DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Safety and Effectiveness of Consumer Antiseptic Rub Products; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph

Docket No. FDA-2016-N-0124

Preliminary Regulatory Impact Analysis

Initial Regulatory Flexibility Analysis

Unfunded Mandates Reform Act Analysis

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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 (Pub. L. 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. Because the consumer antiseptic rub product industry is mainly composed of establishments with 500 or fewer employees, the Agency tentatively concludes the proposed rule may have a significant economic impact 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 1 year." The current threshold after adjustment for inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

B. Summary of Costs and Benefits

There are three active ingredients being considered for use as a consumer antiseptic rub in this proposed rule: ethyl alcohol (referred to subsequently as alcohol), isopropyl alcohol, and benzalkonium chloride. The impact of the proposed rule on the over-the-counter (OTC) consumer antiseptic rub product industry will depend on the outcome of testing and whether we determine that these three active antiseptic ingredients are generally recognized as safe and effective (GRAS/E). It is possible that none, one, two, or all three of the ingredients will be determined to be GRAS/E. We consider two extreme scenarios to capture the entire range of total costs: (1) all three ingredients are determined to be GRAS/E or (2) none of the ingredients is determined to be GRAS/E.

In the table below, we provide a summary of the estimated costs of the proposed rule for the two scenarios. The costs of the proposed rule involve product reformulation and relabeling of products. It is important to note that, to demonstrate that an antiseptic active ingredient is GRAS/E, some manufacturers will also incur additional costs associated with safety and effectiveness testing. We note that the testing costs for this proposed rule are not attributed here because these costs will be realized if manufacturers comply with the proposed rule for health care antiseptics (80 FR 25166) and we do not count costs twice. However, we estimate these costs in this analysis to promote transparency in the event that this rule is finalized before the health care antiseptics proposed rule or if manufacturers conduct the testing for the three ingredients discussed in this proposed rule but do not conduct the testing for these ingredients for the health care antiseptics proposed rule.[1]

In scenario 1, all three ingredients are determined to be GRAS/E and manufacturers of products containing other ingredients will no longer be allowed to market these products under consumer antiseptic rub labels pursuant to the topical antimicrobial monograph. We expect that these manufacturers will reformulate their products to contain one of the monograph ingredients and relabel their products to reflect the change in ingredients. Annualizing upfront costs over a 10-year period at a discount rate of 3% for scenario 1, the costs of the proposed rule are estimated to be between $0.04 million and $0.12 million per year; the corresponding estimated

[1] We do note, however, that manufactures have already proposed to fill the safety and effectiveness data gaps for the three active ingredients of this proposed rule.

cost at a discount rate of 7% is between $0.05 million and $0.14 million per year. In scenario 2, none of the ingredients is determined to be GRAS/E and we expect that manufacturers will reformulate their products to be free of antiseptics and relabel them to reflect the change in ingredients. Annualizing upfront costs over a 10-year period at a discount rate of 3% for scenario 2, the costs of the proposed rule are estimated to be between $1.87 million and $5.52 million per year; the corresponding estimated cost at a discount rate of 7% is between $2.28 million and $6.70 million per year.

Summary of Quantified Total Costs (in millions), by Scenario									
Cost Category	**One-Time Costs**			**Annualized Costs Over a 10-Year Period**					
				3% Discount Rate			7% Discount Rate		
	Low	Med.	High	Low	Med.	High	Low	Med.	High
Scenario 1: Assuming All Ingredients are Determined to be GRAS/E									
Relabeling Costs	$0.11	$0.19	$0.32	$0.01	$0.02	$0.04	$0.02	$0.03	$0.05
Reformulation Costs	$0.23	$0.46	$0.70	$0.03	$0.05	$0.08	$0.03	$0.07	$0.10
Total Costs	$0.34	$0.66	$1.02	$0.04	$0.08	$0.12	$0.05	$0.09	$0.14
Scenario 2: Assuming None of the Ingredients is Determined to be GRAS/E									
Relabeling Costs	$6.55	$11.36	$18.76	$0.77	$1.33	$2.20	$0.93	$1.62	$2.67
Reformulation Costs	$9.44	$18.89	$28.33	$1.11	$2.21	$3.32	$1.34	$2.69	$4.03
Total Costs	$15.99	$30.25	$47.09	$1.87	$3.55	$5.52	$2.28	$4.31	$6.70

A potential benefit of the proposed rule is that the removal of potentially harmful antiseptic active ingredients in consumer antiseptic rub products will prevent health consequences associated with exposure to such ingredients. FDA lacks the necessary information to estimate the impact of exposure to antiseptic active ingredients in consumer antiseptic rub products on human health outcomes. We are, however, able to estimate the reduction in the aggregate exposure to antiseptic active ingredients found in currently marketed consumer antiseptic rub products. As with the total costs, the reduction in aggregate exposure to antiseptic active ingredients in consumer rub products depends on the outcome of testing and a determination of GRAS/E status of the three ingredients that require testing. The proposed rule will lead to an estimated reduction that ranges from 110 pounds to 254 pounds per year in scenario 1 and from 13,080,963 and 67,272,847 pounds per year in scenario 2. Absent information on the change in the short- and long-term health risks associated with a one pound increase in exposure to each antiseptic active ingredient in consumer antiseptic rub products, we are unable to translate the aggregate exposure figures into monetized benefits.

