DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

Docket No. FDA-2015-N-0101

Regulatory Impact Analysis
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, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies 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. Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." We believe that this final rule is a significant regulatory action as defined by Executive Order 12866. This final rule is considered an EO 13771 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 only four small businesses will be adversely affected by the final rule, we find that the final rule will not 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 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 1 year." The current threshold after adjustment for inflation is $148 million, using the most current (2016) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

As discussed in the preamble of this final rule, this rule establishes that 24 eligible active ingredients are not generally recognized as safe and effective for use in health care antiseptics. However, data from the FDA drug product registration database suggest that only one of these 24 ingredients is found in OTC health care antiseptic products currently marketed pursuant to the Tentative Final Monograph (TFM): triclosan. Regulatory action is being deferred on six active ingredients that were included in the health care antiseptic proposed rule: benzalkonium chloride, benzethonium chloride, chloroxylenol, alcohol (ethyl alcohol), isopropyl alcohol, and povidone-iodine. This rule also addresses comments on the eligibility of three active ingredients – alcohol, benzethonium chloride, and chlorhexidine gluconate—and finds that these three active ingredients are ineligible for evaluation under the OTC Drug Review because they were not included in health care antiseptic products marketed for the specified health care antiseptic uses prior to May 1972. To our knowledge, there is only one product that contains one of these active ingredients currently on the market, a surgical hand scrub that contains alcohol, affected by this rule. We note that there are chlorhexidine gluconate products not affected by this rule because they are marketed under an NDA.

The final rule's costs and benefits are summarized in Table 1. Benefits are quantified as the volume reduction in exposure to triclosan found in health care antiseptic products affected by the rule,

but these benefits are not monetized. Annual benefits are estimated to be a reduction in exposure of 88,000 kg of triclosan per year.

Costs are calculated as the one-time costs associated with reformulating health care antiseptic products containing the active ingredient triclosan and relabeling reformulated products.. Annualizing the one-time costs over a 10 year period, we estimate total annualized costs to range from $1.1 to $4.1 million at a 3 percent discount rate, and from $1.2 to $4.7 million at a 7 percent discount rate. The present value of total costs ranges from $9.0 to $34.6 million at a 3 percent discount rate, and from $8.7 to $29.6 million at a 7 percent discount rate.

In this final rule, small entities will bear costs to the extent that they must reformulate and re-label any health care antiseptic containing triclosan that they produce. (The one company affected by the removal of the alcohol surgical hand scrub is not a small business.) The average cost to small firms of implementing the requirements of this final rule is estimated to be $213,176 per firm. The costs of the changes, along with the small number of firms affected, implies that this burden would not be significant, so we presume that this final rule would not have a significant economic impact on a substantial number of small entities. This analysis, together with other relevant sections of this document, serves as the Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

The full discussion of economic impacts is available in docket FDA-2015-N-0101 and at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm*.

Table 1. Economic Data: Costs and Benefits Statement

Category		Low Estimate	Primary Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year					7%	10 years	
	Annualized Monetized $millions/year					3%	10 years	
	Annualized Quantified kilograms/year		88,000			7%	10 years	Reduced antiseptic active ingredient exposure (in kilograms).
	Annualized Quantified kilograms/year		88,000			3%	10 years	
	Qualitative	Potential reduction in antibiotic resistance due to exposure to triclosan and potential adverse effects of triclosan in health care antiseptics.						
Costs	Annualized Monetized $millions/year	$1.23	$2.45	$4.74	2016	7%	10 years	Annualized costs of reformulating and testing antiseptic products. Range of estimates captures uncertainty.
	Annualized Monetized $millions/year	$1.05	$2.10	$4.06	2016	3%	10 years	
	Annualized Quantified billion/year					7%		
	Annualized Quantified billion/year					3%		
	Qualitative							
Transfers	Federal Annualized					7%		
	Monetized $millions/year					3%		
	From/To							
	Other Annualized Monetized $millions/year	$3.6	$2.1	$6.6	2016	7%	10 year	Annualized transfers from the removal of one product from market.
		$3.6	$2.1	$6.6	2016	3%	10 years	
	From/To							
Effects	State, Local, or Tribal Government: Not applicable Small Business: The costs associated with potentially affected small entities range between 0.1 and 22 percent of their average annual revenues. Wages: No estimated effect Growth: No estimated effect							

Table 2. EO 13771 Summary Table (in $ Millions 2016 dollars, over an infinite time horizon)

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)
Present Value of Costs	$17.19	$8.68	$29.47
Present Value of Cost Savings	-	-	-
Present Value of Net Costs	$17.19	$8.68	$29.47
Annualized Costs	$1.20	$0.61	$2.06
Annualized Cost Savings	-	-	-
Annualized Net Costs	$1.20	$0.61	$2.06

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

FDA's proposed rule "Safety and Effectiveness of Health Care 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 May 1, 2015 (80 FR 25166) (2015 Health Care Antiseptic PR). We prepared a full "Preliminary Regulatory Impact Analysis" in connection with the 2015 Health Care Antiseptic PR. In the following paragraphs, we describe and respond to comments we received on our analysis of the impacts presented in those sections. We have numbered each comment 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(s).

(Comment 1) Multiple comments discussed the potential impact of removing povidone-iodine from the market. Specific to the economic analysis, commenters remarked that: (1) the size of the affected market might be higher than estimated, because povidone iodine is used in millions of surgical procedures (gynecological, obstetric, and neurosurgery) every year and there is currently no substitute available; (2) the removal of povidone-iodine may have a higher impact on infection rates than estimated in the regulatory impact analysis in the proposed rule, due to the lack of alternative antiseptic products for these indications; and (3) while the market for povidone-iodine is large, the manufacturing is very consolidated, and the removal of this ingredient from the market could lead to significant exits from the market by manufacturers.

