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; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record

Docket No. FDA-2015-N-0101

Preliminary Regulatory Impact Analysis

Initial Regulatory Flexibility Analysis

Unfunded Mandates Reform Act Analysis

Economics Staff

Office of Planning

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Office of the Commissioner

2. Every Antiseptic Active Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

C. Alternatives for Regulatory Relief

1. No Antiseptic Active Ingredient Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

   a. Delay Testing Compliance One Year

2. Every Antiseptic Active Ingredient with Large Market Share Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

   a. Increase Relabeling Compliance Times

IV.References

I. Introduction and Summary

A. Introduction

FDA has examined the impacts of the proposed 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 (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). The Agency believes that this proposed rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The proposed rule could impose significant economic burdens on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies 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 one year." The current threshold after adjustment for inflation is $141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA expects that this rule could result in a 1-year expenditure that would meet or exceed this amount.

B. Summary of Costs and Benefits

The proposed rule's costs and benefits are summarized in table 1. Benefits are attributed to reducing the potential adverse health effects associated with using antiseptic active ingredients in the event that any active ingredient is not shown to be generally safe and effective for their intended use. Annual benefits are estimated to range between $0 and $0.16 million. We estimate the present value associated with $0.16 million of annual benefits, over a 10 year period, to approximately equal $0 to $1.4 million at a 3 percent discount rate, and $0 to $1.1 million at a 7 percent discount rate.

Costs include the one-time costs associated with reformulating products, relabeling reformulated products, and conducting both safety and efficacy tests. Total upfront costs are estimated to range between $64.0 and $90.8 million. Annualizing these costs over a 10 year period, we estimate total annualized costs to range from $7.3 to $10.4 million at a 3 percent discount rate, and from $8.5 to $12.1 million at a 7 percent discount rate.

Table1. 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	0.0	$0.08	$0.16	2013	7%	10 years	Value of reduced number of adverse events associated with using non-GRAS/GRAE antiseptic active ingredients. Range of estimates captures uncertainty.
	Annualized Monetized $millions/year	0.0	$0.08	$0.16	2013	3%	10 years	
	Annualized Quantified billion/year	0	10.3	20.6		7%	10 years	Reduced antiseptic active ingredient exposure (in milliliters). Range of estimates captures uncertainty.
	Annualized Quantified billion/year	0	10.3	20.6		3%	10 years	
	Qualitative	Value of infection avoidance associated with switching from non-GRAS/GRAE antiseptic active ingredients to NDA or ANDA antiseptics.						
Costs	Annualized Monetized $millions/year	$8.5	$10.3	$12.1	2013	7%	10 years	Annualized costs of reformulating and testing antiseptic products. Range of estimates captures uncertainty.
	Annualized Monetized $millions/year	$7.3	$8.9	$10.4	2013	3%	10 years	
	Annualized Quantified billion/year					7%		
	Annualized Quantified billion/year					3%		
	Qualitative	Where the products affected by this proposed rule are currently chosen over NDA and ANDA alternatives (such as chlorhexidine products), a switch brought on by the rule may lead to search costs or other types of transactions costs. In this scenario, there are also the potential costs associated with adverse reactions if patients are allergic to substitute products.						
Transfers	Federal Annualized					7%		
	Monetized $millions/year					3%		
	From/To							
	Other Annualized					7%		
	Monetized $millions/year					3%		
	From/To							
Effects	State, Local, or Tribal Government: Not applicable Small Business: The costs associated with potentially affected small entities range between 0.60 and 20.64 percent of their average annual revenues. Wages: No estimated effect Growth: No estimated effect							

II. Preliminary Regulatory Impact Analysis

A. Brief History of Health Care Antiseptics

Health care antiseptics are antimicrobial agents that are intended to reduce the number of micro-organisms on the skin. FDA recognizes 29 health care antiseptic active ingredients as being eligible for the over-the-counter (OTC) drug review, each of which it has proposed in the past to group into one of three categories.

- Category I antiseptic active ingredients would be those that FDA had proposed, as part of a proposed rule in 1994, to determine, based on the available data, as generally recognized as safe and effective (GRAS/GRAE) for use in health care antiseptic products;
- Category II antiseptic active ingredients would be those that FDA had proposed to determine to be not GRAS/GRAE for use in health care antiseptics; and finally,
- Category III active antiseptic ingredients are those for which the Agency indicated that the available data were insufficient to determine that they were GRAS, GRAE, or both.

This terminology has been taken from the OTC drug procedural regulations in 21 CFR s. 330.10.

Antiseptics are marketed to consumers and various industries, such as research institutions, food handlers, textile manufacturers, and health care providers. This rule, however, only covers health care antiseptics, which are drug products that are intended for use by health care professionals in a hospital setting or other health care situations outside the hospital, but that are not identified as 'first aid antiseptics' in the 1991 First Aid Tentative Final Monograph (TFM). Health care antiseptics include patient preoperative skin preparations, surgical hand scrubs and rubs, and health care personnel hand washes and rubs. Currently marketed health care antiseptic products contain antiseptic active ingredients that were proposed to be classified under the 1994 tentative final monograph as either

category I or III. No currently marketed products contain antiseptic active ingredients that were proposed to be classified as category II in the 1994 TFM.

Health care antiseptics are available as washes, rubs, and patient preoperative skin preparations. 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 wash products are available as liquids. However, some wash products are also manufactured as foams. Rubs, on the other hand, are generally available as evaporative gels or single-use wipes. Rubs are also known to the public as hand sanitizers.

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, it 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-R17).

C. Need for Regulation

The proposed 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 our ongoing evaluation of the safety and effectiveness of drug products containing these ingredients. (For definitions of these terms see 21 CFR 330.10(a) (4)). As indicated in previous sections, FDA has not yet determined whether category III active antiseptic ingredients, such as the ingredients addressed in this proposed rule, are safe or effective for health care antiseptic use. The proposed rule, if finalized as proposed, would remove these ingredients from the monograph, unless additional safety and effectiveness data on health care antiseptic ingredients are provided to FDA, and FDA makes a determination that health care antiseptic products containing these active ingredients are generally recognized as safe and effective.

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 on a daily basis (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 Center 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 any of the 29 earlier-listed health care antiseptics are GRAS/GRAE for their intended uses. 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.

A body of research has established that, for many environmental toxins, there can be a long latency period between exposure and potential adverse health effects (Ref. R5-R14). 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. R4). 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

The proposed rule's objective is to update the standards and conditions whereby health care antiseptic active ingredients are determined to be GRAS/GRAE for their intended uses in health care

antiseptic products. Hence, this regulatory action is intended to provide a greater level of assurance of safety and effectiveness that is not expected to occur in the existing market for health care antiseptics.

The proposed rule requests data from antiseptic manufacturers and other interested parties, demonstrating that the antiseptic active ingredients included in health care antiseptic products are GRAS/GRAE for their intended uses. To provide evidence that an antiseptic active ingredient is GRAE for health care antiseptic use, we propose that the ingredient must undergo two repetitions of an in vivo test and three types of in vitro tests (i.e. one minimum inhibitory concentration study, one time-kill study, and one spectrum analysis). To provide evidence that an antiseptic active ingredient is GRAS, we propose that the following types of studies should be conducted: human pharmacokinetic maximal use trial (MUsT) studies; absorption, distribution, metabolism, and excretion (ADME) studies in animals; developmental and reproductive toxicity (DART) studies in animals; oral and dermal carcinogenicity studies in animals; studies to characterize potential hormonal effects; and an evaluation of the potential to cause bacterial resistance.

FDA has reviewed the available scientific evidence and concluded that no ingredient categorized as category I in the 1994 TFM (Povidone Iodine, Isopropyl Alcohol, and Ethyl Alcohol) meets the GRAS/GRAE standard under the updated requirements proposed under this rule. Consequently, the rule proposes to categorize antiseptic active ingredients previously proposed as category I as category III ingredients.

When the rule is finalized, if a health care antiseptic active ingredient does not meet the proposed updated standards, and FDA determines that the active ingredient is not GRAS/GRAE, manufacturers of this ingredient would have to stop marketing health care antiseptic products

containing that ingredient within one year of the date of publication of the final rule, unless the manufacturer obtains an approved new drug application (NDA) for that product. Furthermore, manufacturers would not be able to continue marketing products containing that ingredient as health care antiseptics by only relabeling their products.[1] However, if FDA determines that certain health care antiseptic active ingredients are GRAS/GRAE for use in health care antiseptic products, manufacturers of products containing ingredients that do not meet the proposed updated standards could continue to market these products by reformulating them to include those ingredients that *are* demonstrated to be GRAS/GRAE under the same conditions of use.

The proposed rule, when finalized, could cause manufacturers to stop marketing certain health care antiseptic products. For example, manufacturers that produce health care antiseptic products containing less commonly used antiseptic ingredients (i.e., antiseptics with a relatively small share of the market) could choose to exit the market if the costs to comply with the rule exceed the benefits to continue production. However, because such antiseptics would, by definition, make up a small share of the market, discontinuing their production would not affect a substantial number of individuals. Furthermore, individuals using these products may be able to substitute them with products that contain active ingredients that are found to be GRAS/GRAE under the final rule, as well as with new drug application (NDA) and abbreviated new drug application (ANDA) health care antiseptics, which are not covered under this rule and could contain other active ingredients, such as Chlorhexidine Gluconate. For example, a medical worker using health care personnel hand washes containing Benzalkonium Chloride could switch to FDA-approved NDA products containing Chlorhexidine Gluconate.

[1] It is possible that some manufacturers may choose not to reformulate their products. These unreformulated products could not be marketed legally for an intended drug use. The intended use may be discerned from a variety of factors not limited to the wording on the label. Failure to observe these limitations could be grounds for enforcement action by FDA.

E. Baseline Conditions

The rule, when finalized, would require manufacturers to only market antiseptic products containing active ingredients that are GRAS/GRAE for health care antiseptic use, effective one year after publication. These actions could potentially reduce the number of non-GRAS/GRAE products, and shift consumer exposure from products containing non-GRAS/GRAE antiseptic active ingredients to products containing GRAS/GRAE antiseptic active ingredients.

The rule's impact is estimated relative to the baseline, which is the state of the world in the absence of the proposed 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 exposure to, and usage of, antiseptic active ingredients. We assume that, in the absence of this proposed rule, antiseptic usage remains constant over time (i.e. future consumption is expected to be approximately equal to current consumption).

1. Number of Active Ingredients and Affected Products In The Current Market for Health Care Antiseptics

FDA is proposing monograph changes for 29 health care antiseptic active ingredients. However, data from IMS Health and A.C. Nielsen suggest that only 7 of these 29 ingredients are currently marketed in health care antiseptic products (Ref. R18 and R19). These antiseptic active ingredients include Benzalkonium Chloride, Benzethonium Chloride, Chloroxylenol, Ethyl Alcohol, Isopropyl Alcohol, Povidone Iodine, and Triclosan. We recognize that the 1994 TFM proposed to classify Ethyl Alcohol, Isopropyl Alcohol, and Povidone Iodine as category I health care antiseptic active ingredients. However, based on the recommendations of the 2014 Nonprescription Drugs Advisory Committee (NDAC) and a re-evaluation of the available clinical data in light of current standards, FDA has concluded as discussed

in the preamble of the proposed rule that these data are insufficient to support that these antiseptic active ingredients are GRAS/GRAE for use in health care antiseptics. Hence, the rule proposes to classify Ethyl Alcohol, Isopropyl Alcohol, and Povidone Iodine as category III antiseptic active ingredients.

We estimate the number of uniquely packaged health care antiseptic products using the 2013 FDA drug product registration database. The advantage of this database is that we believe it represents a reasonably up-to-date, nationally representative sample studying individual antiseptic products. It also indicates which antiseptics are intended to be used in health care settings, and organizes these products using unique product codes (UPCs). 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. However, we note that other sales databases, such as IMS Health and A.C. Nielsen, may also underestimate the number of health care antiseptic products.

Table 2 reports the number of uniquely packaged health care antiseptic products reported in the 2013 FDA drug product registration database. The data indicate that there are 2,529 uniquely packaged health care antiseptic products in the market. Among these products, most contain Benzalkonium Chloride (20.8 percent), Triclosan (20.3 percent), Isopropyl Alcohol (19 percent) and Ethyl Alcohol (19 percent) as the active ingredient. The next most common ingredient is Chloroxylenol, which is contained in 11.6 percent of products. The least common active antiseptic ingredients of the seven currently marketed ingredients are Povidone Iodine (6.3 percent) and Benzethonium Chloride (2.6 percent).

