(Comment 5) One comment stated that dollar amounts, rather than volume estimates, should be used to estimate the benefits of the rule.

(Response 5) While being able to estimate the monetary benefits of the rule would be ideal, it is impossible to do so with the scientific data currently available. Therefore, the alternative measure of volume of active ingredients was used as a proxy. Executive Order 12866 allows for non-monetized costs or benefits, recognizing that it is sometimes impossible to monetize an outcome.

(Comment 6) One comment provided alternative numbers for the relabeling costs. The commenter used the information from one member firm to estimate that total relabeling

costs would be $182 million (while the consumer antiseptic wash proposed rule RIA estimated the costs to be $88 million).

(Response 6) The alternative relabeling cost numbers were not added to the analysis because they came from the experiences of only one firm, which may or may not have been representative of the average firm in the market.

(Comment 7) One comment requested that we reevaluate the reformulation costs, suggesting that they were higher than estimated in the consumer antiseptic wash proposed rule RIA. The commenter estimated that total reformulation costs could cost between $52 million to $1 billion, with an average cost per product of $1 million. The comment provided an alternative cost based on an estimate from a single firm. (The consumer antiseptic wash proposed rule RIA estimated total reformulation costs at between $70 million to $281 million.)

(Response 7) We cannot be sure that this firm is representative of the average firm in the market. We believe that our reformulation costs estimate is representative of the average firm in the industry and continue to use those estimates in the analysis.

(Comment 8) One comment questioned the accuracy of the cost estimates for conducting safety and efficacy trials. The comment asserted that the cost of these studies could be higher, but did not provide a data source or information that would allow us to assess the accuracy of the estimates.

(Response 8) We included the discussion regarding the costs of conducting safety and efficacy trials to elucidate potentials costs should a manufacturer decide to pursue a new drug application (NDA) for triclosan or triclocarban. These estimates do not factor into

the final estimates of the costs of the rule, and were only meant to provide an overview of potential additional costs.

(Comment 9) A number of commenters supported the removal of triclosan from consumer use due to concerns that the chemical may be negatively affecting the water supply, waterways, and aquatic life, and this might be an important corollary benefit to the rule.

(Response 9) We acknowledge that these may be important benefits of the rule, but we are unable to quantify (other than providing a volume reduction estimate) or monetize these possible benefits.

D. Summary of Changes

While we did not make changes to the regulatory impact analysis that were directly related to the public comments that we received on the 2013 Consumer Wash PR, FDA has considered public comments submitted in drafting the final rule. The central difference between the final rule and the proposed rule is that regulatory action is being deferred on three active ingredients: benzalkonium chloride, benzethonium chloride, and chloroxylenol. The preliminary RIA estimated the costs and benefits associated with the rule including products that utilized these three active ingredients. In this final RIA, we removed the estimates of these three ingredients from both costs and benefits. However, these three products made up only 6% of the total liquid and bar antiseptic UPCs that were estimated in the rule. The update of removing them from the analysis therefore contributed very little change to the overall estimates of the final RIA.

Additionally, although an updated labeling cost model was used to estimate this section of the costs, the changes due to this update were very minor. The requirements for

conducting non-clinical safety studies for an NDA submission were also changed between the proposed and final rule. While these costs do not directly enter costs estimated in the RIA, updated estimates of these potential costs are provided. Lastly, we updated values for inflation, where possible, into 2014 dollars.

II. Regulatory Impact Analysis

A. Background

Antiseptic washes (or more commonly known as "antibacterial soaps") are intended to be used with water to cleanse hands or the entire body. They are marketed in several formulations: liquids, foams, gels, and bars. While antibacterial soaps were introduced over fifty years ago, more recently their use expanded rapidly beyond the hospital and institutional settings. A physician-performed survey of national chain, regional grocery, and internet stores found that 76 percent of liquid soaps and 29 percent of bar soaps that were marketed contained the active ingredients triclosan or triclocarban (Ref. R1).

Along with the proliferation of antibacterial soaps, other personal care products containing antiseptic active ingredients have become much more prevalent for everyday use. In the mid-1990s, the number of antibacterial products available to the general population was estimated to be only a few dozen, but within a few years grew quickly to over 700 (Ref. R2). For example, many personal hygiene products contain the antiseptic active ingredient triclosan (Refs. R4, R5, R6). In addition to FDA-regulated uses, some antiseptic agents, such as triclosan, are also registered with the Environmental Protection Agency (EPA) as pesticides and are often applied to industrial equipment, textiles, and plastics as material preservatives (Ref. R4).

Since the proposal of the generally recognized as safe and effective (GRAS/E) conditions for OTC antiseptic active ingredients in the 1994 tentative final monograph or proposed rule (the 1994 TFM) (59 FR 31402), there have been several important scientific developments that affect the safety evaluation for these products. Because the

rapid expansion of antiseptic active ingredients in a variety of settings was not anticipated, the proposed conditions for GRAS/E in the 1994 TFM did not account for the potential health risks that could result from widespread, long-term exposure. Likewise, considerations for effectiveness requirements were not made in the context of widespread, long-term exposure, in settings where the risk of infection is relatively low.

In recent years, the scientific knowledge regarding the impact of widespread antiseptic use has evolved. Antibacterial soaps may be used on a daily basis by consumers over the course of a lifetime. Potential damage to human health, resulting from use of consumer antiseptic washes, may occur due to extended exposure to antiseptic active ingredients and may be difficult to link to a particular product.

Associated with the overall upward marketing trend of products (including products not regulated by FDA) containing antiseptic active ingredients, new studies indicate that there has been an increase in the level of aggregate exposure to certain antiseptic active ingredients. In contrast to exposure levels thought to exist when the 1994 TFM was proposed, systemic exposure to antiseptic active ingredients is much higher today. Only recently, the National Health and Nutrition Examination Survey (NHANES) began collecting bio-monitoring data on triclosan to quantify aggregate exposure. In a U.S. representative subsample of NHANES 2003-2004, researchers found measurable urinary triclosan levels which, while not exceeding toxic thresholds, reflect exposure in 75 percent of the population (Refs. R7, R8, R9). The amount of triclosan found in urine samples collected from 2005 to 2006 was 42 percent higher than the amount found in the 2003-2004 samples (Ref. R8). In the most recent assessment,

triclosan has been found at relatively consistent levels in urine samples collected from a since sampling began in 2003 (Ref. R10).

While the evidence associating long-term exposure to washes containing antiseptic active ingredients with adverse health effects is inconclusive at best, evaluations by FDA and the Nonprescription Drugs Advisory Committee identified several potential and hypothetical risks (Ref. R11). Specifically, certain antiseptic active ingredients may show hormonal effects or contribute to the development of bacterial resistance. Some laboratory studies suggest that triclosan and other antiseptic active ingredients may contribute to antibacterial resistance to clinically important antibiotics (Ref. R12).

Some animal studies also suggest that consumer antiseptic active ingredients, such as triclosan and triclocarban, could potentially be hormonally active (Refs. R13 through R22). A hormonally active compound is a chemical that interferes with the production, release, transport, metabolism, binding, activity, or elimination of natural hormones, which can potentially lead to adverse effects on the reproductive system and development (Ref. R23). Certain subpopulations, including children and developing fetuses, are potentially more sensitive to exposure and are potentially more susceptible to adverse health effects. Hormonal effects, in general, may be involved in a wide-range of adverse health effects, including severe endpoints such as breast cancer, endometrial cancer, testicular cancer, ovarian cancer, prostate cancer, endometriosis, infertility, thyroid disorders, and male reproductive tract abnormalities (Refs. R24, R25). We note, however, that these specific outcomes represent more extreme toxic hormonal effects and that the majority of antiseptic active ingredients have never been evaluated for these

specific adverse health effects. In addition, there is no data from laboratory animal studies or human studies that suggest these severe endpoints as potential outcomes of exposure to antiseptic active ingredients.

Furthermore, FDA's review of the available published literature and data determined that there is insufficient evidence to demonstrate a health benefit from use of antibacterial soap over non-antibacterial soap and water in reducing the incidence of disease in the consumer setting. The previously proposed effectiveness standards in the 1994 TFM were intended to demonstrate efficacy in high-risk settings for healthcare uses, based on the assumption that reductions in bacteria left on skin treated with an antiseptic active ingredient correspond to reductions in infection rates or the transmission of disease. Because there is relatively low risk for infection in the consumer setting, the use of surrogate endpoints alone do not show there is a clinically meaningful benefit from the use of antibacterial soaps compared to non-antibacterial soap and water. Taken together, these recent scientific developments have prompted the re-evaluation of safety and effectiveness requirements to take into account how antibacterial soaps are currently used by the general consumer population.