(Response 1) As discussed above, rulemaking on povidone-iodine has been deferred, and so these comments are not being addressed in this analysis.

(Comment 2) One commenter expressed concerns that requiring antiseptic products containing active ingredients found not to be GRAS/E to obtain an approved NDA prior to marketing, with the resulting exclusivity period, would lead to substantial price increases for consumers and payers, and this cost should be accounted for within the cost section of the RIA.

(Response 2) The regulatory impact analysis is intended to estimate the total economic costs associated with the rule. If manufacturers submit an NDA for a health care antiseptic containing triclosan (or one of the other antiseptic ingredients found not GRAS/GRAE in this rule), it is possible that these manufacturers could pass on the costs associated with obtaining an NDA to consumers and payers. This could lead to increases in the price of the product. We agree that it is important to acknowledge that this outcome could occur. However, we are unable to quantify what the amount of cost pass-through might be, or even how likely this outcome might be. We have added language in the RIA to discuss this potential manifestation of costs.

(Comment 3) One commenter suggested that the estimated testing costs are significantly understated.

(Response 3) In the PRIA we requested comment supported by data to be submitted for consideration. However, the commenter did not provide any alternative estimates or submit data that would support different estimates, and we therefore continue to find our estimates of the testing costs to be those that are the best available.

(Comment 4) One commenter noted their belief that we have overestimated the potential benefits of the rule, because if the ingredients are determined to be safe, then there is no reduction in harm of using them.

(Response 4) We agree with this comment that estimating the benefits of this rule is difficult because of the uncertainty in the relationship between exposure to the antiseptic active ingredients and adverse health effects. Therefore, for the final rule, we have only quantified the reduction of antiseptics once the final rule is implemented, rather than trying to monetize these benefits.

(Comment 5) One commenter was concerned that the PRIA did not go far enough in stating the potential benefits of reducing antiseptic use at the population level. They specifically noted that our benefits section did not contain an assessment of bacterial resistance, as well as other potential health benefits such as decreased endocrine disruption, and associated IQ loss, due to triclosan exposure.

(Response 5) We agree with the commenter that the benefits of this rule may not be fully quantified. However, we are unable to monetize these potential benefits due to limitations in the data on the relationship between exposure to the antiseptic active ingredients and their health effects. We have added language in the RIA to describe our potential underestimate of benefits, and our inability to monetize these benefits.

II. Regulatory Impact Analysis

A. Brief History of Health Care Antiseptics

Health care antiseptics are antimicrobial agents that are intended to reduce the number of microorganisms on the skin. Health care antiseptics are drug products that are generally intended for use by health care professionals in a hospital setting or other health care situations outside the hospital. (We note that this rule does not cover OTC drug products that are identified as "first aid antiseptics" in the 1991 First Aid Tentative Final Monograph (TFM) (56 FR 33644).)

Health care antiseptics include patient preoperative skin preparations (which include products that are used for preparation of the skin prior to an injection (i.e., preinjection)), surgical hand scrubs and rubs, and health care personnel hand washes and rubs. These products are usually packaged in either multiple use containers, such as bottles, or single-use applicators, such as wipes, swabs, and cotton pads. Many antiseptic wash products are also available as liquids. However, some antiseptic wash products are also manufactured as foams. Surgical hand rub and health care personnel hand rub products, on the other hand, are generally available as evaporative gels or single-use wipes.

B. Background

Antiseptics are one part of multi-part infection control regimens implemented by hospitals and other health care facilities to reduce the spread of infection. Health care personnel generally use antiseptics to disinfect their skin prior to patient interactions, and to disinfect their patients' skin prior to certain medical procedures. This practice is designed to reduce patients' exposure to bacteria, subsequently reducing their risk of infection. However, this practice also causes health care workers to use antiseptic products many times per day on a daily basis (Ref. R1, R2, and R3).

Several important scientific developments that potentially affect the safety evaluation of these ingredients have occurred since FDA's 1994 evaluation of the safety of health care antiseptic active ingredients under the OTC Drug Review. Improved analytical methods now exist that can detect and more accurately measure these active ingredients at lower levels in the bloodstream and tissue. Consequently, we now know that, at least for certain health care antiseptic active ingredients, systemic exposure is higher than previously thought, and new information about the potential risks from systemic absorption and long-term exposure have become available. New safety information also hypothetically suggests that widespread antiseptic use could have an impact on the development of bacterial resistance. At this time, the significance of these new information sources is not known (Ref. R4-R16).

In this final rule, the FDA finds that 24 active ingredients are not generally recognized as safe and effective for use in OTC health care antiseptics, while deferring rulemaking on six health care antiseptic active ingredients to allow for the development and submission of new safety and effectiveness data.

C. Market Failure Requiring Federal Regulatory Action

The final rule attempts to address the market failures that arise when adequate information is unavailable on the potential health risks associated with using health care antiseptic products that are marketed according to the terms of the tentative final monograph. This rule is also a part of the FDA's ongoing evaluation of the safety and effectiveness of OTC drug products containing these ingredients.

To reduce the risk of infection to patients, it is common practice for health care personnel to use products containing antiseptic active ingredients many times per day (Ref. R1, R2, and R3). Health care antiseptics continue to be an integral part of multifaceted infection control regimens recommended by organizations such as the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC), and, in some cases, mandated by professional organizations (e.g. Joint Commission) (Ref. R1 and R3). However, FDA does not have sufficient evidence to determine that the active ingredients addressed in this rule are GRAS/GRAE for use as OTC health care antiseptics. As long as the private marginal cost of gathering safety and effectiveness information exceeds the private marginal benefit, there is insufficient incentive for manufacturers or any particular entity to undertake studies in the absence of regulation. Because it is time-consuming and resource intensive to generate the evidence needed for consumers to make informed choices, private market incentives are insufficient to provide adequate assurances of safety and effectiveness. Under these circumstances, regulation is needed to ensure that minimum standards are met.