Table 2. Total Estimated Number of Affected Uniquely Packaged Health Care Antiseptic Products (UPCs)

Health care Antiseptic Washes, Scrubs, and Rubs	Liquids, Gels, Foams, and Sprays		Wipes, Swabs, Prep Pads		Creams, Lotions		
	Number of UPCs	Percent of UPCs	Number of UPCs	Percent of UPCs	Number of UPCs	Percent of UPCs	Total UPCs
Benzalkonium Chloride	321	16.15%	206	40.23%	1	3.45%	528
Benzethonium Chloride	68	3.42%	2	0.39%	0	0.00%	70
Chloroxylenol	283	14.24%	5	0.98%	4	13.79%	292
Ethyl Alcohol	429	21.58%	34	6.64%	14	48.28%	477
Isopropyl Alcohol	282	14.19%	206	40.23%	0	0.00%	488
Povidone Iodine	95	4.78%	58	11.33%	7	24.14%	160
Triclosan	510	25.65%	1	0.20%	3	10.34%	514
Total	1988	100.00%	512	100.00%	29	100.00%	2529

The data also indicate that health care antiseptic products are generally available in a variety of forms, including: creams, lotions, liquids, solutions, sprays, gels, foams, and applicators containing solutions, such as wipes, swabs, and prep pads. The data indicate that most health care antiseptics are available as bulk liquids, gels, foams, or sprays (78.6 percent). The next most common are applicators containing a liquid solution, such as wipes, swabs, and prep pads (20.2 percent). Finally, some health care antiseptics are also available as creams and lotions (1.2 percent).

Health care antiseptics are sold as washes, rubs, and patient preoperative skin preparations. Washes (which include scrubs) are generally used with water, whereas rubs (some of which are also referred to as “hand sanitizers”) are leave-on products that are not used with water. Table 3 reports the number of uniquely packaged health care antiseptic washes and rubs. We group together washes and scrubs because these products are used along with water. The data indicate that most antiseptic products are washes, approximately 70 percent, with several active ingredients available only in products that are washes (Chloroxylenol, Povidone Iodine, and Triclosan). Rubs account for 30 percent of all health care antiseptic products. We note that the categories in table 3 do not perfectly correlate to

the proposed health care antiseptic indications, and thus the rub and wash categories in table 3 also include patient preoperative prep products.

Table 3. Percentage of Total Affected Products Available as Washes, Scrubs, and Rubs

Health care Antiseptic Washes, Scrubs, and Rubs	**Health care Antiseptic Washes and Scrubs**		**Health care Antiseptic Rubs / Sanitizers**		Total UPCs
	Number of UPCs	Percent of UPCs	Number of UPCs	Percent of UPCs	
Benzalkonium Chloride	266	15.21%	262	33.98%	528
Benzethonium Chloride	19	1.09%	51	6.61%	70
Chloroxylenol	295	16.87%	0	0.00%	295
Ethyl Alcohol	37	2.12%	440	57.07%	477
Isopropyl Alcohol	460	26.30%	18	2.33%	478
Povidone Iodine	160	9.15%	0	0.00%	160
Triclosan	512	29.27%	0	0.00%	512
Total	1749	100.00%	771	100.00%	2520
This table contains fewer UPCs than table 2 because it omits some creams that are not washes or rubs.					

Most health care antiseptic rubs contain Isopropyl Alcohol, Ethyl Alcohol, Benzalkonium Chloride, or Benzethonium Chloride. Ethyl Alcohol and Benzalkonium Chloride are the most popular antiseptic active ingredients for health care antiseptic rubs, with 440 uniquely packaged rubs containing ethyl alcohol and 262 containing Benzalkonium Chloride. Benzenthonium Chloride is the next most popular ingredient and is contained in 51 products. The data also indicate that most health care antiseptic products containing Ethyl Alcohol and Benzethonium Chloride are available as rubs. Among Ethyl Alcohol products, roughly 90 percent are health care antiseptic rub products, while among Benzethonium Chloride products, 73 percent are health care antiseptic rubs. Finally, although not indicated in the above table, almost every health care antiseptic rub product is formulated as an evaporative gel or liquid.

2. Antiseptic Active Ingredient Usage in Health Care Antiseptic Products

There are several obstacles associated with measuring any category of antiseptic usage. The available sales databases on utilization underestimate usage because they do not capture all sales channels for antiseptic products. For example, A.C. Nielsen only **c**ollects data on products containing a few antiseptic ingredients—primarily Alcohols, with some data on Povidone Iodine and Benzalkonium Chloride products—and it does not indicate which antiseptics are health care antiseptics (Ref. R19). IMS Health, on the other hand, collects data on every antiseptic ingredient (Ref. R18). However, it only collects data for a small fraction of products containing these ingredients. Furthermore, it only collects these products' retail pharmacy sales, which A.C. Nielsen data suggests would substantially understate total sales. FDA registration database does not collect either sales or usage measures. Therefore, we do not use these three databases to measure antiseptic usage.

Rather, to estimate potential annual baseline antiseptic exposure, we use the 2013 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 imported to the United States. (The unit measure associated with liquid antiseptic units is liters, while the unit measure associated with single-use antiseptic applicators is the total number of single-use applicators.) We use the ORADDS database because it collects data on every antiseptic active ingredient, unlike the A.C. Nielsen database, and it also collects substantially more data on antiseptic products than IMS Health. Despite these advantages, however, we emphasize that this database contains gaps. ORADDS only collects antiseptic imports, which implies that 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. A solution to this problem would be to adjust total antiseptic imports with the ratio between antiseptic imports and domestic antiseptic production. However, domestic antiseptic product data are

unavailable, and thus we welcome any comments providing representative data on domestic antiseptic production, or alternative solutions to this issue.

Like the A.C. Nielsen and IMS Health data sets, ORADDS also does not distinguish health care antiseptics from other antiseptic products. To address this problem, we have checked the manufacturer's Web site for each antiseptic product in an attempt to verify whether the manufacturer markets the particular product as a health care antiseptic product and/or supplies the product to health care providers for use as a health care antiseptic product.

It is difficult to distinguish which ingredients are marketed as rubs versus washes. To supplement the analysis, we use the 2009 A.C. Nielsen data, which collects sales at most major retailers. The advantage to this database is that it provides the most comprehensive data on antiseptic rub sales; however, we are still unable to distinguish which antiseptic products are marketed as health care antiseptics. To identify potential health care antiseptic products, we have checked the manufacturer's Web site for each specific antiseptic product to verify whether the manufacturer supplies it to health care providers or otherwise markets it as a health care antiseptic. A problem with this method is that it might include some antiseptics that are *not* intended to be used in the health care setting, while also excluding other products that *are* intended to be used in the health care setting. However, these biases may approximately offset each other.

Another problem with the A.C. Nielsen data is that it was collected in 2009. To adjust for growing sales since 2009, we use antiseptic growth rates reported in an industry report for antiseptic rubs (Ref. R20). The results indicate that annual antiseptic sales grew approximately 5.6 percent during 2007 to 2012.

Table 4 reports the total estimated antiseptic unit imports in 2013 that are reported by ORADDS, and the total antiseptic unit rub sales reported in A.C. Nielsen. Table 5 provides an illustrative example of how we calculate usage of antiseptic active ingredients based on product volume. For each antiseptic product, ORADDS reports total unit imports and the unit of measure. (Liquids are reported in liters and single-use products are reported as the total number of single-use applicators or pieces.) To supplement the analysis, we check the manufacturer's Web site to collect the volume of antiseptic per product, and each product's concentration level (percentage antiseptic active ingredient per 1 milliliter (ml) antiseptic).

We calculate the total volume of antiseptic imported, per product, by multiplying that product's total unit imports by volume. For example, the table indicates that we imported 12,000 liters of antiseptic from product D. Given that 1 liter contains 1000 milliliters (mLs), we calculate that we imported 12,000,000 mLs antiseptic from product D (= 12,000 liters product D imported * 1,000 mLs antiseptic per liter). Using this value, we calculate the total imported volume of pure antiseptic ingredient (antiseptic with a 99.99 concentration level) associated with product D by multiplying its total imported volume by its concentration level. Given that product D's concentration level is 98 percent, we calculate that this product's total imported volume contains 11,760,000 mLs pure antiseptic ingredient (= 12,000,000 mLs antiseptic * 0.98 mLs pure antiseptic ingredient per 1 ml antiseptic).

Another method to measure exposure is to estimate total single uses. For single-use products, such as products A and B, we use their respective total unit measures to estimate their total single-uses. For non-single use products, such as product D, we divide the product's total pure antiseptic ingredient volume by the mode concentration of antiseptic ingredient associated with single-use antiseptics

containing the active ingredient. Using Chloroxylenol as our example, the data indicate that the average single-use antiseptic containing Chloroxylenol contains roughly 0.05 mLs pure Chloroxylenol antiseptic per every 1 mLs antiseptic. Hence, using product D as our example, we estimate that roughly 235,200,000 single uses are associated with the total volume of pure antiseptic ingredient imported for product D (= 11,760,000 mLs pure antiseptic ingredient / 0.05 mLs pure antiseptic per single-use). The rationale is based on our understanding that most antiseptics contain a certain percentage of antiseptic active ingredient and water. For example, we understand that most alcohol antiseptics are 60 to 70 percent active ingredient and 30 to 40 percent water. Hence, we divide the total volume of pure antiseptic concentrate by the antiseptic's mode concentration for single-use products to take into account how much the antiseptic is diluted with water.

This calculation assumes that the mode single-use applicator contains roughly 1 ml antiseptic (not pure concentrated antiseptic). We acknowledge that not every single-use applicator contains 1-ml antiseptic. For example, the products in table 4 indicate that some single-use applicators contain upwards to 12 mLs antiseptic. However, discussions with FDA scientists indicate that most products nonetheless contain roughly 1-ml antiseptic. An Internet search of single-use antiseptic products also indicates that most products contain roughly 1-ml antiseptic. We welcome comments on this assumption and alternative methods.

Table 4. Total Estimated Antiseptic Sales in 2013

Health care Antiseptic Active Ingredient	**Washes & Scrubs**		**Rubs / Sanitizers**	
	Number of ingredients sold in 2013 (in mLs pure, 100 percent concentrate,)	Number of single use equivalent uses sold in 2013 (1 ml swab)	Number of ingredients sold in 2009 (in mLs pure, 100 percent concentrate,)	Number of single use equivalent uses sold in 2009 (1 ml swab)
Alcohol	3,937,130,457	5,624,472,081	5,959,817,965	9,505,748,492
Benzalkonium Chloride	7,540	6,562,253	33,530	762,680,821
Benzethonium Chloride	8,067	8,020,056	0	0
Chloroxylenol	18,186,156	354,154,060	0	0
Povidone Iodine	53,009,813	565,422,245	0	0
Triclosan	11,481,713	3,791,847,025	0	0
Total	4,019,823,745	10,350,477,720	5,959,851,495	10,268,429,314

Above antiseptic categories do not correlate precisely to the proposed health care antiseptic indications

Table 5. Calculating Total Antiseptic Usage for Chloroxylenol

Product	Units	Unit of Measure	Concentration Antiseptic Active Ingredient per 1-ml antiseptic	Volume (mLs)	Total Volume in mLs [Units x Volume]	Total Volume Pure Antiseptic [Total Volume x Concentration]	Total Equivalent Single-Uses [Total Volume Pure Antiseptic x Mode Concentration Level]
A	2,060,060	1 Single-Use	0.033	12	24,720,720	815,784	2,060,060
B	2,400	1 Single-Use	0.05	2.7	6,480	324	2,400
C	116,876	Liters	0.048	1000	116,876,000	5,610,048	116,876,000
D	12,000	Liters	0.98	1000	12,000,000	11,760,000	235,200,000
Total						18,186,156	354,138,460

Mode concentration level is roughly 0.05. Omit Product names to maintain manufacturer privacy.

The results in table 4 indicate that consumers use approximately 20.6 billion mLs of single-use equivalent health care antiseptics. Of these 20.6 billion 1-mL uses, 10.27 billion are from rubs (49.8 percent) while 10.35 billion are from washes (50.2 percent).

Using the number of mLs of pure concentrate of antiseptic active ingredients sold, the data indicate that the most common antiseptic active ingredients are Alcohol and Povidone Iodine (we

aggregate Isopropyl and Ethyl Alcohol together due to data limitations). The data indicate that over 9 billion mLs of pure concentrate Alcohol antiseptic active ingredients are sold every year. The next most common antiseptic active ingredient is Povidone Iodine, with over 50 million mLs of pure concentrate antiseptic active ingredients sold every year. On the other hand, the ingredient with the smallest market share is Benzethonium Chloride, with only 8,067 mLs of pure concentrate antiseptic active ingredients sold every year.