B. Need for Regulation

This regulation addresses the market failure arising from inadequate information on the potential health risks associated with daily use of antibacterial soaps and the effectiveness of these products relative to non-antibacterial soap and water. As discussed in previous sections, most antiseptic active ingredients have not been shown to be safe for this use, not effective for this use, or both. This final rule will respond to our obligation to ensure that drugs are both safe and effective (21 CFR 330.10(a)(4)).

Consumer wash products containing antiseptic active ingredients differentiate themselves from non-antibacterial soaps by making antibacterial claims on their labels. The purpose behind the distinctive labeling as an antiseptic drug is to convey information about an added health benefit relative to non-antibacterial soap and water. In the consumer setting antibacterial soaps have not been shown to reduce the incidence of infection or disease and there are unresolved safety considerations regarding long-term daily use, as discussed in previous sections.

Despite the lack of evidence demonstrating safety and effectiveness of antibacterial soaps in the consumer setting, demand for these products has continued to grow. The level of information currently utilized by consumers may be less than optimal because of consumer perceptions that soaps labeled as antibacterial may be superior to non-antibacterial soaps (Ref. R26). As long as the private marginal cost of gathering safety and effectiveness information exceeds the private marginal benefit, there is insufficient incentive for producers or any particular entity to undertake studies in the absence of regulation. In this case, due to market failure arising from inadequate information, manufacturers may behave strategically by making antibacterial claims in order to avoid losing sales to their competitors.[1] Because it would be time-consuming and resource intensive to generate the evidence needed to make informed choices, private market incentives are insufficient to provide adequate assurances of safety and effectiveness. Under these circumstances, where it is difficult for consumers to evaluate

[1] Such a situation can be characterized as a prisoner's dilemma, in which each decision-making party, when acting independently, has an incentive to make choices that harm other parties, thus leading to an outcome that is suboptimal for all the decision-makers.

complex information about products or services, regulation is needed to ensure that minimum standards are met.

A body of research has established that for many environmental toxicants, there can be a long latency period between exposure and any potential adverse health effects. Unintended negative effects on public health as a result of widespread use of antiseptic active ingredients, such as potential bacterial resistance, could also impose costs on society that are most likely external to the production and consumption decisions in the current market for consumer antiseptic wash, which only account for private costs and private benefits. These potential negative externalities represent an additional well-established market failure that provides an economic rationale for regulation. An externality is defined as a cost or benefit resulting from an action that is borne or received by parties not directly involved. In the case of widespread antiseptic active ingredient use, a negative externality may arise because some of the costs—for example, the costs associated with a possible increased prevalence of bacterial resistant infections—are external to those who may benefit from their use.

C. Purpose of this Rule

With the exception of three consumer antiseptic wash active ingredients – benzalkonium chloride, benzethonium chloride, and chloroxylenol – for which rulemaking has been deferred, this rulemaking finalizes the nonmonograph status of the remaining 19 active ingredients intended for use in consumer antiseptic washes identified in the 2013 Consumer Wash PR (78 FR 76444). These 19 active ingredients have been found not to have sufficient data to support monograph conditions, and therefore no

monograph is being established at this time. These products are thus not GRAS/E and are misbranded (nonmonograph).

The final rule requires all consumer washes containing any antiseptic active ingredient to provide a clinically meaningful benefit over non-antibacterial soap and water. Those products that have not been shown through clinical outcome studies to reduce disease transmission or the number of infections in a population compared to non-antibacterial soap and water are not be considered GRAE. The rule also requires those products to demonstrate safety under revised standards for GRAS consideration. For each active ingredient, a GRAS determination must be supported by all of the following studies: human pharmacokinetic studies; absorption, distribution, metabolism, and excretion (ADME) studies in animals, toxicokinetic, reproductive toxicity, and carcinogenicity studies in animals; data to characterize potential hormonal effects; and an evaluation of the potential to cause bacterial resistance.

Based on the available data and studies, FDA finds that the 19 active ingredients, including triclosan and triclocarban, intended for use in OTC consumer antiseptic washes listed in this final rule fail to meet the standards for GRAS/E classification as proposed in the 1994 TFM and the 2013 Consumer Wash PR (78 FR 76444). Continued marketing of consumer antiseptic washes containing any of these nineteen active ingredients requires that manufacturers first obtain an approved new drug application (NDA). Alternatively, current manufacturers of consumer antiseptic washes can comply with this final rule by reformulating those products to remove the antiseptic active ingredients and marketing them as non-antibacterial soaps.

D. Baseline Conditions

The effects of the final rule are estimated relative to a baseline. The baseline represents the state of the world in absence of the regulatory action. In our analysis, we describe baseline conditions in terms of the projected market for consumer antiseptic wash products and aggregate exposure to antiseptic active ingredients linked to consumer antiseptic washes. It would be a reasonable assumption that if there were no changes to the monograph conditions for OTC consumer antiseptic wash products, future use of consumer antiseptic wash products and exposure to antiseptic active ingredients could be approximated by the levels estimated in this rule.

For this rule, we estimate a baseline using data from 2009 to represent the state of the world without the rule. This ensures that all changes in the market that occurred due to the publication of the proposed rule, in anticipation of the final rule, are captured as costs.[2] However, we acknowledge that there are numerous important factors that may have acted on the consumer antiseptic wash market outside of this rule between this time and when the final rule was published.

While estimating how these confounding factors have affected the antiseptic market would be a desirable addition to this regulatory impact analysis, disentangling the effects of the rule with those outside of the rule is not feasible. These other factors may include: changing consumer tastes away from antiseptic ingredients in wash products, consumer awareness that efficacy has not been established, and state legislation

[2] It appears that many manufacturers have reformulated and relabeled their products to remove antiseptic ingredients between the time the data used in this rule was collected (2009), and the time this final rule was published (2016).

prohibiting the sale of antiseptic ingredients in washes (such as the triclosan ban in Minnesota, which was signed in 2014, and will enter into effect in 2017).[3]

1. Active Ingredients in Currently Marketed OTC Consumer Antiseptic Washes

This final rule will classify all nineteen of the listed antiseptic active ingredients for use in OTC consumer hand or body washes as nonmonograph. However, our analysis of the current market finds that the majority of the affected products contain either triclosan or triclocarban. In determining the distribution of antiseptic active ingredients across affected products, we used data from A.C. Nielsen, which provides nationally representative sales information from drugstores, supermarkets, and mass merchandisers (excluding Walmart). At the time of this analysis, the most recently available data reflect sales of hand and body wash products for the last 52 weeks ending on September 5, 2009. While the A.C. Nielsen data does not include information on active ingredients contained in products, we are able to identify antiseptic soaps and body washes from those products that include "antibacterial" in the name or part of the product description. Additional information was gathered from extensive internet searches to determine active ingredients associated with specific universal product codes (UPCs), representing individual products, packages, and sizes. For most nationally branded products, ingredient listings were available on the manufacturer's or other online retailer's website.

Based on a search of 725 individual UPCs, categorized as antibacterial hand or body wash in A.C. Nielsen, we identified active ingredients for approximately 40 percent

[3] Although less likely, it is possible that, in the absence of FDA activity, the number and consumption of consumer antiseptic washes would have increased, which would make the results we present an underestimate.

of 585 antibacterial liquid, gel, and foam soaps and 72 percent of 140 antibacterial bar soaps (including active ingredients other than triclosan and triclocarban). A summary of the active ingredients found in our survey of antibacterial soaps is reported in Table E1. Approximately 93 percent of antibacterial liquid soaps contained triclosan as the active ingredient and 85 percent of antibacterial bar soaps contained triclocarban as the active ingredient. As a percentage of annual total equivalent (16 oz.) unit sales, we estimate those containing triclosan constitute 99.8 percent of antibacterial liquid soap sales and those containing triclocarban constitute 99 percent of antibacterial bar soap sales. The survey suggests chloroxylenol, benzalkonium chloride, phenoxyethanol, and a few natural ingredients, such as tea tree oil, are far less common than triclosan and triclocarban as active ingredients in consumer antibacterial soaps.