Short-term animal studies indicate that these antiseptic active ingredients, specifically triclosan, may have adverse health effects (Ref. R5-R13). However, while the long-term effects of exposure on adverse health effects is not well characterized for antiseptic active ingredients, there is a body of literature that has established this connection for other environmental toxicants, such as known carcinogens. Hypothetical unintended negative effects on the 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 health care antiseptic products, which only account for private costs and private benefits (Ref. R17-25). These potential negative externalities would represent an additional well-established market failure that provides an economic rationale for regulation. An externality is defined here as a cost or benefit resulting from an action that is borne or received by parties not directly involved. In the case of widespread health care 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.

D. Purpose of This Rule

In this rule, the FDA finds 24 health care antiseptic ingredients to be not GRAS/GRAE for use in OTC health care antiseptics. These 24 active ingredients are listed in the final rule. To our knowledge, the only one of these 24 ingredients that is found in a currently marketed OTC health care antiseptic is triclosan.

The FDA also defers rulemaking on six antiseptic active ingredients for use in OTC health care antiseptics, pending the submission of additional safety and efficacy data by sponsors. The deferred ingredients are: benzalkonium chloride, benzethonium chloride, chloroxylenol, ethyl alcohol, isopropyl alcohol and povidone-iodine. We have not included these ingredients in the costs of this final rule because they are outside the scope of the rule, which is consistent with the approach taken in previous regulatory impact analyses. When a final rule is issued addressing any of these active ingredients, a regulatory impact analysis describing the costs and benefits associated with any testing, formulation, or labeling requirements would accompany that rule. If any costs were incurred in anticipation of such final rule, they would also be included in the analysis.

This rule also addresses comments on the eligibility of three active ingredients – alcohol (ethyl alcohol, see section V.C.3 in the final rule), benzethonium chloride, and chlorhexidine gluconate—and finds that these three active ingredients are ineligible for evaluation for some health care indications under the OTC Drug Review (see section IV.D.1, table 3 in the final rule). To our knowledge, there is only one product currently on the market that contains one of these active ingredients, a surgical hand scrub that contains alcohol, affected by this rule. We note that there are chlorhexidine gluconate products not affected by this rule because they are marketed under an NDA.

E. Baseline Conditions

This final rule is expected to lead to the removal from the market of OTC health care antiseptic drug products containing the 24 active ingredients that are found to not GRAS/GRAE for use in OTC health care antiseptics within one year after publication (the effective date of the rule is one year after publication). The rule's impact is estimated relative to the baseline, which is the state of the world in the absence of the final regulatory action. To establish the baseline market, we estimate the number of potential unique health care antiseptic products available in the market, and society's potential aggregate usage of OTC health care antiseptic products and exposure to the relevant antiseptic active ingredients. We assume that, in the absence of this final rule, antiseptic usage remains constant over time (i.e. future consumption is expected to be approximately equal to current consumption).

The FDA is finding 24 health care antiseptic active ingredients to be not GRAS/GRAE for use in OTC health care antiseptics. However, data from the FDA drug product registration database suggest that only one of these 24 ingredients is found in OTC health care antiseptic products currently marketed pursuant to the TFM: triclosan. (We also conducted additional internet searches to find any products containing these other 23 ingredients for the affected indications. No products were found.)

We estimate the number of uniquely packaged health care antiseptic products using the 2016 FDA drug product registration database. The advantage of this database is that we believe it represents

a reasonably up-to-date, nationally representative sample of antiseptic products. It also indicates which antiseptic products are intended to be used in health care settings. A potential issue with this database is that it only contains products that were voluntarily reported to the FDA, which suggests that it could underestimate the total number of uniquely packaged health care antiseptic products.

The data indicate that there are 161 uniquely packaged health care antiseptic products currently on the market that contain triclosan as the active ingredient. The majority of these products are health care personnel hand washes.

In the proposed rule, it was estimated that approximately 510 triclosan health care antiseptic products were on the market in 2013. This is a significant difference from current estimates, but we believe that this is likely due to independent market forces and is not attributable to this rulemaking. Many scientists, consumers, and consumer groups have raised significant concerns about the use of triclosan, in some cases resulting in action by the states (Ref R26). For example, Minnesota has banned triclosan (Ref. R27). Based on these external factors, a number of large companies are phasing triclosan out of their products worldwide (Ref. R28). These external factors, which are independent of the rule, could indicate that our estimates of costs and benefits are overestimated; however, there are other factors, such as data quality, that limit our ability to precisely estimate the market size, and which could produce an underestimate of the costs and benefits. Because we do not know the magnitudes of these potential over and underestimations, and how they may or may not balance out, we do not alter our estimates to account for over- or underestimation.

F. Benefits

1. Unquantified Benefits

Finalizing this rule is expected to generate several potential benefits. First, it may reduce the probability that certain microbes develop antibiotic resistance. Although no scientific studies examine this issue specifically for health care antiseptics, it is possible that the active ingredients in this rule may contribute to antibacterial resistance to antibiotics (Ref. R17-R32). Because the ingredients have been found not GRAS/GRAE, the reduction of any potential for antibiotic resistance is a benefit.

Second, it is possible that the active ingredients addressed in this rule could cause adverse health effects in the long-term. This potential has not been investigated in humans, but given that effectiveness has also not been demonstrated, the reduction in any potential for long-term adverse health effects by the removal of these ingredients is a benefit.