The results indicate that the following antiseptic active ingredients have a large market share: Benzalkonium Chloride, Chloroxylenol, Ethyl Alcohol, Isopropyl Alcohol, Povidone Iodine, and Triclosan. For each active antiseptic ingredient, enough bulk ingredients are sold to potentially produce several hundred million to several billion single-use products. (Please see table 5 to view a sample calculation method for Chloroxylenol.) We consider each ingredient to have a large market share because enough of each ingredient is imported to produce over 100 million single-use antiseptic products containing the ingredient. On the other hand, Benzethonium Chloride appears to have a relatively small market share. The total amount of bulk Benzethonium Chloride sold could potentially produce only several million single-use products.

F. Benefits

If FDA determines that the health care antiseptic active ingredients that are subject to the proposed rule are not GRAS/GRAE for their intended uses, then finalizing the proposed rule is expected to generate several potential benefits. It could potentially reduce the probability that certain microbes develop antibiotic resistance. Although no scientific studies examine this issue specifically for health care antiseptics, a study argues that non-GRAS/GRAE antiseptic active ingredients were never intended to be used with such frequency as in current practice, and that their chronic use, with the exception of

ethyl and isopropyl alcohol, may contribute to antibacterial resistance to antibiotics (Ref. R4). However, the evidence provided by this paper is inconclusive, and it is not clear whether it studies health care antiseptics as opposed to other antiseptic products.

Other studies suggest that non-GRAS/GRAE antiseptic active ingredients are potentially toxic. They argue that their chronic use might interfere with various chemical messengers, resulting in adverse health effects, including various cancers (Refs. R15 and R17). However, once again, we emphasize that these studies are inconclusive and that they only study consumer antiseptics, not health care antiseptics.

Finally, requiring health care antiseptic products to contain active ingredients that have been shown to be GRAE could possibly reduce a user's risk of developing infections under health care settings. Benefits depend on current non-GRAS/GRAE antiseptic usage, and the extent to which the proposed rule, when finalized, would cause end users to substitute non-GRAS/GRAE antiseptics with health care antiseptic products that either contain active ingredients shown to be GRAS/GRAE for use in health care antiseptics or have an FDA-approved NDA or ANDA. To illustrate the rule's potential hypothetical range of benefits, we examine the following hypothetical scenarios: (1) no antiseptic active ingredient is demonstrated to be GRAS/GRAE for use in health care antiseptics; and (2) every antiseptic active ingredient with a large market share is demonstrated to be GRAS/GRAE for use in health care antiseptics. To review, an antiseptic ingredient is considered to have a large market share if enough of the ingredient is imported to potentially produce over 100 million single-use products containing the ingredient.

Another possible scenario is that every antiseptic active ingredient (including those with small market share) is demonstrated to be GRAS/GRAE for use in health care antiseptics. However, we provide evidence in the cost section that manufacturers of health care antiseptic products containing health care antiseptic active ingredients with a small market share can be expected to reformulate and relabel their products rather than conduct testing to demonstrate that the ingredients in their products are GRAS/GRAE for health care antiseptic use. For manufacturers of products containing ingredients with a small market share, testing costs are expected to substantially exceed reformulation and relabeling costs, while for manufacturers of products containing ingredients with a large share, reformulation and relabeling costs are expected to exceed testing costs. Hence, even if it is expected that an ingredient with small market share could be demonstrated to be GRAS/GRAE for use in health care antiseptic products, manufacturers of products containing this ingredient are likely to reformulate and relabel (rather than conduct tests to demonstrate GRAS/GRAE) to reduce their costs to comply with the rule.

1. Benefits Assuming No Antiseptic Active Ingredient is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

a. Reducing Resistant Microbial Strains

Adopting the proposed rule could reduce the probability of developing microbes that are resistant to clinical antibiotics. However, we expect that bacteria in the health care setting will be exposed to multiple sources of antimicrobials - regardless of the use of health care antiseptics - which may lessen the impact of the role of health care antiseptics in the development of bacterial resistance. Further, calculating any possible benefit would require data that estimates the expected reduction of developing antibiotic resistant microbes. However, these data are unavailable. Furthermore, no studies

or other sources provide proxies to estimate this value. Hence, we are unable to quantify this potential benefit.

b. Reducing Adverse Health Effects of Antiseptic Usage

The rule could reduce the probability of adverse health effects that are potentially associated with exposure to non-GRAS/GRAE antiseptic active ingredients. Calculating this benefit requires data that estimate the relationship between exposure to these ingredients and adverse health effects. However, no studies estimate this value.

As an intermediate measure, we estimate the reduction in exposure to non-GRAS/GRAE antiseptic active ingredients. Under this scenario, we assume that the available scientific evidence is not sufficient to demonstrate that Benzalkonium Chloride, Benzethonium Chloride, Chloroxylenol, Ethyl Alcohol, Isopropyl Alcohol, Povidone Iodine, and Triclosan are GRAS/GRAE for use in health care antiseptic products, resulting in medical workers switching to NDA health care antiseptic products. Reducing the public's exposure to non-GRAS/GRAE antiseptic active ingredients that are not shown to fall within the monograph is expected to reduce the risks that are potentially associated with using these products, resulting in positive health benefits. Using the single-use values reported in table 4, our results indicate that adopting the proposed rule could reduce society's annual exposure by approximately 20.6 billion mLs of potentially non-GRAS/GRAE antiseptic active ingredients. This value includes 3.8 billion mLs of non-GRAS/GRAE Triclosan, 0.35 billion mLs of non-GRAS/GRAE Chloroxylenol formula, 8 million mLs of non-GRAS/GRAE Benzethonium Chloride formula, 0.77 billion mLs of non-GRAS/GRAE Benzalkonium Chloride formula, 15.3 billion mLs of potentially non-GRAS/GRAE Alcohol formulas, and 0.53 billion mLs of potentially non-GRAS/GRAE Povidone Iodine formula.

c. Reducing Infections Associated With Using Non-GRAS/GRAE Health Care Antiseptics

If finalization of this proposed rule results in the removal from the market of products containing health care antiseptic active ingredients that are not GRAS/GRAE (nonmonograph ingredients) for their intended uses, we expect that health care providers using products containing nonmonograph ingredients would switch to FDA approved health care antiseptic products, which FDA has found to be safe and effective. These products include NDA and ANDA products that contain health care antiseptic active ingredients or combinations of health care antiseptic active ingredients that are not covered under the proposed rule, such as Chlorhexidine Gluconate or a combination of Chlorhexidine Gluconate and either Ethyl or Isopropyl Alcohol. Because these products have been demonstrated to be safe and effective, this switch could possibly reduce the probability that individuals develop various health care associated infections (HAIs), where HAIs refer to infections that individuals acquire during the course of receiving treatment for other conditions within a health care setting.

If the rule results in the removal of products that are not found to be GRAS/GRAE, the benefit to end users would be the difference between their willingness to pay for those products minus what they would have been paying otherwise in the absence of the rule. From a social perspective, part of the increase in consumer surplus represents a transfer from sellers to consumers, and the remaining gain to consumer surplus would represent the net social benefit under this scenario (also known as the 'deadweight loss' associated with information asymmetry). We estimate this net social gain indirectly by estimating the willingness to pay for corresponding potential health gains resulting from switching from products found to be nonmonograph to either GRAS/GRAE or FDA-approved products.[2] To

[2] We note that the implicit assumption in this analysis is that FDA's determination of GRAS/E status would mean that a product is both safe and effective. The scenario in which products are not found to be GRAS/E consists of several possibilities, all with their own implications for benefits, costs and transfers. They are:
(1) The non-monograph products are safe but not effective. In this case, the benefits would consist of health improvements due to more effective infection control.

estimate the value of public health benefits under this scenario, we would ideally multiply the average value associated with an avoided HAI by the potential reduction in HAIs associated with switching from a nonmonograph product to an FDA-approved health care antiseptic product [=(Average value associated with avoiding an HAI) x (Current annual usage of health care antiseptics containing nonmonograph antiseptic active ingredients) x (Expected probability of getting an HAI by using antiseptic active ingredients that are not GRAE - expected probability of getting an HAI by using NDA or ANDA antiseptic active ingredients)].[3] We request detailed comment and data on all aspects of the prospective benefits estimation method outlined below.

No studies report the risk of HAI due to using nonmonograph antiseptic active ingredients. Instead, we might proxy this value using the average risk of HAI when exposed to antiseptics in medical settings. Recent studies indicate that this probability approximately equals 0.0014 (Ref. R21 and R22). Further studies estimate the average risk that HAIs are potentially associated with antiseptic use, versus other pathways, to roughly equal 0.00008 (Ref. R23). Together, these values indicate that the average risk that an individual gets an HAI due to using a health care antiseptic potentially equals 0.000000112 (= 0.0014 average risk of developing an HAI under health care settings * 0.00008 average risk that the HAI is potentially associated with using nonmonograph antiseptics). If we were to use this value as a proxy

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(2) The non-monograph products are neither safe nor effective. In this case, the results would include the same benefits and costs associated with case (1) and would also include the benefits of avoided adverse health effects of using unsafe products.
(3) The non-monograph products are effective but not safe. In this case, benefits would consist of avoided adverse health effects of using unsafe products (not improved infection control).
(4) The non-monograph products are both effective and safe, but no one finds it sufficiently profitable to conduct the necessary testing to establish GRAS/GRAE status. In this case, there would be no health benefits.
We are able to estimate the benefits associated with health improvements due to more effective infection control, however due to lack of data we cannot estimate the benefits of avoided adverse health effects of using unsafe products; in other words, our quantitative estimates most closely reflect case (1). To the extent that the rule results in health improvements from removing unsafe products from the market, the benefits would be underestimated. We welcome comment and data to allow us to better estimate these effects.

[3] The potential for product switches to lead to new adverse reactions is discussed in the cost section, below.

for the risk that an individual gets an HAI solely due to using an OTC health care antiseptic product that contains a nonmonograph active ingredient, we would be assuming that the current estimate of risk that an individual may get an HAI due to using a health care antiseptic product is entirely due to the use of nonmonograph active ingredients.

There are several limitations associated with the above estimate. An important limitation is that multiple pathways contribute to the probability that individuals develop HAIs when they use antiseptics (Ref. R23). Causes could include the following: (1) the antiseptic product was ineffective (i.e. it did not eliminate enough microbes); (2) the antiseptic product was itself contaminated with microbes; and (3) the individual used less than the recommended dosage of antiseptic product. Beggs et al. attribute most cases to the last of these, and emphasize that the others rarely cause HAIs (Ref. R23). Given these findings, we assume that the above estimate would capture the upper bound probability of getting a HAI by using products containing nonmonograph antiseptic active ingredients, and thus that using this estimate would estimate upper bound benefits.

Another important limitation is that it is unclear what percentage of health care antiseptics used to develop these estimates were NDA products. Because NDA products have been shown to be safe and effective, HAIs associated with using NDA products are probably attributed to end users not using the recommended dosage rather than to the product not eliminating enough microbes on the skin or containing microbes itself. Hence, the greater the percentage of NDA products used in the study, the greater the estimate captures the probability that end users are developing HAIs because they are not using the recommended antiseptic dosages rather than developing HAIs because the antiseptic product was not effective.

Ideally, we would estimate antiseptic exposures in inpatient and outpatient hospitals, clinics, blood donor centers, and other relevant settings (including homes, such as for pre-injection swabbing by diabetics); however, in the absence of comprehensive data, we focus on inpatients surgeries. The individuals most likely to develop HAIs due to exposure to non-GRAE antiseptics are patients that receive inpatient surgery. CDC indicates that there are roughly 51,400,000 inpatient surgeries per year (Ref. R24). Assuming every patient is exposed to a single-dose of potentially nonmonograph antiseptic active ingredient per visit, we would estimate that patients are exposed to 51,400,000 single-doses of potentially nonmonograph antiseptics per year (=51,400,000 inpatient surgeries per year * 1 single-dose of potentially nonmonograph antiseptic active ingredient per visit). In our benefits estimation approach, we assume that only the patient is at risk for infection, but note that although we do not quantify to the potential risk to healthcare providers, the risk may not be zero. We request comment and data that would allow estimation of benefits to healthcare providers.

The above value might overestimate exposure to non-GRAS/GRAE antiseptics, and thus using this value would be expected to overstate overall potential benefits under this scenario. Some health care workers already use NDA antiseptics. Hence, this estimate captures exposure to both non-NDA OTC antiseptics and NDA antiseptics. Estimating exposure to only potentially non-GRAS/GRAE antiseptics requires data on the percentage of health care workers using NDA products. However, these data are unavailable, and thus we welcome comments that provide data estimating the percentage of health care workers using NDA products.

Given the above values, we would estimate, at the upper bound, that roughly 6 patients (=51,400,000 patients are exposed to single-doses of potentially nonmonograph antiseptics per year *

0.000000112 upper bound probability of getting an HAI per exposure to one single-dose of nonmonograph antiseptic active ingredient) are expected to get one HAI by using a nonmonograph antiseptic active ingredient per year.