Table E1. Estimated Distribution of Active Ingredients in Consumer Antiseptic Washes by Product Form

	Liquid, Gel, and Foam		Bar	
Antiseptic Active Ingredient	Percent of UPCs	Percent of Total Equivalent (16 oz.) Units Sold	Percent of UPCs	Percent of Total Equivalent (16 oz.) Units Sold
Triclosan	93.1	99.8	7.9	0.98
Triclocarban	0	0	85.1	99.01
Chloroxylenol	1.7	0.01	4.0	0.01
Benzalkonium Chloride	0.4	0.0	0	0
Phenoxyethanol	0.4	0	0	0
"Natural" Ingredients	3.9	0.2	3.0	0.002
Total	100	100	100	100

Note: Numbers may not sum due to rounding.

2. Number of Affected Products in the Current Market for OTC Consumer Antiseptic Washes

For this analysis, we will only use the UPCs containing triclosan and triclocarban, because these two active ingredients were the only two of the nineteen affected active

ingredients that we were able to identify in our dataset. According to the 2009 A.C. Nielsen sales data, total sales for our sample of 675 affected UPCs (products containing either triclosan or triclocarban as an active ingredient) were $309 million (in 2014 dollars). However, there are likely affected products that we were unable to identify as antibacterial and affected products not captured in the A.C. Nielsen data, such as sales from warehouses, internet, and other specialty outlets. To account for underrepresentation as recommended and adopted in the RTI Labeling Cost Model Report for this product category, we apply an adjustment factor of 3.1 to the raw UPC counts, formulas, annual unit sales, and annual dollar sales to obtain estimates representing the entire market of affected products (Ref. R3). The adjustment factor is based on the assumption that consumer antibacterial soaps are sold in a similar range of outlets and retailers as dietary supplements, for which sales represented by A.C. Nielsen was estimated as 32.5 percent of total sales from all sources. The dietary supplement adjustment factor provides a reasonable approximation because our adjusted estimates of sales are similar in order of magnitude to industry estimates. (Refs. R27 and R28)

Correcting for underrepresentation in our base sample, we estimate there are approximately 2,100 affected UPCs with total annual sales of approximately $960 million (in 2014 dollars) in the current market for OTC consumer antiseptic washes. Table E2 shows the estimated size of the affected OTC market for consumer antibacterial soaps assuming the distribution of product characteristics in the base sample is proportional to that of the population of the affected products.

Table E2. Estimated Total Number of Affected Products

Antiseptic Washes by Dosage Form	Number of UPCs	Total Dollar Sales (in millions) for 52 weeks Ending in September 5, 2009 (in 2014 dollars)
Liquid, Gel, and Foam	1,690	$612
Bar	403	$348
Total	2,093	$960

3. Aggregate Production Volume of Antiseptic Active Ingredients

We lack the data needed to quantify the relationship between exposure from consumer antiseptic wash use and potential adverse health outcomes. Furthermore, we lack certainty regarding the relationship between exposure and adverse health outcomes.

Without such data, we cannot estimate a baseline level of risk associated with consumer antiseptic use. Instead, we estimate production volume of the corresponding antiseptic active ingredients as an intermediate measure of baseline risk resulting from consumer antibacterial soap use. Estimated ranges for the annual volume of antiseptic active ingredients produced are based on data from EPA's Inventory Update Reporting (IUR) program and represent production volumes for all uses.

The IUR program, which began in 1986, requires manufacturers and importers to report annual production amounts of chemical substances exceeding a certain threshold at a particular site. The original program set the trigger reporting amount at 10,000 pounds and required reports every four years. New regulations implemented in 2006 raised the threshold to 25,000 pounds and lengthened the reporting intervals to every five years. These data may underestimate actual total production of certain chemicals if there are a substantial number of sites with production or import volumes below the reporting threshold.

We were able to find estimates on aggregate production volumes for both triclosan and triclocarban in the IUR database. The estimated ranges of production are reported in Table E3.

According to the publicly available data, the range for aggregate production volume of triclosan was between 1 and 10 million pounds in 1998, while no reports were provided in 2002. Aggregate production volume of triclocarban was between 0.5 and 1 million pounds in 1998, increasing to between 1 and 10 million pounds in 2002. The most recently available data report that aggregate national production volume of triclocarban was less than 500,000 pounds. No reports were provided for triclosan in 2006. The absence of reports in certain years may reflect a change in production or import patterns rather than an overall decline in actual total production and imported volume. If a substantially large number of sites produce or import amounts below the reporting threshold, we may underestimate actual total production and import volumes.

Table E3. Aggregate Production Volume Range in Pounds

Chemical	CAS No.	1986	1990	1994	1998	2002	2006
Triclosan	3380-34-5	10K - 500K	10K - 500K	>500K - 1M	>1M - 10M	No Reports	No Reports
Triclocarban	101-20-2	10K - 500K	>1M - 10M	>1M - 10M	>500K - 1M	>1M - 10M	< 500K

Source: EPA Inventory Update Reporting Data

To our knowledge these data represent the best publicly available information characterizing aggregate production volume of the affected active ingredients, but we recognize several limitations. Because production data are not tracked systematically elsewhere, it is not possible for FDA to estimate the magnitude of unreported production

and imported amounts. Furthermore, the IUR data lack specific detail on end-uses of manufactured and imported chemicals. From these data alone, we are unable to ascertain the share of the reported amounts attributable to consumer antiseptic wash uses.

Defining usage more broadly, there is a general consensus that, although antiseptic active ingredients fall under both FDA and EPA jurisdiction, most of these chemicals are primarily used in FDA-regulated products (Ref. R4). Specifically, over 95 percent of the uses of triclosan, the most common antiseptic active ingredient, are in consumer products that are washed down the drain (Refs. R6, R29). Based on the concentration of antimicrobials found in wastewater systems between 2002 and 2004, it was estimated that at least 300,000 kg (or 661,387 pounds) of triclosan per year and at least 330,000 kg (or 727,526 pounds) of triclocarban per year are used in personal care products (Ref. R30).

For comparison, we also reviewed the available information quantifying the extent of antiseptic active ingredient use in other countries. In its assessment of triclosan uses in the E.U., the Scientific Committee on Consumer Products (SCCP) reports patterns similar to the U.S. The total quantity of triclosan used was approximately 450 tons (or 992,080 pounds) in 2006, with 85 percent used in personal care products, 5 percent in textiles, and 10 percent in plastics and food contact materials (Ref. R31). We lack data characterizing the patterns and extent of use regarding the other antiseptic active ingredient in non-personal care products.

4. Antiseptic Active Ingredient Usage in Consumer Antibacterial Soaps

To obtain baseline estimates of the annual amount of antiseptic active ingredients used specifically for marketed products affected by this rule, we begin by distributing our estimated total annual equivalent (16 oz.) unit sales of antibacterial liquid and bar soaps proportionally across the distribution of identified antiseptic active ingredients. Note that we collectively refer to liquid, gel, and foam dosage forms as liquid. Table E4 shows the estimated annual consumption of antibacterial liquid and bar soaps, expressed in common units and disaggregated by antiseptic active ingredient.

Table E4. Estimated Annual Consumption of Antibacterial Liquid and Bar Soaps

Antiseptic Active Ingredient	Total Equivalent Unit (16 oz.) Sales for 52 weeks Ending in September 5, 2009	
	Liquid	Bar
Triclosan	277,000,000	1,000,000
Triclocarban	0	140,000,000
Total	277,000,000	141,000,000

By standardizing sales units, we can approximate the equivalent annual consumption of antibacterial soaps, in which liquid dosage forms are expressed in volume (liters) and bars are expressed in weight (pounds). We estimate annual consumption of liquid soap containing triclosan to be approximately 131 million liters (277.0 million 16 oz. units x 0.473 liters per 16 oz.) and bar soaps containing triclocarban to be approximately 140 million pounds. Table E5 shows the full set of estimated annual soap consumption for each category of antiseptic active ingredient.