Finally, requiring that health care antiseptic products marketed pursuant to the OTC Topical Antimicrobial monograph be reformulated to contain active ingredients that have been shown to be GRAE could possibly reduce a patient's risk of developing a health-care related infection. Benefits depend on current usage of health care antiseptic products containing active ingredients that FDA has determined are not GRAE for use in OTC health care antiseptics, and the extent to which the rule would cause end users to substitute such antiseptics with health care antiseptic products that contain either active ingredients shown to be GRAS/GRAE for use in health care antiseptics or health care antiseptic products have an FDA-approved new drug application (NDA) or abbreviated new drug application (ANDA).

While all of these potential benefits are important, we are unable to quantify them due to limitations of the available evidence and data.

2. Quantified Benefits

This final rule will prevent health care antiseptic drug products that contain active ingredients that have not been shown to be safe or effective from continued marketing under the OTC Topical Antimicrobial monograph. The primary benefit of this market change is the value of any resulting health improvements. While the evidence associating long-term exposure to triclosan with adverse health effects is inconclusive, there are data suggesting that triclosan may have certain hormonal effects. The data include a broad range of hormonal effects in animals, including effects on estrogen, testosterone, and thyroid hormones (Ref. R5-R16).

Without data on the relationship between exposure to triclosan and adverse health outcomes in humans, it is difficult to quantify the value of a health risk reduction. Quantifying the benefits of health improvements 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.

As an intermediate measure, however, we estimate the reduction in exposure to triclosan. The benefits of this rule would come from the reduction in the potential risks (related to both safety and efficacy) associated with the use of triclosan in health care antiseptic products. If the level of exposure to triclosan is correlated with risks to public health, any change away from the use of triclosan should reduce any risk associated with exposure to those ingredients, resulting in positive public health benefits.

We estimate the volume (in kilograms) of the reduction in exposure to health care antiseptics containing triclosan using the following method. To estimate potential annual baseline antiseptic product exposure, we use the 2015 Office of Regulatory Affairs Reporting Analysis and Decision Support System (ORADSS) database. ORADSS is an internal FDA database that reports the total number of antiseptic units (in kilograms, liters, and "pieces") imported to the United States. However, because ORADSS only collects antiseptic imports, our analysis won't include the antiseptic usage associated with antiseptics that are domestically produced. This results in potentially underestimating antiseptic usage and thus benefits.

ORADSS also does not distinguish health care antiseptics from other antiseptic products. To address this problem, we have checked the importer's web site for each import in an attempt to verify whether they market the particular product as a health care antiseptic product or supply the product to health care providers for use as a health care antiseptic product. However, because the data does not explicitly state the setting in which these products are used, this could have led to an overestimation of benefits.

We find that the reduction in exposure to health care uses of triclosan is approximately 88,000 kilograms per year, based on the ORADSS import data from 2015. Because the data was reported in different units of measurement, we made the following assumptions. First, we assumed that any imports reported in kilograms were bulk ingredients that were 99% pure triclosan. Second, we assumed that imports reported in liters and "pieces" were finished products and contained 0.5% pure triclosan

(the higher end of active ingredient concentration for health care personnel handwashes containing triclosan). Once converted into a pure triclosan measure, we assume a 1-1 ratio for the ingredients measured in kilograms and liters, and reported our estimate in kilograms.

The present value of this reduction (discounted over ten years) is 750,658 kilograms at a 3% discount rate, and 618,075 kilograms at a 7% discount rate.

G. Costs

The final rule is expected to impose costs on health care antiseptic manufacturers. The primary one-time costs include the costs of reformulating and relabeling health care antiseptic products that contain triclosan. These costs are discussed in more detail in the following sections.

1. Reformulation

Reformulation costs vary across products, processes, and complexity. For instance, it is more expensive to reformulate products that are more chemically sophisticated, that have manufacturing processes that are more complex, and that are manufactured on a greater scale. We estimate these costs using the reformulation cost results reported in a previous regulatory impact analysis (Docket No. FDA-1975-N-0012). The previous impact analysis studied consumer antiseptic washes, and estimated that the average cost to reformulate consumer antiseptic washes range from $195,840 to $979,200 (in 2016 dollars).[1]

We estimate an average cost per product reformulation at the lower level of $195,840. This follows the assumptions made in the consumer antiseptic wash final rule, which we believe hold true for this market as well (Ref R29). First, most manufacturers already have non-antiseptic washes in their product lines, so they could more readily reformulate their antiseptic washes to non-antiseptic washes. We also believe that removal of antiseptic ingredients to reformulate products does not result in a net increase in ingredient costs. That is, the cost of substitute ingredients would be no more than the cost of the antiseptic active ingredient being removed. Second, the higher levels of the reformulation estimates are for more complex products, such as OTC cough-cold products, where manufacturing may be difficult. For example, with a more complex product, a manufacturer may need to redo production processes, change suppliers, and conduct stability testing. The manufacture of a wash is not as complex and therefore costs to reformulate are likely at the lower end of the estimate.

We use the estimate of 161 unique health care antiseptic products containing triclosan as the active ingredient. Given the low number of health care antiseptic products that contain triclosan in this market, we assume that all products are unique formulations, to account for possible missing data and ensure that the estimates are not biased downward. Table 3 reports the range of possible total costs from reformulations, which range from $7.8 to $31.5 million.

[1] Original estimates on reformulation costs 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 from 2002 to 2016 dollars to reach the current estimates.

Table 3. Reformulation Costs (in 2016 dollars)

	Percentage of Unique Formulations Reformulated		
	25%	50%	100%
Cost of Reformulation Per Product	$195,840	$195,840	$195,840
Number of Reformulations	40	81	161
Total Reformulation Costs	$7,833,600	$15,863,040	$31,530,240

We use the 25%, 50%, and 100% reformulations as the low, midpoint, and high estimates, respectively. We use the reformulation of 50% of products as the midpoint estimate because many manufacturers already have non-antiseptic washes as part of their product line, and therefore will not need to reformulate the antiseptic washes to create a new product line. Additionally, some manufacturers may exit the market, if the cost of compliance is greater than the cost of exiting, and not incur these costs. These assumptions are in line with those made in the context of the consumer wash final rule.