We estimate the value of avoided non-fatal health care associated infections. HAIs reduce an individuals' quality of life by impeding their ability to participate in activities that they value, such as working, enjoying leisure, and enjoying good health. Furthermore, treating these infections also requires medical resources that society could otherwise use to treat other conditions. Although direct willingness-to-pay (WTP) measures for avoided HAIs are unavailable, we indirectly measure this value by estimating the sum of the average value of resources used to treat an HAI and the average monetized value of avoiding decreases in quality-adjusted life years (QALYs) due to developing HAIs.

The standard method to estimate the latter value is to multiply the expected reduction in QALYs due to developing an HAI with the average monetary value corresponding to one QALY. The Cost-Effectiveness Analysis Registry (CEA Registry) reports health-related quality of life reductions associated with various adverse events. The index values range from 0 to 1; 0 indicates that the person is equivalent to dead, while 1 indicates that they have perfect health. Values between 0 and 1 represent intermediate quality of life.

To estimate the QALY associated with HAIs, we use the values associated with surgical site infections considering the population at risk are those undergoing inpatient surgery (Ref. R25). The Cost Effectiveness Analysis (CEA) Registry indicates that there are various surgical site infections (SSIs), which include staphylococcus, streptococcus, pseudomonas, and methicillin-resistant staphylococcus aureus. The average health-related quality of life index values associated with various SSIs range between 0.30

and 0.78. These results indicate that the average value associated with more severe SSIs (e.g. SSI associated with organ surgery) is 0.30, while the average value associated with more minor SSIs (e.g. SSI associated with superficial surgery or minor cuts) is 0.78 (Ref. R26). Henceforth, we refer to SSIs and HAIs interchangeably.

To estimate the extent to which SSIs reduce patient well-being, we subtract the average individual's health-related quality of life value by the expected value associated with various SSIs. Empirical studies indicate that the average is 0.87 (Ref. R.27 and R28). We estimate that a surgical site infection is expected to reduce an average individual's health-related quality of life index by between 0.09 (= 0.87 – 0.78) and 0.57 QALYs (= 0.87 – 0.30).

The full QALY loss represents the reduction in health-related quality of life with the time the condition lasts. A QALY captures an individual's quality of life for an entire year. Recent studies indicate that the average duration associated with severe SSIs is roughly 21 days, while the average duration associated with weaker SSIs is roughly 7 days (Ref. R29 and R30). These values imply that the average SSI reduces a patient's quality of life by roughly 0.09 for 7 days to 0.57 for 21 days.

Given these values, we estimate that the average SSI reduces a patient's QALY over an entire year by a number ranging from approximately 0.0017 QALYs (= [(0.09 average reduction for weakest SSIs) x (Average duration for weakest SSIs is 7 days)/ (365 days per year)] to 0.033 QALYs (= [(0.57 average reduction for strongest SSIs) x (Average duration for strongest SSIs is 21 days)/ (365 days per year)].

A previous regulatory impact analysis estimates the value per statistical life year to range between $100,000 and $300,000 in 2006 dollars (FR Doc. E7-16607). Between 2006 and 2013, prices rose 12.415 percent. Hence, we estimate the value per QALY to range between $112,415 (= $100,000 * 1.12415 inflation factor) and $337,245 (= $300,000 * 1.12415 inflation factor) in 2013 dollars. These estimates represent the value associated with a statistical life year with average health. Because the average individual's QALY is 0.87, we divide these values by 0.87 to estimate the value per QALY. We estimate these values to range between $129,213 (= $112,415 lower bound value per statistical life/0.87 QALY) and $387,639 (= $337,245 upper bound value per statistical life / 0.87 QALY) in 2013 dollars.

To summarize, we estimate that roughly 6 patients per year could possibly develop SSIs by using products containing what may be determined to be nonmonograph antiseptic active ingredients. The expected reduction in QALY associated with developing such an SSI ranges between 0.0017 and 0.033 QALYs, and the expected value associated with one QALY ranges between $129,123 and $387,639. Given these values, we would estimate the value associated with avoiding nonmonograph health care antiseptic related HAIs to range between $1,317 (= 6 patients expected to develop SSIs * lower bound reduction in QALYs associated with SSI is 0.0017 QALYs * lower bound expected value associated with one QALY is $129,123) and $76,753 (= 6 patients expected to develop SSIs * upper bound reduction in QALYs associated with SSI is 0.033 QALYs * upper bound expected value associated with one QALY is $387,639).

Recent research indicates that the average value of resources used to treat an HAI is approximately equal to $14,424 (Ref. R31). Estimating that 6 individuals may potentially develop SSIs by using nonmonograph antiseptic active ingredients, we estimate the average value of resources used to treat SSIs due to using nonmonograph health care antiseptic active ingredients to range up to $86,544 (=

6 individuals expected to develop SSIs * $14,424 average value of resources used to treat one SSI).Table 6 summarizes the above results and presents total benefits under this scenario. We estimate the value that could be associated with avoiding the surgical site infections associated with using nonmonograph antiseptic active ingredients to range between $0.09 million (= $86,544 value of resources used to treat these SSIs + $1,317 value reduction in QALY associated with patients getting SSIs) and $0.16 million (= $86,544 value of resources used to treat these SSIs + $76,753 value reduction in QALY associated with patients getting SSIs). Given these annual values, we estimate the rule's lower bound present discounted value, over a 10 year period, to range between $0.7 million at a 3 percent discount rate to $0.6 million at a 7 percent discount rate, while its highest upper bound present discount value ranges between $1.4 million at a 3 percent discount rate to $1.1 million at a 7 percent discount rate.

We reemphasize that the values associated with the benefit estimates might overstate the proposed rule's benefits because the probability measure is largely attributed to medical providers using less than the recommended dosage of any health care antiseptic product (including NDAs) rather than the possibility that nonmonograph health care antiseptics alone are ineffective. Furthermore, our analysis assumes that every antiseptic active ingredient eligible for the OTC health care antiseptic monograph is nonmonograph. However, it is possible that some or all of these ingredients will be shown to be generally recognized as safe and effective for use in health care antiseptics, and/or that medical providers are using NDA antiseptics.

Table 6. Total Benefits Assuming Every Antiseptic With Large Market Share Is Demonstrated To Be Non-GRAS/GRAE.

Total Benefits (in dollars)	Annualized Benefits			Present Discounted Value Over 10-Year Period					
				3 % Discount Rate			7 % Discount Rate		
	Low	Midpoint	High	Low	Midpoint	High	Low	Midpoint	High
Assuming No Antiseptic Active Ingredient is Demonstrated to be GRAS/GRAE and using the Upper Probability (7 in every 62,500,000 Exposures Leads to an SSI)									
Reduction in QALYs (Patients)	1,317	39,035	76,753	11,234	332,976	654,719	9,250	274,166	539,081
Total Value Resources to Treat SSI	86,544	86,544	86,544	738,238	738,238	738,238	607,849	607,849	607,849
Total Upper Bound Benefits	87,861	125,579	163,297	749,472	1,071,214	1,392,957	617,099	882,014	1,146,930

For patients, low values include the HAI durations associated with minor HAIs (7 days) and the lowest monetary value associated with a QALY ($112,415). High values include the HAI durations associated with severe HAIs (21 days) and the highest monetary value associated with a QALY ($337,245). An antiseptic ingredient is considered to have a large market share if enough of the ingredient is imported to produce over 100 million single-use antiseptic products containing the ingredient.

2. Benefits Assuming Every Antiseptic Active Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

As the above data indicate, of the seven health care ingredients currently on the market, only Benzethonium Chloride does not have a large market share, accounting for 0.08 percent of all health care antiseptic active ingredients sold. Hence, under this scenario, FDA would determine that all health care antiseptic active ingredients except Benzethonium Chloride are GRAS/GRAE for health care antiseptic use.

Using the upper bound risk measure of developing an HAI, we estimate that under this scenario, only 0.005 individuals are expected to develop an HAI per year (= 51,400,000 individuals are exposed to health care antiseptics * 0.08 percent of end users are potentially exposed to Benzethonium Chloride * 0.000000112 upper bound probability of getting an HAI per exposure to one single-dose of nonmonograph antiseptic active ingredient). This value roughly indicates that 0 individuals are expected to develop an HAI per year, resulting in no reduction in QALYs and no reduction in resource costs to treat the HAI.

3. Summary of Total Benefits

Table 7 summarizes the proposed rule's expected total benefits. Assuming every health care antiseptic active ingredient with a large market share is shown to be GRAS/GRAE for its intended use, we estimate expected benefits to equal $0. On the other hand, assuming no antiseptic active ingredients are shown to be GRAS/GRAE for use in health care antiseptics, we estimate that the value associated with avoiding the SSIs that are potentially associated with using nonmonograph antiseptic active ingredients could range between $0.09 million (= $86,544 value of resources used to treat these SSIs + $1,317 value reduction in QALY associated with patients getting SSIs) and $0.16 million (= $86,544 value of resources used to treat these SSIs + $76,753 value reduction in QALY associated with patients getting SSIs). Given these annual values, we estimate the rule's lower bound present discounted value, over a 10 year period, to range between $0.7 million at a 3 percent discount rate to $0.6 million at a 7 percent discount rate, while its highest upper bound present discount value ranges between $1.4 million at a 3 percent discount rate to $1.1 million at a 7 percent discount rate.

Given these values, we estimate that the rule's lowest benefits are expected to occur under the scenario where every antiseptic active ingredient with large market share is demonstrated to be GRAS/GRAE for use in health care antiseptics, while the highest benefits are expected to occur under the scenario where no antiseptic active ingredient is demonstrated to be GRAS/GRAE for use in health care antiseptics. Annualized benefits under these scenarios are expected to range between $0.0, assuming every antiseptic active ingredient with a large market share is demonstrated to be GRAS/GRAE, and $0.16 million, assuming no antiseptic active ingredient is demonstrated to be GRAS/GRAE and that the upper bound risk of getting an HAI is approximately equal to 0.00000112.

Table 7. Summary of Total Benefits

Total Benefits (in dollars)	Annualized Benefits			Present Discounted Value Over 10-Year Period					
				3 % Discount Rate			7 % Discount Rate		
	Low	Midpoint	High	Low	Midpoint	High	Low	Midpoint	High
Assuming No Antiseptic Active Ingredient is Demonstrated to be GRAS/GRAE and using the Upper Bound Probability (7 in every 62,500,000 Exposures Leads to an SSI)									
Reduction in QALYs (Patients)	1,317	39,035	76,753	11,234	332,976	654,719	9,250	274,166	539,081
Total Value Resources to Treat SSI	86,544	86,544	86,544	738,238	738,238	738,238	607,849	607,849	607,849
Total Estimated Benefits	87,861	125,579	163,297	749,472	1,071,214	1,392,957	617,099	882,014	1,146,930
Assuming Every Antiseptic Active Ingredient with a Large Share is Demonstrated to be GRAS/GRAE									
Reduction in QALYs (Patients)	0	0	0	0	0	0	0	0	0
Total Value Resources to Treat SSI	0	0	0	0	0	0	0	0	0
Total Estimated Benefits	0	0	0	0	0	0	0	0	0
Range of Total Benefits Under Both Scenarios									
Reduction in QALYs (Patients)	0	39,035	76,753	0	332,976	654,719	0	274,166	539,081
Total Value Resources to Treat SSI	0	43,272	86,544	0	369,119	738,238	0	303,924	607,849
Total Benefits	0	82,307	163,297	0	702,095	1,392,957	0	578,090	1,146,930

For patients, low values include the HAI durations associated with minor HAIs (7 days) and the lowest monetary value associated with a QALY ($112,415). High values include the HAI durations associated with severe HAIs (21 days) and the highest monetary value associated with a QALY ($337,245). An antiseptic ingredient is considered to have a large market share if enough of the ingredient is imported to produce over 100 million single-use antiseptic products containing the ingredient.

G. Costs

The proposed rule is expected to impose costs on health care antiseptic manufacturers. Potential costs include the costs associated with conducting tests to provide evidence that health care antiseptic products containing these antiseptic active ingredients are GRAS/GRAE, reformulating and relabeling products to contain GRAS/GRAE ingredients, and exiting the market. These individual costs are discussed in the following sections:

1. Reformulation and Relabeling

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 which 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 (78 FR 76443-76478). The previous impact analysis studied consumer antiseptic washes, and estimated that the average cost to reformulate consumer antiseptic washes range from $143,618 to $718,090.