Table E5. Estimated Annual Liquid and Bar Antibacterial Soap Consumption

Antiseptic Active Ingredient	Estimated Annual Consumption of Antibacterial Soaps by Dosage Form (in liters or pounds)	
	Liquid (in liters)	Bar (in pounds)
Triclosan	131,000,000	1,000,000
Triclocarban	0	140,000,000

Total	131,000,000	141,000,000

The next step in translating consumption of antibacterial soaps into annual usage of antiseptic active ingredients requires estimating concentration levels in marketed products. Combining published estimates along with data from FDA's Drug Listing system, we estimate the concentration level range for each identified antiseptic active ingredient. Concentration is expressed as weight per unit of volume (w/v) for liquid soaps and weight per unit of weight (w/w) for bar soaps. The concentration level of triclosan typically found in consumer antibacterial liquid soaps ranges from 0.1 percent (or 0.001 g/mL) to approximately 0.5 percent (or 0.005 g/mL) (Ref. R9). We assume that the concentration level of triclosan found in bar soaps falls within a similar range as liquid soaps. Triclocarban, however, is an antiseptic active ingredient used in bar soaps only, and in concentration levels usually between 0.5 percent (or 0.005 g/g) and 1.5 percent (or 0.015 g/g) (Ref. R32). In Table E6, we show a summary of the ranges and midpoint between the low and high estimates of antiseptic active ingredient concentration levels identified in marketed consumer antibacterial soaps, as well as the marketed dosage forms associated with each ingredient found in our analysis.

Table E6. Range of Estimates for Antiseptic Active Ingredient Concentration Levels

Antiseptic Active Ingredient	Estimated Concentration Level (in w/v or w/w)			Dosage Form Marketed	
	Low	Midpoint	High	Liquid	Bar
Triclosan	0.1%	0.3%	0.5%	X	X
Triclocarban	0.5%	1.0%	1.5%		X

Finally, to derive annual usage of antiseptic active ingredients linked to consumer antibacterial soaps, we multiply the estimated concentration level for each active

ingredient by the corresponding annual consumption (measured in volume or weight) of antibacterial soap. For example, if a 16-oz. (or 473.18 mL) package of liquid soap contains a triclosan concentration of 0.3 percent, we estimate approximately 1.3 g (or 473.18 mL x 0.003 g/mL) of triclosan by weight is used in that product. Aggregating the estimated antiseptic active ingredient usage derived from both dosage forms yields the total annual usage from consumer antibacterial soaps as reported in Table E7. We express these amounts in pounds per year to facilitate comparison with EPA's IUR data on aggregate antiseptic active ingredient production from all uses.

With a kilogram equivalent to approximately 2.2 pounds, we estimate that the annual usage of triclosan ranges from 290,000 to 1.3 million pounds with a midpoint estimate of 799,426 pounds per year, and triclocarban usage ranges from 699,156 to 2.1 million with a midpoint estimate of 1.4 million pounds per year. The combined usage of these antiseptic active ingredients from consumer antiseptic washes ranges from 989,856 to 3.4 million, with a midpoint estimate of 2.2 million pounds per year. For antiseptic active ingredients reported to EPA, the estimated usage from consumer antiseptic washes fall within the range of previously reported amounts of aggregate production.

Table E7. Estimated Annual Usage of Antiseptic Active Ingredients in Consumer Soaps and Washes

Antiseptic Active Ingredient	Estimated Usage of Antiseptic Active Ingredient in Consumer Antibacterial Soaps (in pounds per year)		
	Low	Midpoint	High
Triclosan	290,700	799,426	1,308,152
Triclocarban	699,156	1,398,311	2,097,467
Total	989,856	2,197,737	3,405,619

E. Benefits of the Rule

This final rule prevents continued marketing of products containing consumer antiseptic wash active ingredients that have not been demonstrated to be GRAS/E as consumer antiseptic washes without an approved NDA. The primary benefits of this market change will be the value of any resulting health improvements.[4] New data suggests potential risks from long-term exposure to washes containing antiseptic active ingredients, but at this time the data is not conclusive with regard to specific adverse health effects. Quantifying the benefits of health improvements typically requires identification of specific physical endpoints, a dose-response analysis, exposure analysis, and risk characterization. In characterizing risk, data from the dose-response and exposure analyses are integrated to estimate the expected level of risk posed in the particular scenario being examined. The change in risk associated with this rule will come from the effects of the reduction in exposure to products not shown to be GRAS/E (assuming the manufacturers of these products do not obtain approval under an NDA).

It is difficult to quantify the value of a health risk reduction because we do not have conclusive data on the particular adverse health effects caused by the widespread use of consumer antiseptic active ingredients. As an intermediate measure, however, we estimate the reduction in exposure to certain antiseptic active ingredients found in consumer antiseptic washes. The benefit resulting from the rule will be the reduction in the potential risks (related to both safety and efficacy) associated with widespread use of antiseptic active ingredients in consumer washes. If the level of exposure to consumer

[4] Under the scenario in which consumers washing with antibacterial soaps use less effective hand-washing practices because they erroneously believe that antimicrobial agents provide an added benefit, it is theoretically possible that this rule could generate health benefits in the form of reduced infections if it leads to better hygiene practices. However, we do not have any evidence to address these potential effects.

antiseptic active ingredients is correlated with risks to public health discussed in previous sections, the potential public health benefit of the rule will be the value of avoided health damages as a result of reduced exposure to potentially harmful ingredients found in consumer antiseptic washes.

While we cannot estimate the potential reductions in adverse health outcomes, any change away from the widespread use of antiseptic active ingredients should reduce any risk associated with exposure to those ingredients, resulting in positive public health benefits. Using the midpoint estimates of antiseptic active ingredient usage from consumer antiseptic washes to proxy for exposure, we estimate combined antiseptic active ingredient exposure could be reduced by 2.2 million pounds per year; the combined total consists of a reduction in triclosan exposure by 799,426 pounds per year, and triclocarban exposure by 1.4 million pounds per year.[5]

F. Costs of the Final Rule

The costs of the rule are determined by how manufacturers react to the nonmonograph status of the nineteen consumer antiseptic ingredients. We expect manufacturers, distributors, relabelers, and repackers of consumer antiseptic wash products may react in two ways, each associated with different costs. In response to this rule, it is plausible that firms could reformulate and relabel the affected products as non-antimicrobial soap by removing the antiseptic active ingredient and relabeling or obtain an approved new drug application (NDA) to continue marketing for consumer antiseptic

[5] To put the reduction of antiseptic ingredients into perspective, we estimate that approximately 30 million pounds of antimicrobial active ingredients per year are sold for use in food-producing animals and over 7 million pounds of antibiotics per year are sold for human use (Refs. R32 and R33). Considering only uses that we can quantify, antiseptic active ingredients in consumer washes contribute roughly 3 to 8 percent [= 1/(30+7+1) to 3/(30+7+3)] of overall usage of antimicrobials.

wash use, which will require conducting safety and efficacy testing. The overall costs and potential health effects generated by this rule will depend both on how manufacturers choose among these two options to comply and how consumers will react to those changes in marketed products. The possible reactions by any individual manufacturer, and the private costs and benefits experienced by the manufacturer as a direct result of that reaction (as opposed to indirect impacts resulting from rule-induced changes in the market as a whole), are presented in Table E8; however, we believe that the last two relabeling scenarios are unlikely to occur. Also appearing in Table E8 are the implications for consumers of the various potential manufacturer reactions.

Table E8. Manufacturer Potential Reactions to the Rule, Associated Private Benefits and Costs (Independent of Potential Offsetting Replacement Revenue*), and Implications for Consumers

Potential Reaction to the Rule	Private Benefits to the Manufacturer	Private Costs to the Manufacturer	Implications for Consumers
Relabel and reformulate product	- Ongoing cost savings due to discontinued use of antimicrobial ingredients	- Relabeling costs - Potential for reduced sales and thus reduced profit due to loss of "antibacterial" claim in marketing * - Upfront reformulation costs - Increased use of other ingredients to replace antimicrobial agents	-Exposure to active ingredients reduced by the amount currently used in reformulated products (i.e., if all manufacturers reformulated their products, estimates in Benefits section will be achieved).
Discontinue product		- Reduced sales revenue and thus reduced profit *	-Exposure to active ingredients reduced by the amount currently used in discontinued products (i.e., if all manufacturers discontinued their products, estimates in Benefits section will be achieved).
Relabel product as cosmetic soap, without reformulation		- Relabeling costs - Potential for reduced sales and thus reduced profit due to loss of "antibacterial" claim in marketing *	- Estimates in Benefits section overstate reduction in exposure brought about by the rule by the amount of active ingredients in relabeled products.