2. Relabeling

Reformulation would also require manufacturers to relabel their products to indicate that their products now contain a different antiseptic active ingredient. To calculate the average cost to revise a label, we use a model developed by an independent contractor, RTI International (RTI) (Ref. R30). The model takes into account various inputs contributing to relabeling costs, such as labor, materials, and market testing. For antiseptic products, labor costs include administrative activities and non-administrative activities (e.g., recordkeeping, prepress activities, and graphic design), while material costs include prepress materials and printing plates. The costs also include the costs of the potential marketing tests, such as conducting focus groups.

The costs associated with the above resources vary with printing method and compliance time. For instance, more intricate printing methods, such as color or graphic changes, cost more than simpler printing methods, such as revising black and white text. Furthermore, longer compliance times reduce costs because it enables manufacturers to "coordinate" their labeling activities with other regularly scheduled labeling updates (i.e. update their labels when they are planning to use resources to make labeling changes). The revisions resulting from this rule include label changes that require color changes. Furthermore, it provides a 12-month compliance time, which the RTI model indicates would allow only 4 percent of manufacturers to coordinate their labeling activities.

The model also reports the costs associated with relabeling private versus branded labels because private labels are updated less frequently, leaving less room to coordinate activities. We assume that 30% of the affected Universal Product Codes (UPCs) are private label products, which in this case amounts to 48 products. The remaining 113 products are assumed to be branded.

Table 4. Number of Products by Type and Coordination Ability

	Uncoordinated UPC	Coordinated UPC
Branded	108	5
Private	46	2

The relabeling cost model estimates average uncoordinated relabeling costs to range between $8,406 and $30,971 per UPC, whereas average coordinated relabeling costs range between $395 and $2,989 (in 2016 dollars) per UPC. The model estimates total cost of one-time label changes for all UPCs ranging from $1.45to $4.2 million.

Table 5. Labeling Change Costs per UPC (in 2016 dollars)

	Costs per Uncoordinated UPC			Costs per Coordinated UPC		
Brand Type	Low	Medium	High	Low	Medium	High
Branded	$8,406	$14,951	$25,010	$395	$1,330	$2,989
Private	$11,983	$19,721	$30,971	$395	$1,330	$2,989

Table 6. Total Costs of Label Change by Brand Type (in 2016 dollars)

Brand Type	Low	Medium	High
Branded	$909,802	$1,621,376	$2,716,066
Private	$552,006	$909,811	$1,430,656
Total	$1,461,808	$2,531,187	$4,146,722

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

This final rule determines that triclosan is not GRAS/GRAE for use in OTC health care antiseptics and must be removed from the market. If companies wish to use triclosan in their OTC health care antiseptic products they must submit an NDA and have the NDA approved prior to marketing their products. Multiple types of studies must be conducted, and the sponsor must show that triclosan is both safe and effective. Estimating the costs of these studies is difficult: study designs are variable, the actual studies required may slightly vary for each NDA, and there are few reliable estimates of the costs of preclinical and clinical trials. However, the types of studies that most likely would be required, along with an estimate of their costs, are outlined below. While, as noted above, the types of studies required for each NDA may vary, we assume for the purposes of these calculations that an NDA sponsor would be required to conduct studies similar to those being required to show that the deferred active ingredients are GRAS/GRAE for use in OTC health care antiseptics.

a. Efficacy Testing

We assume that a manufacturer would be required to conduct two in vivo tests and three types of in vitro tests (i.e. minimum inhibitory concentration tests, time-kill tests, and antimicrobial spectrum tests).

We lack precise data on the cost of clinical simulation studies. However, a reasonable approximation may be the estimated cost of efficacy studies conducted for new drug development. Updated to 2016 dollars, estimates of efficacy studies range from $2.1 million to $15.7 million per clinical trial (Ref. R31). However, given the likely limited clinical trial size for a study of the efficacy of triclosan, we believe that costs will be at the low end of this estimate, and therefore use a value of $2.1 million for the cost of the efficacy testing.

b. Safety Testing

We assume that manufacturers would have to provide adequate data from the following nonclinical studies: absorption, distribution, metabolism, and excretion (ADME) in animals, human pharmacokinetic (MUsT), oral and dermal carcinogenicity in animals, developmental and reproductive toxicity (DART) in animals, and resistance potential. Each study requires several tests, which are discussed in a previous regulatory impact analysis (78 FR 76443-76478). The analysis also calculates the average costs associated with each safety study. These results are summarized and reported in Table 6.

Table 7. Estimated Cost Per Study Associated With Nonclinical Safety Data Requirements (2016 dollars)

Safety Study	Human Pharmacokinetic (MUsT)	Animal Pharmacokinetic (ADME)	Oral Carcinogenicity	Dermal Carcinogenicity	Developmental and Reproductive Toxicity	Potential Hormonal Effects	Bacterial Resistance	Sum Total Costs (000,000's 2016 dollars)
Total Costs (000,000's of 2016 dollars)	$2.75	$0.59	$3.16	$3.16	$0.23	$1.22	No Data Available	$11.12

c. Total Possible Costs for an NDA

There may be adequate data for oral carcinogenicity and developmental and reproductive toxicity for triclosan such that additional studies on these issues would not be required in an NDA submission. Removing these two studies from the costs, we estimate total costs to approximately equal $9.9 million. We also assume that a study assessing bacterial resistance would also be required. However, no data is available to estimate this cost, and thus our total safety testing cost does not include the expenditures associated with conducting a resistance study. The user fee costs to submit an NDA in 2016 are $2.4 million.