The above measure reflects costs in 2009 dollars. To update these costs to the most recent year that data is available, 2013, the previous analysis recommends adjusting for the rise in the annual manufacturer price index for pharmaceutical preparation manufacturing (Ref. 32). The data indicate that prices rose 23 percent from 2009 to 2013 (from $469.2 in 2009 to $577.7 in 2013) and thus we calculate that average reformulation costs range from $176,650 (=1.23 * $143,618) to $883,251 (1.23 * $718,090).

We note that the above measure may understate reformulation costs for health care antiseptics. To estimate reformulation costs, the previous analysis estimated the expenses associated with removing antiseptic ingredients from over-the-counter cough-cold products. For this rule, reformulation is more complicated; manufacturers would not only need to remove current antiseptic ingredients from their products, but also replace these ingredients with GRAS/GRAE ingredients. Furthermore, underlying the earlier analysis was an assumption that reformulation would not require manufacturers to substitute their original antiseptic active ingredient with a substantially more expensive ingredient. However, we use this measure because it is the best estimate available given our data constraints. We welcome comments that provide representative costs data for reformulating health care antiseptic products.

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. R33). 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 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 rule proposes revisions that would result in 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 relabeling cost model estimates average uncoordinated relabeling costs to range between $32,641 and $74,558, whereas average coordinated relabeling costs range between $620 and $1,580. These results are interpreted to mean that the average cost to change one unique label ranges between $32,641 and $74,558 when the manufacturer cannot coordinate its activities, and $620 and $1,580 when the manufacturer can coordinate its activities. These costs include the material, marketing, and labor costs associated with a major relabeling whose compliance time is 12 months. The costs also include the costs to conduct focus groups. 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. However, because the data does not indicate which products contain private versus branded labels, we use the average cost between private and branded labels.

To review, average reformulation costs are expected to range from $176,650 to $883,251, while relabeling costs are expected to range from $32,641 and $74,558. Given these values, we estimate total reformulation costs to range from $209,291 (= $176,650 lower bound reformulation cost + $32,641 lower bound relabeling cost) to $957,809 (= $883,251 upper bound reformulation cost + $74,558 upper bound relabeling cost).

2. Testing

For conducting tests, FDA requires only one set of adequate data demonstrating an ingredient is GRAS and GRAE for use in health care antiseptic products for each specific antiseptic active ingredient to be added to the monograph. This requirement implies that every manufacturer producing a particular antiseptic active ingredient would not need to conduct separate tests, rather, only one manufacturer among every manufacturer producing a particular active ingredient needs to conduct the tests. These manufacturers are probably going to be each ingredient's largest bulk manufacturer because they stand to incur the greatest costs if the active ingredient becomes nonmonograph.

a. GRAE Testing

To show general recognition of effectiveness, under the proposed rule, a manufacturer must conduct an in vivo test twice and three types of in vitro tests (i.e. minimum inhibitory concentration tests, time-kill tests, and antimicrobial spectrum tests). These studies must also meet stricter standards than those under the 1994 TFM. These stricter standards require that the test be superior to a vehicle, that neutralization is validated, that the active control meets a 2-$\log_{10}$ for pre-injection, a 2-$\log_{10}$ on

abdomen (dry site), and a 3-$\log_{10}$ on groin, and that 70 percent of test subjects meet these effectiveness criteria.

We estimate these costs using the results reported in an unpublished internal analysis, which estimates that it costs approximately $318,600 to conduct the in-vivo test twice, and $1,239,300 to conduct the three in vitro studies (Ref. R34). Hence, we estimate that it costs approximately $1.6 million to conduct one set of efficacy tests (= $318,600 to conduct two vivo studies + $1,239,300 to conduct two in vitro studies).

b. GRAS Testing

To show general recognition of safety, under the proposed rule, manufacturers must provide adequate data on the following nonclinical studies: absorption, distribution, metabolism, and excretion (ADME) in animals, human pharmacokinetic (MUsT), oral and dermal carcinogenicity in animals, hormonal effects, 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 8. The results indicate that the average cost (in 2013 dollars) to conduct a series of the following tests is: $0.5 million for human pharmacokinetics; $1.40 million for ADME; $3.12 million for oral carcinogenicity; $3.12 million for dermal carcinogenicity; $4.03 million for developmental and reproductive toxicity; and $1.2 million for potential hormonal effects.

Table 8. Estimated Cost Per Study Associated With Nonclinical Safety Data Requirements (2013 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 2013 dollars)
Total Costs (000,000's of 2013 dollars)	$0.5	$1.4	$3.1	$3.1	$4.0	$1.2	No Data Available	$13.3

The previous impact analysis (78 FR 76443-76478) reports that it costs roughly $250,000 to $750,000 to conduct most human pharmacokinetic studies, and, in some rarer cases, some studies can cost up to $23.2 million. To estimate the cost to conduct a human pharmacokinetic study for health care antiseptic active ingredients, we conducted a literature review to identify other studies that estimate the cost to conduct pharmacokinetic studies. We identified only one study, which estimated the average cost to conduct a pharmacokinetic study to approximately equal $800,000 (Ref. R35).

The above study likely overstates the cost to conduct a human pharmacokinetic study for health care antiseptic active ingredients. The above study involved over 500 subjects, whereas the rule proposes using only 50 subjects. Given the above study's value, we estimate the average cost to conduct a human pharmacokinetic study for antiseptic ingredients to approximately equal to $500,000 (=mean of $250,000 and $750,000).

The previous impact analysis (78 FR 76443-76478) was unable to calculate the costs associated with carrying out resistance studies. We conducted a literature review to check whether other researchers estimated this particular cost. However, we were unable to identify any papers studying this topic. Hence, our cost estimates understate the actual safety testing costs.

We note that some manufacturers have already submitted adequate data for certain tests. Table 9 reports the available adequate studies for each health care antiseptic active ingredient. The results indicate that the following antiseptic active ingredients have adequate data for:

- Benzalkonium Chloride: none of the above tests;
- Benzethonium Chloride: dermal carcinogenicity only;
- Chloroxylenol: none of the above tests;
- Ethyl Alcohol: animal pharmacokinetic (ADME), oral and dermal carcinogenicity, developmental and reproductive toxicity (DART), potential hormonal effects, and bacterial resistance;
- Hexylresorcinol: oral carcinogenicity only;
- Iodine Tincture USP: animal pharmacokinetic (ADME), oral carcinogenicity, developmental and reproductive toxicity (DART), and potential hormonal effects;
- Iodine Topical Solution USP: animal pharmacokinetic (ADME), oral carcinogenicity, developmental and reproductive toxicity (DART), and potential hormonal effects;
- Isopropyl Alcohol: developmental and reproductive toxicity (DART) and bacterial resistance;
- Povidone Iodine: animal pharmacokinetic (ADME), oral carcinogenicity, developmental and reproductive toxicity (DART), and potential hormonal effects;
- Triclocarban: oral carcinogenicity only;
- Triclosan: oral carcinogenicity and developmental and reproductive toxicity (DART).

Table 9. Adequate Safety Data That Is available for Each Antiseptic Active Ingredient

Active Ingredient	Human Pharmacokinetic (MUsT)	Animal Pharmacokinetic (ADME)	Oral Carcinogenicity	Dermal Carcinogenicity	Developmental and Reproductive Toxicity (DART)	Potential Hormonal Effects	Bacterial Resistance (Resistance Potential)
Benzalkonium Chloride							
Benzethonium Chloride				X			
Chloroxylenol							
Ethyl Alcohol		X	X	X	X	X	X
Hexylresorcinol			X				
Iodine Tincture USP		X	X*		X	X	
Iodine Topical Solution USP		X	X*		X	X	
Isopropyl Alcohol					X		X
Povidone Iodine		X	X*		X	X	
Triclocarban			X				
Triclosan			X		X		

X = Indicates that available data is sufficient to make a GRAS determination; * indicates based on studies of potassium iodide

IMS Health data indicates that Hexylresorcinol, Iodine Tincture USP, and Iodine Topical Solution USP are currently not marketed in health care antiseptic products (Ref. R18). However, we request comments that provide data that may be used to confirm or refute this result.

Given the above values, we estimate the total one-time costs to conduct the various safety tests associated with each antiseptic active ingredient that is currently marketed as follows:

- Benzalkonium Chloride and Chloroxylenol: Because there are no adequate studies for Benzalkonium Chloride and Chloroxylenol, we estimate their total GRAS testing costs to approximately equal $13.3 million each (=$0.5 million per human pharmacokinetic study + $1.4 million per animal pharmacokinetic study + $3.1 million per oral carcinogenicity study + $3.1 million per dermal carcinogenicity study + $4.0 million per developmental and reproductive toxicity study + $1.2 million per potential hormonal effects study). Benzalkonium Chloride and Chloroxylenol would also require resistance studies. However, no data is available to estimate

this cost, and thus these total GRAS testing costs do not include the expenditures associated with conducting resistance studies.

- Benzethonium Chloride: Because there is adequate dermal carcinogenicity data for Benzethonium Chloride, we estimate total costs to approximately equal $10.2 million (=$0.5 million per human pharmacokinetic study + $1.4 million per animal pharmacokinetic study + $3.1 million per oral carcinogenicity study + $4.0 million per developmental and reproductive toxicity study + $1.2 million per potential hormonal effects study). Benzethonium Chloride also requires a resistance study. However, no data is available to estimate this cost, and thus this total GRAS testing cost does not include the expenditures associated with conducting a resistance study.
- Ethyl Alcohol: Ethyl alcohol only requires one human pharmacokinetic study. We estimate these costs to approximately equal $0.5 million.
- Isopropyl Alcohol: Because there is adequate developmental and reproductive toxicity and bacterial resistance data for Isopropyl Alcohol, we estimate total costs to approximately equal $9.3 million (=$0.5 million per human pharmacokinetic study + $1.4 million per animal pharmacokinetic study + $3.1 million per oral carcinogenicity study + $3.1 million per dermal carcinogenicity study + $1.2 million per potential hormonal effects study).
- Povidone iodine: There is adequate data for animal pharmacokinetic, oral carcinogenicity, developmental and reproductive toxicity, and potential hormonal effects. Hence, we estimate total costs to approximately equal $3.6 million (=$0.5 million per human pharmacokinetic study + $3.1 million per dermal carcinogenicity study). Povidone Iodine also requires a resistance study. However, no data is available to estimate this cost, and thus this total GRAS testing cost does not include the expenditures associated with conducting a resistance study.

- Triclosan: There is adequate data for oral carcinogenicity and developmental and reproductive toxicity for this ingredient. Hence, we estimate total costs to approximately equal $6.2 million each (= $0.5 million per human pharmacokinetic study + $3.1 million per dermal carcinogenicity study + $1.4 million per animal pharmacokinetic study + $1.2 million per potential hormonal effects study). Triclosan also requires a resistance study. However, no data is available to estimate this cost, and thus our total GRAS testing cost does not include the expenditures associated with conducting a resistance study.

To summarize, total efficacy and safety testing costs (not including potential bacterial resistance testing) are expected to range between $2.1 and $14.9 million per unique antiseptic active ingredient, while reformulation and relabeling costs are estimated to range between $209,291 and $957,809 per uniquely formulated product.

3. Exiting the Market

Manufacturers of health care antiseptic products may exit the market if their products contain non-GRAE/GRAS antiseptic active ingredients, and if there are no GRAS/GRAE ingredients that they can use to reformulate their product. FDA is not aware of any evidence that would suggest this outcome would impose substantial new costs on society beyond those quantified above. For most intended antiseptic uses, there exists an NDA or ANDA approved alternative. We request comment on whether there could be situations in which alternatives would not exist. We also note there may be search costs or other types of transactions costs associated with a need to switch to NDA and ANDA alternative products (such as chlorhexidine gluconate products). For example, if NDA products are more allergenic than currently-used products, medical providers may have to put forth more effort to determine patient allergies and respond to allergic reactions. Based on an informal review of relative prices of monograph

and NDA or ANDA alternative products, we do not find that there would be higher out-of-pocket costs associated NDA or ANDA alternative products. We welcome any comments providing data that would enable us to more accurately measure these costs.

Unlike the above costs, there is another impact of market exit that may entail a cost to society. For health care antiseptics, manufacturer surplus is attributed to information asymmetry; manufacturers potentially know that the available scientific evidence cannot conclusively demonstrate antiseptic active ingredients to be GRAS/GRAE for use in health care antiseptics, while end users probably assume that these ingredients are GRAS/GRAE for use in health care antiseptics. Failure to demonstrate that an ingredient is GRAS/GRAE for use in health care antiseptics could cause the manufacturers of that ingredient to exit the market, resulting in the product's previous end users to substitute these non-GRAS/GRAE products with health care antiseptics that are either shown to be GRAS/GRAE or that have an FDA-approved NDA or ANDA. Hence, the reduction in manufacturer surplus associated with exiting the market would transfer completely to the product's previous end user, potentially resulting in no cost to society. However, if exit is sufficiently widespread, among drug products under patent, market power may initially become concentrated enough to allow for remaining producers to restrict quantities below the amount provided in a competitive equilibrium. As patents expire, we would expect entry by generic competitors to mitigate these effects.