Relabel product as health care antiseptic, without reformulation		- Relabeling costs - Potential reduced sales and reduced profit due to unknown consumer reaction to "health care" label * - Potential need to relabel again or reformulate if health care antiseptic provisions of 1994 TFM are finalized as proposed	- Estimates in Benefits section likely overstate reduction in exposure brought about by the rule by the amount of active ingredients in relabeled products.

* Although individual manufacturers may experience reduced sales as a result of relabeling or discontinuing their products, FDA has not found evidence to suggest that removal of antibacterial claims will decrease sales (and thus profits) in the soap market as a whole. Instead, we expect sales of other brands and formulations to offset any reduced sales of discontinued or relabeled products.

1. Relabeling Costs

The cost of relabeling varies depending on the type of printing method, the number of color changes, whether the products are nationally branded or private label, and the compliance period for implementing label changes. Under this rule, each compliance option described above will require a label change. We also assume for purposes of this analysis that the consumer antiseptic wash products are not discontinued as a result of this rule, but, rather, are reformulated and relabeled. To estimate the costs of relabeling, we use a model developed by our contractor, RTI International (RTI). The estimates based on the model include the cost of labor, materials, analytical testing, market testing, and discarded inventory. Labor costs associated with a label change include administrative activities, non-administrative activities, such as graphic design and prepress activities, and recordkeeping activities. The primary material costs include the costs of printing plates and prepress materials, which depend on the type of packaging and printing method used. On a per formula basis, we assume manufacturers incur the costs of conducting market tests using focus groups.

For the relabeling required by this rule, involving multiple color changes in the label redesign, the extent of change will be considered major according to the labeling cost model. Of the affected UPCs, we estimate that there are 1,820 unique formulations, based on the RTI model assumptions that approximately 91 percent of UPCs in the liquid soap product category and 70 percent UPCs in the bar soap category were unique formulations. Table E9 shows the estimated number of affected products, and formulations by dosage form and brand type.

Table E9. Estimated Number of Affected Products by Brand Type and Form				
Antiseptic Washes by Dosage Form	Number of UPCs		Number of Formulations	
	Branded	Private-Label	Branded	Private-Label
Liquids, Gels, and Foams	1,082	608	985	553
Bars	351	52	246	36
Total	1,433	660	1,231	589

Depending on the frequency of manufacturers' scheduled label redesign, a portion of regulatory label changes may be coordinated with routine voluntary label changes, resulting in significantly lower incremental costs. Assuming a compliance period of 12 months, we estimate that label changes for approximately 4 percent of branded UPCs and 3 percent of private-label UPCs can be coordinated with planned changes. As shown in Table E10, the remaining 1,376 branded UPCs and 640 private-label UPCs will be uncoordinated label changes.

Table E10. Number of UPCs by Brand Type			
Brand Type	Uncoordinated	Coordinated	Total

Branded	1,376	57	1,433
Private	640	20	660
Total	2,016	77	2,093

For the majority of affected UPCs, we estimate that the uncoordinated relabeling cost per UPC will be between $8,241 and $24,520 for branded labels and between $11,748 and $30,364 for private labels (in 2014 dollars). As described in detail in the RTI Labeling Cost Model Report, the costs of labeling changes for an uncoordinated change include discarded inventory and disposal costs for labels that become obsolete as a result of the labeling requirement. Because private labelers update and re-design their packages less frequently, they tend to have higher label inventories than branded manufacturers. The difference in the costs per uncoordinated label change between branded and private reflects the higher cost associated with discarded inventory for private labelers. Low, medium, and high per UPC cost estimates for uncoordinated and coordinated label changes by brand type are shown in Table E11. As shown in table E11, we assume the coordinated costs are the same for both branded and private. The model estimates that the total costs of a one-time label change for all affected UPCs ranges from $18.9 to $ 53.4 million, as reported in Table E12.

Table E11. Labeling Change Costs per UPC

	Costs per Uncoordinated UPC			Costs per Coordinated UPC		
Brand Type	Low	Medium	High	Low	Medium	High
Branded	$8,241	$14,658	$24,520	$387	$1,304	$2,930
Private	$11,748	$19,334	$30,364	$387	$1,304	$2,930

Table E12. Total Costs of Label Change by Brand Type

Brand Type	Low	Medium	High
Branded	$11,361,675	$20,243,736	$33,906,530

Private	$7,526,460	$12,399,840	$19,491,560
Total	$18,888,135	$32,643,576	$53,398,090

2. Reformulation Costs

The decision to reformulate will likely depend on a firm's product portfolio and the expected return from its reformulation investments compared to the expected return from not reformulating (i.e. discontinuing). The expected return from reformulation to remove antiseptic active ingredients will depend on the expected revenues generated by the resulting non-antimicrobial product and the expected costs of relabeling and reformulation. Manufacturers will have two possible reformulation options: converting the antiseptic wash to non-antibacterial soap, or switching antiseptic ingredients to one of the three active ingredients whose regulatory action is being deferred. However, we assume that the costs of either type of reformulation will be similar. Due to uncertainty in how manufacturers will respond, we establish the range of possible costs associated with reformulation, including an upper bound of 100% product reformulation.

The cost to reformulate a product varies greatly depending on the nature of the change in formulation, the product, the process, and size of the company. To guide our analysis on reformulation costs for consumer antiseptic wash products, we reviewed previously published estimates on the reformulation cost of OTC cough-cold products. Based on this review, we estimate the per product reformulation cost for consumer antiseptic wash products ranges from $192,000 to $960,000.[6] Because many manufacturers already have non-antibacterial soap in their product lines, we expect that

[6] Original estimates on reformulation cost previously published in the rule for OTC cough-cold products (67 FR 78158 at 78167) ranged from $100,000 to $500,000. These values were inflated by 92 percent to reflect the rise in the annual Producer Price Index for pharmaceutical preparation manufacturing between 2002 and 2014 (from 326.7 to 628.8).

the cost of removing the antiseptic active ingredient in consumer washes to become non-antibacterial soap will be closer to the lower bound of the per product reformulation range. However, reformulation will require resources to re-evaluate product lines, formula development, and process validation. Using an estimate of $192,000 cost per product, the total costs of reformulation will range from $87.4 to $349.4 million corresponding to the assumed proportion of products undergoing reformulation, as reported in Table E13. We also assume that removal of antiseptic ingredients to reformulate products as non-antibacterial soap does not result in increased ingredient costs. That is, the cost of substitute ingredients will be no more than the cost of the antiseptic active ingredient being removed.

Table E13. Reformulation Costs			
	Percentage of Unique Formulations Reformulated		
	25	50	100
Cost of Reformulation Per Product	$192,000	$192,000	$192,000
Number of Reformulations	455	910	1,820
Total Reformulation Costs	$87,360,000	$174,720,000	$349,440,000

3. Cost of Conducting Tests and Studies to Support a New Drug Application (NDA)

In order to continue marketing antiseptic active ingredients for consumer antiseptic wash use, some manufacturers may decide to apply for marketing authorization for the antiseptic ingredient using the NDA regulatory pathway. To submit an NDA, the manufacturers will need to conduct studies to show that the antiseptic ingredient is both

safe and effective. As discussed in previous sections, the efficacy determination may require: (1) clinical outcome studies showing a benefit of consumer antiseptic washes over and above washing with non-antibacterial soap and (2) non-clinical studies verifying antiseptic activity (i.e. in vitro data from time-kill studies).

For the safety determination, the clinical and non-clinical studies that would be required vary by active ingredient, depending on whether there exist adequate data to demonstrate a particular aspect of safety. As discussed in previous sections, the scope of required safety data may include: (1) data from nonclinical pharmacokinetic studies that describe the Absorption, Distribution, Metabolism, and Excretion (ADME) from both oral and dermal administration in animal models, (2) data from human pharmacokinetic studies describing the ADME properties of a drug via dermal administration using multiple formulations under maximum use conditions, (3) data from developmental and reproductive toxicity (DART) studies, (4) oral carcinogenicity study, (5) dermal carcinogenicity study, and (6) data to evaluate development of resistance.

While there will be associated NDA user fees costs as well, which are approximately $2.2 million in FY 2014 for each application containing clinical data, sponsors of an approved NDA will receive marketing exclusivity. During a period of exclusivity, profit is expected to be higher than it would be otherwise when there are competing firms in the market place. The potential gain will also be greatest for products approved for specific indications of use with few substitutes available. In addition to the cost to manufacturers of preparing and submitting an NDA, the submission of an NDA will also generate incremental review costs to FDA. The most recent available data based on standard costs published by FDA indicate that in FY 2013 the average cost to

FDA for reviewing an NDA with clinical data (for a non-new molecular entity) is approximately $1.5 million (Ref. 34).