We note that it is possible that, if a manufacturer does submit and have an NDA approved, the costs of health care washes that include triclosan as the active ingredient could rise considerably. However, we are unable to quantify this potential manifestation of these costs.

4. Summary of Total Costs

Table 8 summarize the final rule's total costs. The total one-time costs from relabeling and reformulating range from $9.3 to $35.7 million. Annualized total costs range from at $1.1 to $4.1 million at a 3 percent discount rate, and from $1.2 to $4.7 million at a seven percent discount rate. The present value of total costs ranges from $9.0 to $34.6 million at a 3 percent discount rate, and from $8.7 to $29.5 million at a 7 percent discount rate.

Costs to complete the testing required for submitting an NDA for triclosan are estimated separately. There are two reasons we estimate these costs separately. First, we have limited ability to estimate these costs. Second, public feedback received by the FDA from multiple industry stakeholders in recent years shows a strong trend towards phasing out OTC antiseptic products containing triclosan. Additionally, many consumer and science groups have called for the removal of triclosan, and at least one state, Minnesota, is limiting the use of or requiring the elimination of triclosan in consumer products. Based on this, a number of large companies are phasing triclosan out of their products worldwide. While we don't know for sure whether or not there will be future NDA submissions for triclosan, or any of the other nonmonograph products, based on the current information we have received from industry, the likelihood appears to be low.

We estimate the one-time costs per NDA submission for studies to assess safety and effectiveness (excluding resistance testing) to be $9.89 million.

Table 8. Cost Summary for 12-month Compliance Period, Present Value and Annualized (in millions of 2016 dollars)

	Present Value of Costs						Annualized Costs over a 10-Year Period					
	Present Value 3%			Present Value 7%			Annualized 3%			Annualized 7%		
	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High
Relabeling	$1.42	$2.46	$4.03	$1.36	$2.36	$3.88	$0.16	$0.29	$0.47	$0.19	$0.34	$0.55
Reformulation	$7.60	$15.40	$30.61	$7.32	$14.82	$29.47	$0.89	$1.81	$3.59	$1.04	$2.11	$4.19
Total	$9.02	$17.85	$34.64	$8.68	$17.19	$29.47	$1.05	$2.10	$4.06	$1.23	$2.45	$4.74

H. Distributional Effects (Removing Alcohol-containing Surgical Hand Scrub Product from the Market)

This final rule also addresses comments on the eligibility of three active ingredients -ethyl alcohol, benzethonium chloride, and chlorhexidine gluconate—and finds that these three active ingredients are ineligible for evaluation under the OTC Drug Review for use in certain health care antiseptic products (see section IV.D.1, table 3 of the final rule). Only one product, a surgical hand scrub that contains ethyl alcohol, is affected by this rule, Triseptin (ethyl alcohol 70%), which is marketed by BD. We believe that the most likely action for this product is for it to be removed from the market. While it would be possible to reformulate the product to not need to be used with water, the company that markets this product already has a marketed line of OTC health care antiseptic no-rinse products that contain this and other active ingredients used in health care antiseptics. Other types of

reformulations would require the company to submit an NDA for the product. Therefore, because reformulation appears to be an unlikely outcome for this product, we estimate the costs of removing it from the market. We expect that there may be some small amount of producer surplus loss, but most of the loss in revenue due to removal would be categorized as a transfer because we assume that supply is highly elastic and that supply would be diverted to other channels (or highly substitutable products) rather than lost producer surplus. We make the determination that this is a transfer rather than a cost because this is a special case where a single product is being removed from the market, rather than a product class.

According to its 2016 annual report, BD's worldwide revenue was $12.5 billion (Ref R32). The company made approximately $1.2 billion from their sales of "Pharmaceutical systems", which we believe include health care antiseptic washes. Approximately 55% of this revenue came from the United States, which brings the total sales in this sector to $660 million. According to the BD website, there are approximately 93 product lines, including Triseptin, which constitute this sector of their revenue. If we assume that each product line produces an equal amount of sales, we arrive at $7.1 million in sales per year per product line.

We therefore estimate that the removal of Triseptin from the market will cost the company approximately $7.1 million per year in lost sales revenue. A low and high estimate range is calculated by dividing the total sales by a range for the number of applicable product lines from 140 (low estimate; approximately doubling the number of product lines) to 50 (high estimate; approximately halving the number of product lines). We include this because there is uncertainty around which product lines are included in the sales of the reported "Pharmaceutical systems" category in the annual report. The low estimate of yearly sales of Triseptin is $4.7 million, and the high estimate is $13.2 million.

While we use $7.1 million as our central estimate, we believe that the true sales of this product line may be lower. In a recent search of Amazon.com, a 32oz container of Triseptin cost $54. Other product lines in this "Pharmaceutical systems" category include surgical instruments, which are likely to be much more expensive. Additionally, the category also includes product lines such as sharps (e.g., syringes), which, while not high cost individually, are high volume, and may therefore produce more revenue than the Triseptin product line. Lastly, Triseptin is not a central product line that is promoted by BD, and therefore is unlikely to be a strong driver of the company's sales.

Additionally, we believe that it is likely that the lost sales from Triseptin will be mitigated by the migration of sales to other product lines, such as the company's antiseptic rubs, or the creation of new product lines, such as a new antiseptic wash, or the marketing by the company of a line of plain soaps that do not contain active ingredients used in health care antiseptics. We therefore estimate the total amount of transfer from the removal of Triseptin to be approximately 50% of the total estimated sales of the product line, with middle, low and high estimates of $3.6, $2.1, and $6.6 million, respectively. We assume that these effects would reoccur yearly, over a ten-year period. We categorize these effects as transfers, which are therefore not included in the final costs estimates.