The above costs and transfers depend on the number of active ingredients that are demonstrated to be GRAS/GRAE for health care antiseptic use. To illustrate the rule's potential range of costs and transfers, we study the following scenarios: (1) that no antiseptic active ingredient is demonstrated to be GRAS/GRAE for use in health care antiseptics; and (2) that every ingredient with high market share is demonstrated to be GRAS/GRAE for health care antiseptic use.

4. Costs Assuming Every Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

In this scenario, every health care antiseptic active ingredient (that is known to FDA to be used in marketed health care antiseptic products) undergoes testing, except Benzethonium Chloride, and is demonstrated to be GRAS/GRAE for use in health care antiseptic products. The 2013 FDA drug product registration database indicates that most manufacturers are small in size (employ under 500 employees) and produce 1 to 2 uniquely formulated health care antiseptic products. However, it also indicates that there are roughly six large manufacturers that each produce approximately 30 to 90 uniquely formulated health care antiseptic products containing a single antiseptic active ingredient. For these companies, reformulation costs per antiseptic ingredient could roughly range between $6.3 million (=30 potential reformulations per ingredient * $209,291 per uniquely formulated product) and $86.2 million (=90 potential reformulations per ingredient* $957,809 per uniquely formulated product). These calculations indicate that, for these larger companies, reformulation costs could substantially exceed testing costs, which implies that these companies would probably choose to test their antiseptic active ingredients rather than reformulate their health care antiseptic products. Furthermore, our calculation assumes that every manufacturer produces only one uniquely packaged product per unique formulation. However, the data indicate that there are more uniquely packaged products than unique formulations, which implies that the above values modestly understate total reformulation costs.

However, this would not be the case for manufacturers of products containing Benzethonium Chloride. Even if manufacturers believe that Benzethonium Chloride is GRAS/GRAE for use in health care antiseptics, we project that manufacturers of health care antiseptics containing Benzethonium Chloride would reformulate their products to contain other GRAS/GRAE ingredients rather than conduct testing given their relatively small market share. The 2013 FDA drug product registration database indicates

that the largest manufacturers of health care antiseptic products containing Benzethonium Chloride only produce a couple uniquely formulated Benzethonium products, which implies that their testing costs would substantially exceed their reformulation costs. Hence, this scenario does not imply that Benzethonium Chloride may not be GRAS/GRAE for health care antiseptic use. Rather, it suggests that manufacturers of health care antiseptics containing Benzethonium Chloride could choose to reformulate their products to include other antiseptic active ingredients rather than conduct testing because reformulation might be more cost effective than testing.

To summarize, we expect manufacturers of health care antiseptic products containing Benzethonium Chloride to reformulate their products because their testing costs are expected to substantially exceed their reformulation costs. In contrast, we expect every other antiseptic active ingredient (Benzalkonium Chloride, Chloroxylenol, Ethyl Alcohol, Isopropyl Alcohol, Povidone Iodine, and Triclosan) to undergo testing because the reformulation costs associated with the products containing these ingredients are expected to exceed their testing costs. The data indicate that there are 6 companies that are inclined to test these ingredients versus reformulate, which suggests that these companies could coordinate to distribute their potential testing costs.

To estimate costs under this scenario, we sum together total reformulation and relabeling costs for Benzethonium Chloride with total testing costs for Benzalkonium Chloride, Chloroxylenol, Ethyl Alcohol, Isopropyl Alcohol, Povidone Iodine, and Triclosan. We estimate reformulation costs by multiplying the average cost to reformulate with the total number of uniquely formulated Benzethonium Chloride products [= (average reformulation costs) x (total number of uniquely formulated products containing Benzethonium Chloride as its active antiseptic ingredient)]. Given the above values, we estimate the total one-time costs to reformulate Benzethonium Chloride to range

from $6.0 million (=$176,650 per reformulation * 34 potential reformulations) to $30.0 million (= $883,251 per reformulation * 34 potential reformulations).

Reformulation would also require manufacturers to relabel their products to indicate that their products now contain an antiseptic active ingredient that is GRAS/GRAE for its intended use. Table 2 indicates that there are 70 uniquely packaged products that contain 34 potentially unique formulations of Benzethonium Chloride. Labeling costs depend on whether the changes required prior to reformulating the product can be coordinated with regular or already planned labeling changes. The labeling cost model projects that manufacturers can coordinate the labeling changes associated with 4 percent of these unique labels, which translates to 3 unique labels (= 70 unique labels * 0.04). As a result, we estimate that manufacturers cannot coordinate the labeling changes associated with the remaining 96 percent unique labels, which translates to 67 unique labels (=70 unique labels * 0.96).

To summarize, our data indicate that there are approximately 3 unique labeling changes that manufacturers could coordinate at a cost ranging between $620 and $1,580, and 67 unique labeling changes that manufacturers could not coordinate at a cost ranging between $32,641 and $74,558. Together, these values indicate that the one-time costs associated with relabeling the 70 uniquely packaged, reformulated antiseptic products that currently contain Benzalkonium Chloride is expected to range between $2.2 million (=3 coordinate labeling changes * $620 per coordinated labeling change + 67 uncoordinated labeling changes * $32,641 per uncoordinated labeling change) and $5.0 million (=3 coordinate labeling changes * $1,580 per coordinated labeling change + 67 uncoordinated labeling changes * $74,558 per uncoordinated labeling change).

Given these values, we estimate the total costs associated with reformulation and relabeling to range between $8.2 million (= $6 million one-time reformulation costs + $2.2 million one-time relabeling costs) and $35.0 million (= $30 million one-time reformulation costs + $5 million one-time relabeling costs).

We expect the remaining antiseptic active ingredients to undergo testing, which includes one set of efficacy tests and safety tests. As indicated in the above section II.G.2.a "GRAE Testing" conducting one separate set of efficacy tests costs approximately $1.6 million. Given that we expect 6 active antiseptic ingredients to undergo testing, we estimate these one-time efficacy testing costs to approximately equal $9.6 million (= 6 active antiseptic ingredients * $1.6 million for one set of efficacy tests per active ingredient).

GRAS testing costs are reported in the above section "GRAS Testing". To review, we estimate the total one-time costs to conduct safety testing (not including testing for bacterial resistance) to approximately equal $13.3 million for Benzalkonium Chloride, $13.3 million for Chloroxylenol, $3.6 million for Povidone Iodine, $0.5 million for Ethyl Alcohol, $9.3 million for Isopropyl Alcohol, and $6.2 million for Triclosan. Summing these costs, we estimate total safety testing costs to approximately equal $46.2 million (= $13.3 million for Benzalkonium Chloride + $13.3 million for Chloroxylenol + $0.5 million for Ethyl Alcohol + $9.3 million for Isopropyl Alcohol + $6.2 million for Triclosan + $3.6 million for Povidone Iodine).

Given these values, we estimate total one-time testing costs to approximately equal $55.8 million (=$9.6 million GRAE testing costs + $46.2 million GRAS testing costs). Considering testing, relabeling, and reformulation costs, we estimate that the rule would impose one-time costs ranging

from approximately $64.0 million (=$6.0 million reformulation + $2.2 million relabeling costs + $55.8 million efficacy and safety testing costs) to $90.8 million (=$30.0 million reformulation costs + $5.0 million relabeling costs + $55.8 million efficacy and safety testing costs). Annualizing this one-time cost over a 10 year period, we estimate total discounted annual costs to range from $7.3 to $10.4 million at a 3 percent discount rate, and from $8.5 to $12.1 million at a 7 percent discount rate. Table 10 summarizes these results.

Table 10. Summary of Total Costs (in 2013 dollars), Assuming Every Antiseptic Active Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE

Total Costs (in millions of dollars)	One-Time Costs			Annualized Costs Over 10-Year Period					
				3 % Discount Rate			7 % Discount Rate		
	Low	Midpoint	High	Low	Midpoint	High	Low	Midpoint	High
Reformulation Costs (Benzethonium Chloride Only)	6.0	18.0	30.0	0.7	2.1	3.4	0.8	2.4	4.0
Relabeling Costs (Benzethonium Chloride Online)	2.2	3.6	5.0	0.2	0.4	0.6	0.3	0.5	0.7
Efficacy Testing	9.6	9.6	9.6	1.1	1.1	1.1	1.3	1.3	1.3
Safety Testing	46.2	46.2	46.2	5.3	5.3	5.3	6.1	6.1	6.1
Total Costs (in millions of dollars)	64.0	77.4	90.8	7.3	8.9	10.4	8.5	10.3	12.1
Midpoint represents the median value between low and high except for relabeling costs. Totals may not sum due to rounding.									

5. Costs Assuming All Testing Is Completed and No Antiseptic Active Ingredient Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

In this scenario, no monograph antiseptic active ingredient is demonstrated to be GRAS/GRAE for use in health care antiseptics, resulting in every health care antiseptic manufacturer exiting the market. Under this scenario, costs would, at most, approximately equal the total expenditures to test the 7 antiseptic active ingredients (that are known to FDA to be used in currently marketed health care antiseptic products).

Under this scenario, we assume that every antiseptic active ingredient undergoes testing. Unlike the above scenario, where other antiseptic active ingredients are demonstrated to be GRAS/GRAE, we assume that no antiseptic active ingredient can be demonstrated to be GRAS/GRAE for use in health care antiseptics. We further assume that health care antiseptic manufacturers choose to remain in the market until all testing to support the GRAS/GRAE status of every ingredient is completed, and the completed testing fails to support that any of the health care antiseptic active ingredients are GRAS/GRAE for use in health care antiseptics. Under this scenario, we also assume that manufacturers of health care antiseptic products containing Benzethonium Chloride would conduct testing because of the lack of other GRAS/GRAE ingredients that they could use to reformulate their products.

We estimate the costs to conduct one-time efficacy tests to approximately equal $11.2 million (= 7 separate antiseptic active ingredients * $1.6 million per set of efficacy tests). The information on tables 8 and 9 indicate that it would cost roughly $56.4 million to conduct the various safety tests associated with the 7 active antiseptic ingredients (= $13.3 million for Benzalkonium Chloride + $13.3 million for Chloroxylenol + $0.5 million for Ethyl Alcohol + $9.3 million for Isopropyl Alcohol + $6.2 million for Triclosan + $3.6 million for Povidone Iodine + $10.2 million for Benzethonium Chloride). Given these values, we estimate the one-time safety and efficacy testing costs to approximately equal $67.6 million (= $11.2 million + $56.4 million).

Given the above values, we estimate that under this scenario, one-time testing costs could approximately equal $67.6 million. Annualizing these costs over a 10 year period, we estimate total discounted annual costs to roughly equal $7.7 million at a 3 percent discount rate and $9.0 million at a 7 percent discount rate. Table 11 summarizes these results.

Table 11. Summary of Total Costs (in 2013 dollars) Assuming No Antiseptic Active Ingredient is Demonstrated To Be GRAS/GRAE

Total Costs (in millions of dollars)	Initial Upfront Cost	Annualized Costs Over 10-Year Period	
		3 % Discount Rate	7 % Discount Rate
Efficacy Testing	11.2	1.3	1.5
Safety Testing	56.4	6.4	7.5
Total Costs (in millions of dollars)	67.6	7.7	9.0

As discussed previously, we acknowledge that under this scenario there may be transactions and search costs associated with switching to NDA or ANDA alternatives that we are unable to quantify. We request comment and data that would allow for estimation of these costs. Furthermore, manufacturer surplus associated with exiting the market would be transferred to end users that would substitute these manufacturers' non-GRAS/GRAE antiseptics with FDA approved NDA and ANDA antiseptics. These transfers between manufacturers and end users approximately equal manufacturer surplus (= total industry revenues –total industry marginal costs). To estimate an upper bound for this value, we use total health care antiseptic sales because data on total industry marginal costs are unavailable. To estimate these values, we sum together total health care antiseptic sales reported in the 2009 A.C. Nielsen and IMS Health databases. A.C. Nielsen data indicate that roughly $100 million of hand sanitizer antiseptics that are potentially for health care use were sold in retail markets in 2009. Given that prices rose 23 percent from 2009 to 2013 (from $469.2 in 2009 to $577.7 in 2013), we calculate that retail sales of antiseptics that are potentially for health care use to approximately equal $123 million in 2013 dollars (= 1.23 * $100 million). IMS Health data report that non-retail health care antiseptic sales were roughly equal to $19 million in 2009. Updating this value to 2013 dollars, we estimate that non-retail

health care antiseptics sales approximately equal $24 million in 2013 dollars (= 1.23 * $21 million). Summing these costs together, we proxy that the costs for manufacturers to exit the market roughly equals $147 million (=$123 million + $24 million). This value indicates that $147 million is transferred from manufacturers to end users that would substitute these products with FDA approved NDA and ANDA antiseptics.