Estimating the costs of conducting the clinical and nonclinical studies is difficult because there are numerous variables that impact the cost of such studies. Some of the variables include: study design, study setting, study size, complexity of the study design, and logistics of study conduct. In the context of drug development, estimates on the costs vary widely in the literature. According to one study, the expected out-of-pocket cost for an average drug during the clinical period is approximately $75 million (Ref. R33). In other studies, the estimated cost of safety and efficacy studies was reported to range from $1 million to $7.5 million, while the pharmaceutical industry has estimated the cost to range from $5 million to over $35 million (Ref. R37). Because precise data on study costs are not publicly available, it is difficult to determine the representativeness of drug development costs in comparison to study costs related to antiseptic washes.

To estimate the total costs of conducting clinical and nonclinical studies that will be needed to generate the required safety and effectiveness data, we begin by estimating a unit cost for each potential type of study and test.

a. Unit Costs of Conducting Nonclinical Studies to Establish Safety

Due to lack of available detailed data on the testing costs, we estimate the cost of nonclinical safety studies based on published cost estimates of representative antimicrobial testing required for certain pesticides by the EPA (Refs. R38, R39). Nonclinical testing costs vary across laboratories depending on the method and study protocol. Unit testing cost estimates are derived by averaging estimates of high and low cost study protocols provided by surveyed laboratories. Study protocols are based on

guidelines developed by EPA's Office of Pesticide Prevention and Toxic Substances (OPPTS) for use in testing the health effects of pesticides and toxic substances.

In Table E14, we show a series of estimated testing costs, updated to 2014 dollars, as reasonable approximations of the costs to fulfill each category of possible nonclinical safety data requirements. The estimated testing costs associated with all nonclinical safety data requirements omit the costs corresponding to evaluating the development of resistance. We omit resistance testing costs because we lack data on which to base these estimates and it is not possible to generalize these costs across ingredients. While there will be inherent variation in testing costs, we recognize there may be additional uncertainty generated by extrapolating cost estimates for certain data requirements based on EPA testing requirements. If each test listed in Table E14 were conducted, the estimated cost will be approximately $7.1 million.

Table E14. Estimated Cost Per Study Associated With Nonclinical Safety Data Requirements (in 2014 dollars)

Data From Nonclinical Pharmacokinetic Studies That Describe The Absorption, Distribution, Metabolism, And Excretion (ADME) From Oral Administration In Animal Models	
Metabolism And Pharmacokinetics	$217,371
Data From Nonclinical Pharmacokinetic Studies That Describe The Absorption, Distribution, Metabolism, And Excretion (ADME) From Dermal Administration In Animal Models	
Metabolism And Pharmacokinetics	$202,206
Dermal Penetration	$163,254
Data From Developmental And Reproductive Toxicity (DART) Studies	
DART studies (Rodent)	$134,891
DART studies – (Non-Rodent- Rabbit Preferred)	$91,413
Data From Oral Carcinogenicity Study	

Carcinogenicity (Rat) (24 Months)	$1,071,767
Carcinogenicity (Mouse) (24 Months)	$2,057,981
Data From Dermal Carcinogenicity Study	
Carcinogenicity (Rat) (24 Months)	$1,071,767
Carcinogenicity (Mouse) (24 Months)	$2,057,981
Data Required To Evaluate Development Of Resistance	
No Data Available To Estimate Costs	

b. Costs of Conducting Clinical Studies to Establish Safety

In addition to nonclinical data requirements for active ingredients seeking a safety determination for an NDA, data from human pharmacokinetic (PK) studies describing the ADME properties of a drug using multiple formulations under maximum use conditions when applied topically may be required. The costs of human pharmacokinetic studies vary considerably and detailed data on costs are not publicly available. One estimate suggests that each human pharmacokinetic study may cost $250,000 to $750,000 per age group (Ref. R37). Another study reports low, median, and high cost estimates for multi-dose pharmacokinetic studies (Ref. R40). Cost factors included: coordinating center costs, sponsor management costs, site payments, and central lab payments. Updated to 2014 dollars, the cost per trial for a multi-dose PK study cost estimates range from $780,164 to $24.9 million.

c. Costs of Conducting Clinical and Non-Clinical Studies to Establish Efficacy

It is likely that both data from clinical outcome studies and data from in vitro studies will be needed to establish efficacy for an NDA. Clinical outcome studies to

support efficacy may require at least two study arms, a test product arm and a placebo or non-antibacterial soap arm. We may also require two adequate and well-controlled efficacy studies. We lack precise data on the cost of clinical outcome studies. However, a reasonable approximation may be the estimated cost of efficacy studies conducted for new drug development. Updated to 2014 dollars, estimates of efficacy studies range from $2.11 million to $15.4 million per trial (Ref. R40). The requirements for two efficacy studies imply a cost ranging from $4.22 to $ $30.8 million.

In addition to data from clinical outcome studies, data verifying antiseptic activity from in vitro testing may be required. Based on estimates submitted by industry in response to the 1994 TFM, the costs to conduct the necessary time-kill studies may range from $984,976 to $4.28 million, updating to 2014 dollars (Refs. R41, R42).

d. Summary of Costs for Conducting Safety and Efficacy Studies

We summarize the estimated full range of costs to conduct the safety and effectiveness studies for an NDA in Table E15. Excluding the costs of conducting studies to evaluate the development of resistance, the cost of satisfying all the data requirements may range from $19.0 million to $73.1 million, in 2014 dollars. The total costs of conducting safety and efficacy studies are estimated as the cost per study multiplied by the number of studies that may be conducted; however, we lack sufficient information to be able to estimate the number of sponsors that will opt to conduct the necessary clinical trials or who will submit NDAs for these products. Additionally, costs to conduct the trials may vary by ingredient, as not all tests will be necessary for all active ingredients.

Table E15. Summary of Safety and Efficacy Study Costs (in 2014 dollars)			
	Low Estimate	Medium Estimate	High Estimate
Non-Clinical Safety Testing			
PK studies that describe the Absorption, Distribution, Metabolism, and Excretion (ADME) from oral administration in animal models	$217,371	$217,371	$217,371
PK studies that describe the Absorption, Distribution, Metabolism, and Excretion (ADME) from dermal administration in animal models	$365,460	$365,460	$365,460
Developmental and reproductive toxicity (DART) studies	$226,304	$226,304	$226,304
Oral carcinogenicity study	$3,129,748	$3,129,748	$3,129,748
Dermal carcinogenicity study	$3,129,748	$3,129,748	$3,129,748
Data Required to Evaluate Development of Resistance	Not Estimated	Not Estimated	Not Estimated
Total Nonclinical Testing Costs (not including resistance testing)	$7,068,631	$7,068,631	$7,068,631
Clinical Safety Studies	$780,164	$2,732,773	$24,942,354
Clinical Outcome Efficacy Studies	$4,212,475	$15,381,137	$30,806,247
Nonclinical Efficacy Studies	$984,976		$4,282,503
Total Possible Costs	$13,046,747	$25,182,541	$67,099,735

4. Summary of Total Costs

A summary of the total one-time costs and annualized value of those costs is presented in Table E16. There are no expected additional annual costs. The total one-time costs of relabeling and reformulation will range from $106.3 to $402.8 million. Annualizing the costs at a 3 percent discount rate over 10 years results in annualized

costs ranging from $12.1 to $45.8 million and from $14.1 to $53.6 million at a 7 percent discount rate.

Because of the number of variables that influence the cost of doing clinical and safety studies and because we have no way to estimate the number of manufacturers that will choose to seek NDA approval for their products, we lack sufficient information to estimate these costs of the rule. We therefore include only the estimated costs per sponsor in Table E16.

Table E16. Cost Summary for 12-month Compliance Period

				Annualized Costs Over a 10-Year Period					
	One-Time Costs			3% Discount Rate			7% Discount Rate		
Total Costs (in million dollars)	Low	Med.	High	Low	Med.	High	Low	Med.	High
Relabeling	$18.9	$32.6	$53.4	$2.2	$3.7	$6.1	$2.5	$4.3	$7.1
Reformulation	$87.4	$174.7	$349.4	$9.9	$19.9	$39.8	$11.6	$23.2	$46.5
Subtotal	$106.3	$207.3	$402.8	$12.1	$23.6	$45.8	$14.1	$27.6	$53.6
Safety and Efficacy Study Costs per ingredient (excluding resistance testing)	$13.0	$25.2	$67.1	$1.5	$2.9	$7.6	$1.7	$3.4	$8.9

Totals may not sum due to rounding.