Table 9. Summary of Transfers over a Ten Year Period (in 2016 dollars)

	Present Value of Transfers						Annualized Transfers over a 10-Year Period					
	Present Value 3%			Present Value 7%			Annualized 3%			Annualized 7%		
	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High
Total Transfers	$17.9	$30.7	$56.3	$14.7	$25.3	$46.4	$2.1	$3.6	$6.60	$2.1	$3.6	$6.6

I. 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. A secondary impact is that the timing of removal of the alcohol surgical hand scrub would affect revenues at different points.

Therefore, all label changes will incur the full per product redesign costs. Reducing the compliance period by 6 months would increase the total cost of relabeling by $91,800 to $204,000. 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 10. At a 3 percent discount rate, the total annualized costs range from $1.1 to $4.2 million and $1.3 to $4.9 million at a 7 percent discount rate.

Table 10. Cost Summary for 6-Month Compliance Period (in millions of 2016 dollars)

	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	$1.53	$2.55	$4.28	$1.43	$2.55	$4.18	$0.20	$0.31	$0.51	$0.20	$0.41	$0.61
Reformulation	$7.75	$15.61	$31.11	$7.55	$15.10	$30.50	$0.92	$1.84	$3.67	$1.12	$2.14	$4.39
Total Cost for Relabeling and Reformulation	$9.18	$18.26	$35.29	$9.08	$17.65	$34.68	$1.12	$2.14	$4.18	$1.33	$2.55	$4.90
Change in Relabeling and Reformulation Costs from 12-Month Compliance Period	$0.20	$0.41	$0.71	$0.41	$0.51	$1.33	$0.00	$0.00	$0.10	$0.10	$0.10	$0.20

Decreasing the compliance period would also accelerate the accrual of public health benefits by reducing health care professional's exposure to triclosan six months sooner. In Table 11, we approximate the increase in benefits by estimating the change in the present value (over ten years) of antiseptic ingredient exposure reductions when compounded at a 3 percent and 7 percent discount rate. This final rule will reduce triclosan exposure, as compared to a 12-month compliance period, by 11,177 kilograms at a 3 percent discount rate and 21,267 kilograms at a 7 percent discount rate.

Table 11. Potential Reduction in Exposure, Present Value Discounted over Ten Years (in kilograms)

	6-Month Compliance Period		Change from 12-Month Compliance Period	
	Present value- 3%	Present value-7%	Present value- 3%	Present value-7%
Triclosan Exposure	761,835	639,342	11,177	21,267

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 $204,000 to $408,000. 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 6 months, as shown in Table 12. Under this scenario, we estimate total annualized costs range from $1.0 to $4.0 million at a 3 percent discount rate and $1.2 to $465 million at a 7 percent discount rate.

Table 12. Cost Summary for 18-Month Compliance Period (in 2016 dollars)

	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	$1.22	$2.14	$3.57	$1.22	$2.14	$3.47	$0.10	$0.31	$0.41	$0.20	$0.31	$0.51
Reformulation	$7.45	$15.20	$30.19	$7.04	$14.38	$28.46	$0.92	$1.73	$3.57	$1.02	$2.04	$4.08
Total Cost for Relabeling and Reformulation	$8.77	$17.34	$33.76	$8.26	$16.42	$32.03	$1.02	$2.04	$3.98	$1.22	$2.35	$4.59
Change in Relabeling and Reformulation Costs from 12-Month Compliance Period	($0.31)	($0.51)	($0.92)	($0.41)	($0.71)	($1.33)	$0.00	($0.10)	($0.10)	($0.10)	($0.10)	($0.20)

Note: Numbers in parentheses denote a reduction relative to the proposed rule impacts.

The effect of extending the compliance period to 18 months would be a decrease in potential public health benefits resulting from prolonged exposure by health care professionals to triclosan by six months. Discounting the present value of triclosan exposure, we estimate an increased exposure of triclosan to health care professionals, over the 12-month compliance period, to be 11,013 kilograms at a 3 percent discount rate, and 20,559 kilograms at a 7 percent discount rate.

Table 13. Potential Reduction in Exposure, Present Value Discounted over Ten Years (in kilograms)

	18-Month Compliance Period		Change from 12-Month Compliance Period	
	Present value- 3%	Present value-7%	Present value- 3%	Present value-7%
Triclosan Exposure	739,645	597,516	-11,013	-20,559

J. Cost Effectiveness

We measure the effectiveness of this rule as the total reduction in exposure to triclosan, over ten years, in the health care setting. To obtain a measure of cost-effectiveness, we divide the present value of costs by 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 14, under the rule's 12-month compliance period, we estimate that each kilogram of reduced exposure to antiseptic active ingredients will cost $12 to $46 at a 3 percent discount rate and $14 to $54 at a 7 percent discount rate.

Table 14. Cost-Effectiveness Under Alternative Compliance Periods (in $ per kilogram of triclosan reduced, in 2016 dollars))

	3% Discount Rate			7% Discount Rate		
Compliance Period	Low	Med.	High	Low	Med.	High
6-Month	$12.11	$23.93	$46.36	$14.15	$27.63	$54.19
12-Month (rule)	$12.03	$23.79	$46.14	$14.06	$27.82	$53.95
18-Month	$11.82	$23.46	$45.62	$13.90	$27.56	$53.55

III. Small Entity Effects

FDA has examined the economic implications of the final rule as required by the Regulatory Flexibility Act. The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. We estimate that only four small businesses will be adversely affected by the final rule, out of a total of 16 small businesses in the market, and 32 total businesses. (The one company affected by the removal of the alcohol-containing surgical hand scrub is not a small business.) The total average yearly sales of these four companies represent 0.89% of all small business sales in this market. Therefore, we have determined that the final rule will not have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as a regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

The final rule would impact entities that manufacture health care antiseptic products containing the active ingredient triclosan. The 2016 FDA Drug Product Registration Database indicates that there are roughly 32 entities that manufacture health care antiseptics that contain triclosan. Among these entities, we were able to collect revenue and employee data for 30 firms using the Dun and Bradstreet database (Dun & Bradstreet, Inc.). (The two missing manufacturers are not based in the U.S. These two manufacturers account for three of the 163 identified products.)