II. Preliminary Regulatory Impact Analysis

A. Background

In 1994, FDA published a tentative final monograph (59 FR 31402), which proposed conditions under which OTC consumer antiseptic products are GRAS/E. This proposed rule proposes to establish new conditions under which OTC consumer antiseptic products intended for use without water (referred to as consumer antiseptic rubs) are GRAS/E. This regulatory action provides a level of assurance of safety and effectiveness that would not otherwise occur in the existing market for consumer antiseptic rub products.

Antiseptics are marketed to consumers and various industries, such as research institutions, food handlers, textile manufacturers, and health care providers. This proposed rule, however, only covers consumer antiseptic rub products that are sometimes referred to as rubs, leave-on products or hand "sanitizers." Consumer antiseptic rubs are designed as a personal care product to be used if soap and water are unavailable. These products are marketed in various formulations, including liquids, foams, gels, sprays, as well as single-use towelettes and wipes. As opposed to antiseptic washes, antiseptic rubs are products that are not intended to be rinsed off after use. Antiseptic rubs contain active ingredients that are intended to reduce the number of microorganisms on the hand.

The concern over the safety and effectiveness of antiseptic rubs has grown over time, with the increased use of such products in consumer settings. There are many more products containing antiseptic active ingredients in households today relative to the past. For example, a recent study found that while there were just a few dozen products in the mid-1990s containing antibacterial agents, the number today is over 700 (Ref. 6). Total hand sanitizer sales amounted to $173.5 million in 2012, and existing evidence indicates that the market is saturated with products containing alcohol as an active ingredient (Ref. 7).

As discussed in detail below, we also find that alcohol-based antiseptic rubs account for the majority of the consumer hand rub product market. When rubbing hands with alcohol-based

rubs, users are exposed to alcohol through dermal contact and via inhalation and there is a concern that intensive use of these antiseptic rubs may lead to passive alcoholization and adverse health effects (Ref. 8). Through intensive use of alcohol-based rubs, there is evidence that alcohol is absorbed through the intact skin of workers in the health care setting (Ref. 1 and 9). Many health care workers complain about unacceptable skin irritation caused by alcohol-based rubs (Ref. 10). This complaint is consistent with evidence that adverse health effects of topically applied alcohol may include skin irritation or contact dermatitis (Ref. 11). The concern regarding the potential health impact of the body absorbing alcohol through the use of alcohol-based rubs is more pronounced among pregnant health care workers because no safe threshold for fetal alcohol exposure has been identified (Ref. 12 and low doses may potentially induce harmful effects on fetuses (Ref. 13). Despite the worldwide use of alcohol-based antiseptic rubs, the resulting short- and long-run health risks of absorbing alcohol through repeated use of these products are currently unknown. These cases pertain to the health care setting, but this uncertainty applies to both health care and consumer settings.

Several important scientific developments that affect the safety evaluation of consumer rub active ingredients has occurred since FDA's 1994 evaluation of the safety and efficacy of 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 consumer antiseptic active ingredients, systemic exposure is higher than previously thought, and new information about the potential risks from systemic absorption and long-term exposure has become available (Ref. 1-5). Currently, the significance of this new information is unknown. The benefits of any active ingredient will need to be weighed against its risks once both the effectiveness and safety have been better characterized to determine GRAS/GRAE status.

Antiseptic rubs may be used on a daily basis by consumers over the course of a lifetime. Given the growth in the presence and use of consumer antiseptic rubs, extended exposure to antiseptic active ingredients in these products may cause damage to human health. The testing required by this proposed rule will provide the data necessary for FDA to determine whether alcohol, isopropyl alcohol, and benzalkonium chloride are GRAS/E. FDA recently reviewed the

literature on the effectiveness of alcohol, isopropyl alcohol, and benzalkonium chloride in rubs for use in consumer settings. Based on an extensive literature review, FDA concluded that there is not enough evidence in the literature, and that additional evidence is needed to support GRAE status for alcohol, isopropyl alcohol, and benzalkonium chloride when used as a rub in a consumer setting.

B. Need for Regulation

This regulation addresses the market failure arising from inadequate information about the potential health risks associated with consumers' daily use of antiseptic rubs and the effectiveness of these products. This proposed rule is also a part of our ongoing evaluation of the safety and effectiveness of drug products containing these ingredients. As indicated in previous sections, FDA is proposing that more safety and efficacy data are necessary to determine whether the active antiseptic ingredients addressed in this proposed rule (i.e., alcohol, isopropyl alcohol, and benzalkonium chloride), are safe and effective for use in consumer antiseptic rub products given the recent increase in the frequency of their use. Based on the data currently available to the Agency, it cannot be determined whether alcohol, isopropyl alcohol, and benzalkonium chloride are safe for daily use, or effective in reducing microbes on the skin, or both. This proposed rule would respond to our obligation to ensure that products using these three active ingredients are both safe and effective (21 CFR 330.10(a)(4)). The proposed rule, if finalized as proposed, would prevent manufacturers from marketing consumer antiseptic rub products that contain these ingredients under the topical antimicrobial monograph. If FDA obtains additional safety and effectiveness data on these antiseptic ingredients and makes a determination that consumer antiseptic rub products containing these active ingredients are GRAS/E, then manufacturers can continue to market consumer antiseptic rub products that contain these ingredients under the topical antimicrobial monograph.