We note that it is possible that these numbers overestimate the current cost of the final rule to the extent that shifts in the market to remove such products have occurred independently of this rulemaking. For example, since the proposed rule was published,

the state of Minnesota passed legislation to ban triclosan from consumer soap products beginning in 2017, which may have caused some manufactures to begin voluntarily removing these non-monograph products from their formulation (Ref R43). However, we are unable to determine which changes in the market may have been caused by such independent market forces, rather than anticipation of this final rule.

G. Alternatives

In our analysis of alternatives, we compare the effects of the rule to two otherwise identical rules: one with a 6-month and another with an 18-month compliance period. The main impact of changing the compliance period is on the total costs of relabeling. We assume that relabeling required by the rule cannot be coordinated with any planned revisions for compliance periods under 1 year. Therefore, all label changes will incur the full per product redesign costs. Reducing the compliance period by 6 months would increase the cost of relabeling by $4.6 to $42.4 million. It would also move all costs up by about 6 months. We account for this by compounding the present value of costs over 6 months, as shown in Table E17. At a 3 percent discount rate, the total annualized costs range from $13.5 to $53.8 million and $17.2 to $68.7 million at a 7 percent discount rate.

Table E17. Cost Summary for 6-Month Compliance Period

	Present Value						Annualized Costs Over a 10-Year Period					
	3% Discount Rate			7% Discount Rate			3% Discount Rate			7% Discount Rate		
Total Costs (in million dollars)	Low	Med.	High	Low	Med.	High	Low	Med.	High	Low	Med.	High
Relabeling	$23.5	$46.1	$94.0	$24.0	$47.0	$95.8	$2.8	$5.4	$11.0	$3.4	$6.7	$13.6
Reformulation	$91.3	$182.6	$365.3	$96.7	$190.7	$386.8	$10.7	$21.4	$42.8	$13.8	$27.1	$55.1

Safety and Efficacy Study Costs per Ingredient (excluding resistance testing)	$13.2	$25.6	$68.1	$13.4	$26.1	$69.4	$1.5	$3.0	$8.0	$1.6	$3.1	$8.1
Total Cost for Relabeling and Reformulation	$114.8	$228.7	$459.3	$120.6	$237.7	$482.6	$13.5	$26.8	$53.8	$17.2	$33.8	$68.7
Change in Relabeling and Reformulation Costs from 12-Month Compliance Period	$5.3	$15.2	$44.4	$6.9	$15.8	$51.6	$1.4	$3.2	$8.0	$3.1	$6.2	$15.1

Decreasing the compliance period would also accelerate the accrual of public health benefits by reducing exposure to antiseptic active ingredients that are not GRAS/E 6 months sooner. In Table E18, we approximate the increase in benefits by estimating the change in the present value of antiseptic active ingredient exposure reductions when compounded at a 3 percent and 7 percent discount rate. The additional benefit would be equivalent to the public health value of reducing exposure to active ingredients for which there is inadequate data to establish their safety and effectiveness for the specified uses. This final rule will reduce exposure to triclosan by 36,921 to 166,145 pounds at a 3 percent discount rate and 70,253 to 316,138 pounds at a 7 percent discount rate; and reduce triclocarban exposure by 88,798 to 266,394 pounds at a 3 percent discount rate and 168,963 to 506,890 pounds at a 7 percent discount rate.

Table E18. Potential Reduction in Exposures (in pounds)

	6-Month Compliance Period		Change from 12-Month Compliance Period	
	Present value-3%	Present value-7%	Present value-3%	Present value-7%
Reduced Triclosan Exposure	2,516,651 to 11,324,947	2,112,008 to 9,504,050	36,921 to 166,145	70,253 to 316,138
Reduced Triclocarban Exposure	6,052,741 to 18,158,213	5,079,543 to 15,238,621	88,798 to 266,394	168,963 to 506,890
Total	8,569,394 to 29,483,163	7,191,553 to 24,742,673	125,719 to 432,540	239,217 to 823,028

By allowing firms to comply within 18 months of a final rule, we assume that 15 percent of labels can coincide with routine label changes, reducing total one-time costs associated with relabeling by $7.8 to $20.1 million. Extending the compliance period to 18 months would also delay all costs by about 6 months. We account for this by discounting the present value of costs an extra 9 months, as shown in Table E19. Under this scenario, we estimate total annualized costs range from $12.0 to $46.5 million at a 3 percent discount rate and $15.4 to $ 59.8 million at a 7 percent discount rate.

Table E19. Cost Summary for 18-Month Compliance Period

	Present Value						Annualized Costs Over a 10-Year Period					
	3% Discount Rate			7% Discount Rate			3% Discount Rate			7% Discount Rate		
Total Costs (in million dollars)	Low	Med.	High	Low	Med.	High	Low	Med.	High	Low	Med.	High
Relabeling	$11.1	$19.2	$31.4	$11.7	$20.3	$33.3	$1.3	$2.2	$3.7	$1.7	$2.9	$4.7
Reformulation	$91.4	$182.6	$365.2	$96.7	$182.6	$386.7	$10.7	$21.4	$42.8	$13.8	$26.0	$55.1

Safety and Efficacy Study Costs per Ingredient (excluding resistance testing)	$13.6	$26.3	$70.1	$14.4	$27.9	$74.3	$1.6	$3.1	$8.2	$1.7	$3.3	$8.7
Total Cost for Relabeling and Reformulation	$102.4	$201.8	$396.7	$108.5	$202.9	$420.0	$12.0	$23.7	$46.5	$15.4	$28.9	$59.8
Change in Relabeling and Reformulation Costs from 12-Month Compliance Period	($7.1)	($11.7)	($18.2)	($5.3)	($18.9)	($11.0)	($0.1)	$0.1	$0.7	$1.3	$1.3	$6.2

The effect of extending the compliance period to 18 months would be a decrease in potential public health benefits resulting from prolonged exposure to antiseptic active ingredients that are not GRAS/E by 6 months. Discounting the present value of antiseptic active ingredient exposure reductions at 3 percent and 7 percent, we estimate the decrease in public health benefits as the value of increased exposure to triclosan by 36,379.4 to 163,707.7 pounds at a 3 percent discount rate and 67,915.9 to 305,622.2 pounds at a 7 percent discount rate; and increased exposure to triclocarban by 87,495.3 to 262,485.9 pounds at a 3 percent discount rate and 163,343.1 to 490,029.1 pounds at a 7 percent discount rate. These estimates are shown in Table E20.

Table E20. Potential Reduction in Exposures (in pounds)		
	18-Month Compliance Period	Change from 12-Month Compliance Period

	Present value-3%	Present value-7%	Present value-3%	Present value-7%
Reduced Triclosan Exposure	2,443,351 to 10,995,094	1,973,839 to 8,882,290	-36379.4 to -163707.7	-67915.9 to -305622.2
Reduced Triclocarban Exposure	5,876,447 to 17,629,333	4,747,236 to 14,241,701	-87495.3 to -262485.9	-163343.1 to -490029.1
Total	8,319,800 to 28,624,430	6,721,077 to 23,123,994	-123874.8 to -426193.6	-231259.2 to -795651.4

Table E21 summarizes the present value of reductions in exposure to antiseptic active ingredients and costs under each compliance period considered under the regulatory alternatives section.

Table E21. Summary of Benefits and Costs Under Regulatory Alternatives

Compliance Period	Present Value of Total Reduction in Exposure (in million pounds)		Present Value of Total Relabeling and Reformulation Costs (in $million)	
	3% Discount Rate	7% Discount Rate	3% Discount Rate	7% Discount Rate
6-Month	8.6 to 29.5	7.2 to 24.7	$48.6 to $184.0	$49.5 to $187.6
12-Month (Final rule)	8.4 to 29.1	7.0 to 23.9	$47.6 to $180.5	$47.6 to $180.5
18-Month	8.3 to 28.6	6.7 to 23.1	$48.7 to $186.0	$56.1 to $197.0

H. Cost-Effectiveness

We measure the effectiveness of the rule as the total reduction in exposure to antiseptic active ingredients linked to consumer antiseptic washes. We compared the present value of costs, shown in Table E21, to the present value of reduced exposures for the 3 percent discount rate and the 7 percent discount rate to estimate the cost per pound of reduced exposure to antiseptic active ingredients under the rule and the two regulatory alternatives. As shown in Table E22, under the rule, we estimate that each pound of

reduced exposure to antiseptic active ingredients will increase costs by $12.97 to $14.28 at a 3 percent discount rate and $16.36 to $18.02 at a 7 percent discount rate.