The above value could either understate or overstate manufacturer surplus. As indicated above, manufacturer surplus equals total industry revenues minus total industry marginal costs. Because data on the latter measure is unavailable, our estimates could overstate manufacturer surplus. On the other hand, our data also does not capture total health care antiseptic revenues, and thus it might understate manufacturer surplus.

6. Summary of Total Costs

Table 12 summarizes the proposed rule's total costs. Assuming every antiseptic active ingredient with large market share is demonstrated to be GRAS/GRAE for health care antiseptic use, one-time costs are expected to range between $64.0 and $90.8 million. These one-time costs include the expenditures to reformulate and relabel products containing Benzethonium Chloride and to conduct safety and efficacy tests on the remaining antiseptic active ingredients. Annualizing this one-time cost over a 10 year period, we estimate total discounted annual costs to range from $7.3 and $10.4 million at a 3 percent discount rate, and from $8.5 to $12.1 million at a 7 percent discount rate.

Assuming no antiseptic active ingredient is demonstrated to be GRAS/GRAE for use in health care antiseptics, one-time costs are expected to approximately equal, at most, $67.6 million. These one-time costs include the expenditures to conduct various safety and efficacy tests on every marketed

antiseptic active ingredient. Annualizing these costs over a 10 year period, we estimate total discounted annual costs to roughly equal $7.7 million at a 3 percent discount rate, and from $9.0 million at a 7 percent discount rate. Table 12 summarizes these results.

Given these values, we estimate that the rule's lowest and highest costs are expected to occur under the scenario where every antiseptic active ingredient with large market share is demonstrated to be GRAS/GRAE, which implies that the rule's annualized costs, over a 10 year period, are expected to range between $7.3 and $10.4 million at a 3 percent discount rate to $8.5 to $12.1 million at a 7 percent discount rate.

Table 12. Summarized of Total Costs

Total Costs (in millions of dollars)	One-Time Costs			Annualized Costs Over 10-Year Period					
				3 % Discount Rate			7 % Discount Rate		
	Low	Midpoint	High	Low	Midpoint	High	Low	Midpoint	High
Assuming Every Antiseptic Active Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE									
Reformulation Costs (Benzethonium Chloride Only)	6.0	18.0	30.0	0.7	2.1	3.4	0.8	2.4	4.0
Relabeling Costs (Benzethonium Chloride Online)	2.2	3.6	5.0	0.2	0.4	0.6	0.3	0.5	0.7
Efficacy Testing	9.6	9.6	9.6	1.1	1.1	1.1	1.3	1.3	1.3
Safety Testing	46.2	46.2	46.2	5.3	5.3	5.3	6.1	6.1	6.1
Total Costs (in millions of dollars)	64.0	77.4	90.8	7.3	8.9	10.4	8.5	10.3	12.1
Assuming No Antiseptic Active Ingredient Is Demonstrated To Be GRAS/GRAE									
Reformulation Costs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Relabeling Costs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Efficacy Testing	11.2	11.2	11.2	1.3	1.3	1.3	1.5	1.5	1.5
Safety Testing	56.4	56.4	56.4	6.4	6.4	6.4	7.5	7.5	7.5
Total Costs (in millions of dollars)	67.6	67.6	67.6	7.7	7.7	7.7	9.0	9.0	9.0
Range of Total Costs Under Both Scenarios									
Reformulation Costs	6.0	18.0	30.0	0.7	2.1	3.4	0.8	2.4	4.0
Relabeling Costs	2.2	3.6	5.0	0.2	0.4	0.6	0.3	0.5	0.7
Efficacy Testing	9.6	9.6	9.6	1.1	1.1	1.1	1.3	1.3	1.3
Safety Testing	46.2	46.2	46.2	5.3	5.3	5.3	6.1	6.1	6.1
Total Costs (in millions of dollars)	64.0	77.4	90.8	7.3	8.9	10.4	8.5	10.3	12.1

Low values include the lowest monetary value associated with reformulation ($176,650) and relabeling ($32,641). High values include the highest monetary value associated with reformulation ($883,251) and relabeling ($74,558).

H. Alternatives

1. Every Antiseptic Active Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

We examine the potential regulatory alternatives available under the two above scenarios. Under the scenario where every antiseptic active ingredient with large market share is demonstrated to be GRAS/GRAE, regulatory alternatives include adjusting the rule's relabeling compliance times for reformulated products to either 6 or 18 months, as opposed to the proposed 12 month period. Another alternative is to remove requirements, such as the stricter efficacy testing. However, removing these requirements might negatively impact the public health.

Adjusting relabeling compliance times is expected to impact relabeling costs. For instance, increasing compliance times to 18 months is expected to reduce costs because it provides manufacturers 6 more months to coordinate activities and enjoy economies of scale. We estimate the impact using the labeling cost model. The model indicates that increasing compliance times from 12 to 18 months would enable moderately more manufacturers (roughly 11 percent) to coordinate their labeling activities, resulting in a modest reduction in total costs (ranging between $64.0 and $90.8 million under a 12 month compliance period, and between $63.1 and $88.8 million under 18 months). Hence, increasing compliance times from 12 to 18 months is expected to reduce total costs between $0.9 million (= $64.0 million - $63.1 million) to $2.0 million (= $90.8 million - $88.8 million).

An 18 month compliance period would also delay relabeling costs 6 months, resulting in a modest reduction in annualized costs. To incorporate this delay, we compound the present value over

18 months. At a 3 percent discount rate, total annualized costs over a 10-year period range from $7.2 to $10.2 million, while at a 7 percent rate they range from $8.4 to $11.8 million.

Decreasing compliance times to 6 months is expected to increase relabeling costs. However, this reduction is not expected to substantially increase costs considering that most manufacturers (only 4 percent) cannot coordinate their activities in 12 months. We estimate the impact using the labeling cost model. The model indicates that no manufacturers could coordinate under a 6 month compliance time, resulting in a modest increase in costs (ranging between $64.0 and $90.8 million under a 12 month compliance period, and between $64.3 and $92.8 million under a 6 month window). Hence, decreasing compliance times from 12 to 6 months is expected to increase total costs between $0.3 million (= $64.3million - $64.0 million) to $2.0 million (= $92.8 million - $90.8 million).

A 6 month compliance period would also move up relabeling costs 6 months, resulting in a modest increase in annualized costs. To incorporate this move up, we compound the present value over 6 months. At a 3 percent discount rate, total annualized costs under a 10 year period range from $7.4 to $10.7 million, while at a 7 percent rate they range from $8.6 to $12.5 million.

Table 13 indicates that varying compliance times modestly changes total costs. To review, under a 12 month compliance window, total costs are estimated to cost roughly $64.0 to $90.8 million, whereas an 18 month window is expected to cost approximately $63.1 to $88.8 million. Annualizing these total one-time costs, we note that the increase in compliance times reduces annual costs approximately $0.1 to $0.3 million. On the other hand, reducing compliance times to 6 months would raise total costs to range from $64.3 to $92.8 million. Annualizing these total one-time costs, we note that the reduction in compliance times increases annual costs approximately $0.1 to $0.4 million.

Table 13. Cost Summary for 6-Month, 12-Month, and 18 Month Compliance Periods

Total Costs (in millions of dollars)	One-Time Costs			Annualized Costs Over 10-Year Period					
				3 % Discount Rate			7 % Discount Rate		
	Low	Midpoint	High	Low	Midpoint	High	Low	Midpoint	High
Proposed Rule : 12 Month Compliance Period for Labeling Reformulated Products									
Reformulation Costs	6.0	18.0	30.0	0.7	2.1	3.4	0.8	2.4	4.0
Relabeling Costs (12 Months)	2.2	3.6	5.0	0.2	0.4	0.6	0.3	0.5	0.7
Efficacy Testing	9.6	9.6	9.6	1.1	1.1	1.1	1.3	1.3	1.3
Safety Testing	46.2	46.2	46.2	5.3	5.3	5.3	6.1	6.1	6.1
Total Costs (in millions of dollars)	64.0	77.4	90.8	7.3	8.9	10.4	8.5	10.3	12.1
Alternative I : 18 Month Compliance Period for Labeling Reformulated Products									
Reformulation Costs	6.0	18.0	30.0	0.7	2.1	3.4	0.8	2.4	4.0
Relabeling Costs (18 Months)	1.3	2.2	3.0	0.1	0.3	0.4	0.2	0.3	0.4
Efficacy Testing	9.6	9.6	9.6	1.1	1.1	1.1	1.3	1.3	1.3
Safety Testing	46.2	46.2	46.2	5.3	5.3	5.3	6.1	6.1	6.1
Total Costs	63.1	76.0	88.8	7.2	8.7	10.2	8.4	10.1	11.8
Reduction Total Costs Compared to Proposed Rule	0.9	1.5	2.0	0.1	0.2	0.2	0.1	0.2	0.3
Alternative II : 6 Month Compliance Period for Labeling Reformulated Products									
Reformulation Costs	6.0	18.0	30.0	0.7	2.1	3.4	0.8	2.4	4.0
Relabeling Costs (6 Months)	2.5	4.8	7.0	0.3	0.6	0.9	0.4	0.8	1.1
Efficacy Testing	9.6	9.6	9.6	1.1	1.1	1.1	1.3	1.3	1.3
Safety Testing	46.2	46.2	46.2	5.3	5.3	5.3	6.1	6.1	6.1
Total Costs	64.3	78.6	92.8	7.4	9.1	10.7	8.6	10.6	12.5
Increase Total Costs Compared to Proposed Rule	0.3	1.2	2.0	0.1	0.2	0.3	0.1	0.3	0.4
Midpoint represents the median value between low and high except for relabeling costs. Totals may not sum due to rounding.									

2. No Antiseptic Active Ingredient Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

Under this scenario, regulatory alternatives include adjusting the rule's testing compliance times to either 6 or 18 months, versus the proposed 12 month period. Adjusting testing compliance times would not change the proposed rule's costs to society. However, it would change the rule's annual distributional costs to manufacturers, which we estimated above to equal $147 million per year. For instance, increasing compliance times to 18 months is expected to enable manufacturers to continue

marketing their antiseptic products another 6 months, resulting in roughly $74.5 million in sales (=$149 sales per year * 0.5 years). On the other hand, reducing compliance times to 6 months is expected to reduce the time manufacturers can market their products by 6 months, resulting in roughly a $74.5 million reduction in sales (=$149 sales per year * 0.5 years).

I. Cost Effectiveness

We examine the rule's cost effectiveness under the two scenarios. Cost effectiveness analyses typically compare an action's costs to non-monetized outcomes. The only non-monetary outcome we were able to measure was the total expected annual reduction in exposure to antiseptic active ingredients that are determined to be non-GRAS/GRAE for use in health care antiseptic drug products.

1. Every Antiseptic Active Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

Under the scenario where every antiseptic active ingredient with large market share is demonstrated to be GRAS/GRAE for use in health care antiseptics, we estimate that the proposed rule could reduce society's exposure potentially upwards to 8 million single 1-ml use products that contain Benzethonium Chloride, which in this scenario would not be tested. This is because, under this scenario, manufacturers of products containing Benzethonium Chloride would likely choose to reformulate their products rather than conduct testing to show that Benzethonium Chloride is GRAS/GRAE for use in health care antiseptics. For illustration, we assume a midpoint value, 4 million single-uses, since most rules are usually not 100 percent effective. Furthermore, we convert our measurement from milliliters (mLs) to liters, which translates to 4 million liters.

Under this scenario, we estimated annualized costs to range between $7.3 and $10.4 million at a 3 percent discount rate, and $8.5 and $12.1 million at a 7 percent discount rate. Given these values, we estimate the rule's cost effectiveness to range between $1,825 (=$7.3 million/4 thousand liters of Benzethonium Chloride) and $2,600 (=$10.4 million/4 thousand liters of Benzethonium Chloride) at a 3 percent discount rate, and $2,125 (=$8.5 million/4 thousand liters of Benzethonium Chloride) and $3,025 (=$12.1 million/4 thousand liters of Benzethonium Chloride) at a 7 percent discount rate. Table 14 summarizes these results.