Table 15 presents the number of firms that employ the following number of workers: 0 to 4, 5 to 9, 10 to 19, 20 to 49, 50 to 99, 100 to 249, 250 to 499, 500 to 999, and 1,000 and over. The results indicate that most of the firms have over 1,000 employees. The Small Business Administration (SBA) defines entities classified in North American Industry Classification System (NAICS) code 325412 "Pharmaceutical Preparation Manufacturing" to be "small" if they employ fewer than 750 workers. Given this definition, the data indicate that 16 of the 30 entities are small, which translates to 53 percent of firms that manufacture health care antiseptics containing triclosan. Furthermore, each small entity manufactures an average of 11 unique health care antiseptics that contain triclosan.

Table 15. Health care Antiseptic Manufacturers by Number of Employees

Size by Number of Employees	Number of Firms	Average Yearly Sales (in thousands)	Average Number of Products per Firm
0 to 4	0	n/a	0
5 to 9	2	$1,023	2
10 to 19	2	$2,449	1
20 to 49	3	$21,296	10
50 to 99	2	$25,283	3
100 to 249	4	$39,616	17
250 to 499	1	$65,166	49
500 to 999	2	$218,123	6
1,000 and over	14	$40,183,512	71

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

We estimate that the total per firm costs of this final rule range from $206,035 to $223,831, with a midpoint estimate of $213,176. The average yearly sales of the small business in this analysis are $48 million. We estimate, therefore, that on average, the costs of complying with this rule will be approximately 0.4% of sales. We break this down further by firm size in Table 16. These results indicate that the cost of the rule may be significant for the four firms that have between 5 and 19 employees, but the rest of the small businesses will not be substantially affected by implementing the rule. We

therefore conclude that this cost is not significant and certify that the final rule will not have a significant economic impact on a substantial number of small businesses.

Table 16. Costs of Rule as a Proportion of Average Yearly Sales

Size by Number of Employees	Number of Firms	Proportion of Average Yearly Sales (Low Estimate)	Proportion of Average Yearly Sales (Medium Estimate)	Proportion of Average Yearly Sales (High Estimate)
5 to 9	2	20.1%	20.8%	21.9%
10 to 19	2	8.4%	8.7%	9.1%
20 to 49	3	1.0%	1.0%	1.1%
50 to 99	2	0.8%	0.8%	0.9%
100 to 249	4	0.5%	0.5%	0.6%
250 to 499	1	0.3%	0.3%	0.3%
500 to 999	2	0.1%	0.1%	0.1%

C. Alternatives for Regulatory Relief

A longer compliance period could provide regulatory relief for small businesses. However, a longer compliance period would lead to a product containing a non-GRAS/E staying on the market longer, continuing exposure and delaying potential benefits.

For this analysis, we estimate the costs to small businesses if the compliance period were extended to 18 or 24 months. We assume that 15% of health care antiseptic containing triclosan are manufactured by small businesses.

Table 17 presents the values for an 18-month compliance period. Under this scenario, we estimate that the medium present value of average costs for small business would range from $1.3 million at a 3% discount rate, to $154 million at a 7% discount rate. This is equal to 0.6% of average yearly sales, at both discount rates. Changing the compliance period to 18 months for small businesses would results in a decrease in medium estimate of the present value of costs of $75,000 at a 3% discount rate, and $108,000 at a 7% discount rate, as compared to a 12-month compliance period.

Table 17. Summary of Costs for Small Entities Under 18-Month Compliance Period (in $thousands)

	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	$1,312	$2,603	$5,061	$1,245	$2,470	$4,800	$154	$305	$594	$177	$352	$683
Average compliance cost per small entity	$82	$162	$316	$78	$154	$300	$9	$19	$37	$11	$22	$43
Cost as a percent of average yearly sales per entity	0.30%	0.60%	1.20%	0.30%	0.60%	1.10%	0.00%	0.10%	0.10%	0.00%	0.10%	0.20%
Change in Relabeling and Reformulation Costs from 12-Month Compliance Period	($42)	($75)	($135)	($57)	($108)	($201)	($5)	($9)	($15)	($8)	($15)	($29)

Note: Numbers in parentheses denote a reduction relative to the proposed rule impacts.

Table 18 presents the estimates for a 24-month compliance period. Under this scenario, we estimate that the medium present value of average costs for small business would range from $2.3 million at a 3% discount rate, to $2.2 million at a 7% discount rate. This is equal to 0.5% of average yearly sales, at both discount rates. Changing the compliance period to 24 months for small businesses would results in a decrease in medium estimate of the present value of costs of $407,000 at a 3% discount rate, and $472,000 at a 7% discount rate, as compared to a 12-month compliance period.

Table 18. Summary of Costs for Small Entities Under 24-Month Compliance Period (in $thousands)

	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	$1,116	$2,272	$4,523	$1,034	$2,106	$4,193	$131	$266	$530	$147	$300	$597
Average compliance cost per small entity	$69	$142	$283	$64	$132	$262	$8	$16	$33	$9	$18	$38
Cost as a percent of average yearly sales per entity	0.30%	0.50%	1.00%	0.20%	0.50%	1.00%	0.00%	0.10%	0.10%	0.00%	0.10%	0.10%
Change in Relabeling and Reformulation Costs from 12-Month Compliance Period	($238)	($407)	($672)	($268)	($472)	($808)	($28)	($48)	($79)	($38)	($67)	($115)

Note: Numbers in parentheses denote a reduction relative to the proposed rule impacts.

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