Table E22. Cost-Effectiveness Under Alternative Compliance Periods (in $ per pound of antiseptic active ingredient reduced)						
	3% Discount Rate			7% Discount Rate		
Compliance Period	Low	Med.	High	Low	Med.	High
6-Month	$13.40	$12.02	$15.58	$16.78	$14.88	$19.50
12-Month (rule)	$12.97	$11.39	$14.28	$16.36	$14.37	$18.02
18-Month	$12.31	$10.92	$13.86	$16.14	$13.60	$18.16

III. Small Entity Effects

The Regulatory Flexibility Act requires agencies to prepare a regulatory flexibility analysis if a rule would have a significant effect on a substantial number of small entities. We expect this rule to have a significant effect on a substantial number of small entities. Consequently, this analysis, together with other relevant sections of this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

Firms affected by this rule (manufacturers of consumer antiseptic wash products) are classified in the Soap and Other Detergent Manufacturing Industry (NAICS 325611) by the Economic Census of Manufacturers. This classification code includes all manufacturers, but does not include relabelers, repackers, and distributors. The Small Business Administration (SBA) defines an entity as small in this industry if the business has fewer than 1,000 employees. Because the U.S. Census size categories do not

correspond to the SBA designation of 1,000 employees, the agency figures are based on 500 employees.

The 2012 Economic Census indicates that there are 662 establishments classified in the Soap and Other Detergent Manufacturing Industry (Ref R44). Table E23 shows the breakdown of soap and other detergent manufacturers by number of employees. Of these establishments, we estimate that at least 99 percent (656) employ fewer than 1,000 employees and will qualify as small entities as defined by the SBA. FDA notes that using data at the establishment level rather than at the firm level makes the implicit assumption that the typical manufacturing establishment is roughly equivalent to the typical small manufacturing firm. However, if the market is dominated by a few large firms with a large number of small establishments, our estimated number of small entities may be an overestimate of the actual number of businesses with fewer than 1,000 employees. We therefore estimate that small businesses represent 99 percent of firms in this industry, rather than the 100% of firms as outlined in Table E23, to account for this possibility. Based on the annual value of shipments reported in the 2012 Economic Census, we estimate the average annual value of shipments per small entity in the Soap and Detergent Manufacturing Industry is $37.8 million in 2012 dollars.[7] Average annual value of shipments is defined as the total net selling values of a company's products in a year, which should roughly correspond with a company's total annual sales.

[7] We use value of shipments from the 2012 Economic Census to assess the economic significance of the likely compliance costs of the rule for small businesses in the Soap and Other Detergent Manufacturing industry. Value of shipments includes the total sales, receipts, revenue or business done by domestic establishments, and we expect this measure to be more accurate than receipts data from Census Bureau's Statistics on U.S. Businesses when analyzing this rule's impact based on potentially duplicative data in receipts data and potentially greater representativeness in the economic census. There may be variance between average estimated value of shipments and actual revenues, especially for the smallest of businesses in this industry with less than 20 employees. Additionally, there may be uncertainty and a wide range in terms of individual impacts on small businesses.

Table E23. Soap and Detergent Manufacturers by Number of Employees		
Size by Number of Employees	Number of Establishments	Average Value of Shipments ($1,000)
0 to 4	304	$621
5 to 9	91	$2,210
10 to 19	95	$6,624
20 to 49	74	$11,754
50 to 99	45	$37,363
100 to 249	35	$140,639
250 to 499	12	$762,842
500 to 999	6	$1,234,973

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

Manufacturers are expected to incur most product reformulation and relabeling costs, with the impact to relabelers, repackers, and distributors being considerably less. The impact on a manufacturer can vary considerably depending on the number and type of products it produces. For this analysis, we examine the brands of affected UPCs listed in the A.C. Nielsen data to estimate the proportion of products sold by large companies and conservatively assume that the remaining products, including private label products, are manufactured by small companies. Estimating that approximately 63 percent of affected products are produced by small entities, we assume rule-induced costs of relabeling and reformulation borne by small entities are proportional. Assuming these costs are distributed equally, we estimate that the average one-time cost of compliance for a small business ranges from $0.11 million to $0.41 million, which is approximately 0.28 percent to 1.10 percent of the average annual value of shipments for a small business. For small businesses with fewer than 20 employees, these one-time costs could

represent between approximately 1.66 percent and 66 percent of the annual value of shipments, but we believe that costs will be at the lower end of this estimate given that these businesses are unlikely to have a large number of affected products. We estimate that these costs would represent the one-time cost, which would occur in the first year only, per small business. We do not expect small businesses to incur any additional costs after the first year (i.e., once any reformulation and relabeling of antiseptic products is completed). Table E24 shows the summary of the estimated costs for small entities.

Table E24. Summary of Costs for Small Entities Under 12-Month Compliance Period (in $millions)												
	Present Value						Annualized Costs Over a 10-Year Period					
	3% Discount Rate			7% Discount Rate			3% Discount Rate			7% Discount Rate		
	Low	Med.	High	Low	Med.	High	Low	Med.	High	Low	Med.	High
Total costs of relabeling and reformulation for small entities	$69.0	$134.5	$261.4	$71.7	$139.7	$271.5	$7.6	$14.9	$28.9	$8.9	$17.4	$33.8
Average compliance cost per small entity	$0.11	$0.21	$0.40	$0.11	$0.21	$0.41	$0.01	$0.02	$0.04	$0.01	$0.03	$0.05
Cost as a percent of average annual value of shipments per entity	0.28%	0.54%	1.05%	0.29%	0.56%	1.10%	0.03%	0.06%	0.12%	0.04%	0.07%	0.14%

C. Alternatives for Regulatory Relief

1. Exemption for Small Businesses

The exemption of small businesses from the provisions of the rule would provide regulatory relief. Table E24 of this document shows that small businesses are expected to bear total one-time costs of about $69.0 million to $271.5 million as a result of this rule,

an average of $0.11 million to $0.41 million per small business. As a first approximation, then, exempting small businesses would reduce the burden by an average of $0.11 million to $0.41 million per small business.

FDA believes that exempting small businesses would not be desirable. Because a substantial share of the consumer antiseptic wash industry is composed of businesses that are classified as small by the Small Business Administration, if small businesses were exempted, most of the potential benefits from the rule would not be realized.

2. Longer Compliance Period for Small Businesses

Longer compliance periods provide regulatory relief for small businesses. Extending the compliance period to 18 months would lead to an average one-time cost per small entity ranging from $0.10 million to $0.40 million, which would be 0.26 percent to 1.07 percent of the average annual value of shipments.

With small businesses producing approximately 63 percent of the products, extending the compliance period for small businesses would leave many products unchanged for 6 additional months after the effective date. Also, extending the effective date for products containing antiseptic active ingredients not found to be GRAS/E would lead to continued exposure and delay the potential benefits of this rule. Table E25 shows the summary of costs for small entities under the regulatory alternative of an 18-month compliance period.

Table E25. Summary of Costs for Small Entities Under 18-Month Compliance Period (rule) (in $millions)												
	Present Value						Annualized Costs Over a 10-Year Period					
	3% Discount Rate			7% Discount Rate			3% Discount Rate			7% Discount Rate		
	Low	Med.	High	Low	Med.	High	Low	Med.	High	Low	Med.	High

Total costs of relabeling and reformulation for small entities	$64.54	$127.13	$249.89	$68.33	$127.84	$264.59	$7.57	$14.90	$29.29	$9.73	$18.20	$37.67
Average compliance cost per small entity	$0.10	$0.19	$0.38	$0.10	$0.19	$0.40	$0.01	$0.02	$0.04	$0.01	$0.03	$0.06
Cost as a percent of average annual value of shipments per entity	0.26 %	0.51%	1.01%	0.28 %	0.52%	1.07%	0.03 %	0.06 %	0.12 %	0.04 %	0.07 %	0.15 %

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