Table 14. Cost-Effectiveness Assuming Every Antiseptic Active Ingredient with Large Market Share is Demonstrated To Be GRAS/GRAE (in $ per liter of antiseptic active ingredient reduced)

Scenario	3 % Discount Rate			7 % Discount Rate		
	Low	Mid	High	Low	Mid	High
Assuming Every Antiseptic Active Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE	$1,825.00	$2,212.50	$2,600.00	$2,125.00	$2,575.00	$3,025.00

2. No Antiseptic Active Ingredient Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

Under this scenario, we estimate that the annual reduction in exposure to antiseptic active ingredients that are potentially non-GRAS/GRAE for use in health care antiseptics could range between 0 and potentially upwards to 20.6 billion single 1-ml uses. For illustration, we assume a midpoint value, 10.3 billion single-uses, since most rules are not 100 percent effective. Furthermore, we convert our measurement from milliliters to liters, which translates to 10.3 million liters. We estimated above that annualized costs roughly equaled $7.7 million at a 3 percent discount rate and $9.0 million at a 7 percent discount rate. Given these values, we estimate the rule's cost effectiveness to approximately equal $0.75 (=$7.7 million/10.3 million liters) and $0.87 (=$9.0 million/10.3 million liters) at a 7 percent discount rate. Table 15 summarizes these results.

Table 15. Cost-Effectiveness Assuming No Antiseptic Active Ingredient Is Demonstrated To Be GRAS/GRAE (in $ per liter of antiseptic active ingredient reduced)

Scenario	3 % Discount Rate	7 % Discount Rate
Assuming No Antiseptic Active Ingredient Is Demonstrated To Be GRAS/GRAE and a 12 Month Relabeling Compliance Time	$0.75	$0.87

III. Small Entity Effects

FDA has examined the economic implications of the proposed rule as required by the Regulatory Flexibility Act. If a proposed rule is expected to have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires Agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. The proposed rule could impose significant new economic burdens on small entities. Hence, this analysis, as well as other sections in this document, serves as an initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

The proposed rule would impact entities that manufacture health care antiseptic products containing health care antiseptic active ingredients. The 2013 FDA Drug Product Registration Database indicates that there are roughly 225 entities that manufacture health care antiseptic active ingredients. Among these entities, we were able to collect revenue and employee data for 170 using the Dun and Bradstreet database (Dunn & Bradstreet, Inc.). For entities missing revenue data, we gathered revenue data using databases similar to Dunn & Bradstreet, such as Manta.com.

Table 16 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, 1,000 to 2,499, and 2,500 or more. The results indicate a relatively normal distribution, with most firms containing 20 to 249 employees. The Small Business Administration (SBA) defines entities classified in North American Industry Classification System (NAICS) as code 325412 "Pharmaceutical Preparation Manufacturing" to be "small" if they employ fewer than 750 workers. Given this definition, the above data indicate that 126 of the 170 entities are small, which translates to roughly 75 percent of all health care antiseptic manufacturers (126 / 170). Furthermore, each small entity manufactures roughly 3.5 to 8.5 unique health care antiseptic products.

Table 16. Health care Antiseptic Manufacturers by Number of Employees

Size by Number of Employees	Number of Establishments	Average Number of Unique Products	Average Revenues ($1,000)
1 to 4	17	3.5	$303
5 to 9	10	3.5	$928
10 to 19	17	4.5	$2,970
20 to 49	29	7	$12,376
50 to 99	18	6	$24,035
100 to 249	15	8.5	$53,103
250 to 499	12	8.5	$100,982
500 to 749	8	8	$87,075
750 to 2,499	13	11.5	$3,036,892
2,500 or more	31	22	$38,174,739

Average number of unique products excludes outlier values.

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

To assess the rule's economic impact on small entities, we compare each establishment's revenues with its rule-related costs [=(establishment's expected rule-induced costs)/(establishment's annual revenues in 2013). We separately conduct this analysis for the two above scenarios, which

include when every antiseptic active ingredient with large market share is demonstrated to be GRAS/GRAE for health care antiseptic use, and when no antiseptic active ingredient is demonstrated to be GRAS/GRAE for health care antiseptic use.

1. No Antiseptic Active Ingredient Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

Under this scenario, costs include the expenditures to conduct safety and efficacy tests, and to exit the market when these tests indicate that no antiseptic active ingredient is demonstrated to be GRAS/GRAE. Again, we assume that manufacturers exit the market only after testing indicates that no health care antiseptic active ingredients are GRAS/GRAE for use in health care antiseptics. Larger manufacturers are expected to conduct the safety and efficacy tests because they stand to incur the greatest costs if the active ingredient becomes nonmonograph. Hence, under this scenario, small business costs only include the costs to exit the market, which we proxy using an entity's average annual health care antiseptic revenues.

IMS Health and A.C. Nielsen data indicate that annual health care antiseptic sales for small entities are approximately equal to $82 million. Assuming sales are equally distributed across the number of unique products, we estimate annual health care antiseptic sales to roughly equal $71,242 per unique product.

Using the above value, we estimate that the rule could impose a substantial economic burden on small entities. Table 17 summarizes average annual costs as a percentage of average annual revenues. The results indicate that annual costs could range between 0.60 and 82.18 percent of average

annual revenues, with the smallest entities, those employing 1 to 4 employees, expected to incur annual costs roughly equaling 82.18 percent of average annual revenues.

Table 17. Summary of Costs for Entities by Number of Employees

Size by Number of Employees	Average Number of Unique Products	Average Sales per Unique Product	Average Health care Antiseptic Sales ($1,000)	Average Revenues ($1,000)	Average Annual Costs as a % Average Revenues
1 to 4	3.5	$71,242	$249	$303	82.18%
5 to 9	3.5	$71,242	$249	$928	26.83%
10 to 19	4.5	$71,242	$321	$2,970	10.81%
20 to 49	7	$71,242	$499	$12,376	4.03%
50 to 99	6	$71,242	$427	$24,035	1.78%
100 to 249	8.5	$71,242	$606	$53,103	1.14%
250 to 499	8.5	$71,242	$606	$100,982	0.60%
500 to 749	8	$71,242	$570	$87,075	0.65%

2. Every Antiseptic Active Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

Under this scenario, costs include the expenditures to reformulate and relabel Benzethonium Chloride products, and to conduct safety and efficacy testing for the following active antiseptic ingredients: Benzalkonium Chloride, Chloroxylenol, Ethyl Alcohol, Isopropyl Alcohol, Povidone Iodine, Triclosan. As indicated above, larger manufacturers are expected to conduct the safety and efficacy tests because they stand to incur the greatest costs if the active ingredients become nonmonograph. Hence, under this scenario, small business costs only include the one-time costs to reformulate and relabel Benzethonium Chloride products.

Table 17 reports these individual costs across every size category. A value equal to $0 indicates that no establishments in this category produce Benzethonium Chloride products. Our data is not

granular enough to indicate which establishments could coordinate their labeling activities, so we use the uncoordinated relabeling costs to avoid understating relabeling costs. Our data also does not indicate the number of uniquely packaged Benzethonium Chloride products per establishment. For Benzethonium Chloride, the aggregate data indicate that there are 34 unique formulations and 70 uniquely packaged products (roughly two uniquely packaged products per unique formulation). Given these data, we proxy the number of uniquely packaged products containing Benzethonium Chloride, per establishment, by multiplying their number of unique formulations by two.

Table 18. Summary of Costs for Entities by Number of Employees

Size by Number of Employees	Cost per Establishment	
	Low Cost Reformulation	High Cost Reformulation
1 to 4	$0	$0
5 to 9	$41,858	$191,562
10 to 19	$36,934	$169,025
20 to 49	$21,651	$99,084
50 to 99	$11,627	$53,212
100 to 249	$27,905	$127,708
250 to 499	$0	$0
500 to 749	$26,161	$119,726

Table 19 reports the individual costs as a percentage of average annual revenues. The results suggest that the proposed requirements are not expected to impose substantial costs on most establishment categories. Assuming that costs are distributed equally, we estimate average one-time reformulation costs to range between 0.00 and 20.64 percent of average annual revenues. However, mode one-time reformulation costs range between approximately 0 and 1 percent.

Table 19. Summary of Costs Relative To Annual Revenues for Entities by Number of Employees

Size by Number of Employees	Cost per Establishment as a Percentage of Sales					
	Low Cost			High Cost		
	Reformulation	Average Sales	Costs as a Percentage of Sales	Reformulation	Average Sales	Costs as a Percentage of Sales
1 to 4	$0	$303,000	0.00%	$0	$303,000	0.00%
5 to 9	$41,858	$928,000	4.51%	$191,562	$928,000	20.64%
10 to 19	$36,934	$2,970,000	1.24%	$169,025	$2,970,000	5.69%
20 to 49	$21,651	$12,376,000	0.17%	$99,084	$12,376,000	0.80%
50 to 99	$11,627	$24,035,000	0.05%	$53,212	$24,035,000	0.22%
100 to 249	$27,905	$53,103,000	0.05%	$127,708	$53,103,000	0.24%
250 to 499	$0	$100,982,000	0.00%	$0	$100,982,000	0.00%
500 to 749	$26,161	$87,075,000	0.03%	$119,726	$87,075,000	0.14%

Adopting the proposed rule is expected to impose a moderate economic burden on smaller establishments (those that employ 5 – 19 workers). The results in table 19 indicate that one-time costs are expected to range between 4.51 and 20.64 percent of annual revenues for this size category.

The above analysis assumes that costs are distributed equally. However, the data indicate that costs are distributed unevenly, with some manufacturers projected to experience modest costs and others substantial costs. Table 20 reports the number of establishments whose one-time costs as a percentage of sales are expected to fall into the following categories: between 0.01 and 25 percent, 26 and 50 percent, 51 and 75 percent, 75 and 100 percent, and greater than 100 percent. The results indicate that adopting the proposed rule would impose a modest economic burden on roughly 166 of the 170 establishments (where one-time costs as a percentage of annual revenues are less than 25 percent), but a significant burden on roughly 4 establishments (where this ratio is greater than 75 percent).

Table 20. Frequency of Costs Relative to Annual Revenues

Size by Number of Employees	Number of Establishments Whose Cost as a Percentage of Sales Ranges Between									
	Average Low Cost					Average High Cost				
	0.01 - 25 Percent	26 - 50 Percent	51 - 75 Percent	76 - 100 Percent	Greater than 100 Percent	0.01 - 25 Percent	26 - 50 Percent	51 - 75 Percent	76 - 100 Percent	Greater than 100 Percent
1 to 4	17	0	0	0	0	17	0	0	0	0
5 to 9	8	2	0	0	0	8	0	0	0	2
10 to 19	16	1	0	0	0	16	0	0	0	1
20 to 49	28	0	1	0	0	28	0	0	0	1
50 to 99	18	0	0	0	0	18	0	0	0	0
100 to 249	15	0	0	0	0	15	0	0	0	0
250 to 499	12	0	0	0	0	12	0	0	0	0
500 to 749	8	0	0	0	0	8	0	0	0	0

C. Alternatives for Regulatory Relief

1. No Antiseptic Active Ingredient Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

a. Delay Testing Compliance One Year

Under this scenario, one method to provide regulatory relief would be to provide manufacturers an additional year to conduct their testing. This alternative would allow manufacturers to market their products an additional year, resulting in a one-time reduction in costs that approximately equal the establishment's average annual revenues. Given the values reported in table 17, we estimate the total one-time reduction in costs to approximately equal $82 million.

2. Every Antiseptic Active Ingredient With Large Market Share Is Demonstrated To Be GRAS/GRAE for Use In Health Care Antiseptic Products

a. Increase Relabeling Compliance Times

Under this scenario, one method to provide regulatory relief would be to increase relabeling compliance times from 12 months to 18 months. Table 21 recreates the results presented in table 20, assuming 18 month compliance times. The results indicate that this pathway would not provide visible regulatory relief. One-time costs, as a percentage of annual revenues, remain approximately unchanged.

Another option is to increase relabeling compliance times enough so that every manufacturer can coordinate their relabeling activities. However, our analysis indicates that even extending compliance times up to 6 years would not change the results in table 21.

Table 21. Frequency of Costs Relative To Annual Revenues (No Reformulation)

Size by Number of Employees	Number of Establishments Whose Cost as a Percentage of Sales Ranges Between									
	Average Low Cost					Average High Cost				
	0.01 - 25 Percent	26 - 50 Percent	51 - 75 Percent	76 - 100 Percent	Greater than 100 Percent	0.01 - 25 Percent	26 - 50 Percent	51 - 75 Percent	76 - 100 Percent	Greater than 100 Percent
1 to 4	17	0	0	0	0	17	0	0	0	0
5 to 9	8	2	0	0	0	8	0	0	0	2
10 to 19	16	1	0	0	0	16	0	0	0	1
20 to 49	28	0	1	0	0	28	0	0	0	1
50 to 99	18	0	0	0	0	18	0	0	0	0
100 to 249	15	0	0	0	0	15	0	0	0	0
250 to 499	12	0	0	0	0	12	0	0	0	0
500 to 749	8	0	0	0	0	8	0	0	0	0

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