Firms that market antiseptic rub products containing antiseptic active ingredients differentiate these products from other products that are intended for cleansing or moisturizing the skin by making antibacterial claims on their labels. The purpose behind the distinctive labeling as an antiseptic drug is to convey information about a health benefit resulting from the

use of antiseptic rubs. In consumer settings, there currently is insufficient evidence to support the efficacy claim that consumer antiseptic rub products reduce bacteria on the skin, and there are unresolved safety considerations regarding long-term daily use of these products, as discussed in the previous section.

Despite the lack of evidence demonstrating the safety and effectiveness of these three active ingredients in consumer antiseptic rub products, the product demand conditions and revenue growth of the hand sanitizer industry are strong (Ref. 14). Given widespread and growing use of antiseptic rubs, consumers may believe that use of these products offers health benefits above and beyond any health risks. However, information to which consumers have access may not be reflective of the current state of knowledge regarding the safety and effectiveness of antiseptic rubs. If consumers perceive a benefit to using antiseptic rubs, then firms will have an incentive to make antibacterial claims on product labels. Firms are in a better position to know about the health advantages, or lack thereof, from using antiseptic rub products. This is a case of asymmetric information where producers may know more about their product's characteristics than do consumers. Assuming that the private marginal cost of obtaining safety and effectiveness information exceeds the private marginal benefit, there will be insufficient incentive for producers to obtain this information in the absence of regulatory actions requiring producers to provide this information to consumers. Because it is time-consuming and resource-intensive to generate the evidence needed for consumers to make fully informed choices, private market incentives are insufficient to provide adequate assurances of product safety and effectiveness. Regulation is justified in a case such as this because there is a market failure resulting from inadequate information.

If consumers are boundedly rational, complex decision-making may exacerbate the market failure resulting from inadequate information regarding the safety and effectiveness of antiseptic rubs. Consumers are boundedly rational if their rationality is limited by the information they have, their cognitive capacity, or time available when making purchase decisions. Constraints such as these may cause consumers to less than fully understand or be aware of adverse health effects associated with using consumer antiseptic rub products, which could result in suboptimal choices in the marketplace. For example, long periods of time may be required

before potentially health-damaging effects of consumer antiseptic rub consumption are realized. To the extent that benefit-cost calculations associated with using antiseptic rub products are complicated, bounded rationality among consumers may result in overconsumption of these products relative to a benchmark in which consumers are fully informed and rational.

Given the popularity and frequent use of consumer rub products containing antiseptic active ingredients, there has been growing concern over the emergence of antibiotic-resistant bacteria associated with the use of some hand-hygiene products (Ref. 15). While FDA has sufficient data to conclude that alcohol and isopropyl alcohol do not increase antibacterial resistance, additional data are needed to make this determination for benzalkonium chloride. Frequent use of consumer antiseptic rub products may increase the chance of bacterial resistance, which could increase the risk of infection or disease for others in the population. These potential negative externalities, or costs borne by parties not directly involved in the use of consumer antiseptic rub products, provide an additional economic rationale for regulation.

C. Purpose of this Rule

The proposed rule's objective is to update the standards and conditions whereby consumer antiseptic active ingredients are determined to be GRAS/E for their intended uses in consumer antiseptic rub products. The proposed rule would require a demonstration of safety and effectiveness for use in consumer antiseptic rub products for the following antiseptic active ingredients: benzalkonium chloride, alcohol, and isopropyl alcohol. To demonstrate a consumer antiseptic rub active ingredient is GRAE, only one manufacturer of an active antiseptic ingredient would need to conduct 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 demonstrate that a consumer antiseptic rub active ingredient is GRAS, only one manufacturer of an active antiseptic ingredient would need to conduct, depending on the active antiseptic ingredient, the following types of studies: human pharmacokinetic maximal use trial (MUsT); 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 of the active ingredient to cause bacterial resistance. Details on which active antiseptic ingredient require which tests are discussed further in the costs section. If finalized as proposed, this rule would require manufacturers to only market consumer antiseptic rub products containing antiseptic active ingredients that are GRAS/GRAE, effective one year after publication, unless the manufacturer seeks approval of its product under a new drug application (NDA).

Based on the available data and studies, FDA tentatively determines that the antiseptic ingredient categorized as category I in the 1994 TFM (i.e., alcohol) does not meet the GRAS/E standard under the updated requirements proposed under this rule and that more data are necessary to make a GRAS/E determination for use of alcohol in consumer antiseptic rub products. FDA also proposes that additional data are still necessary to make a GRAS/E determination for isopropyl alcohol and benzalkonium chloride for use in consumer antiseptic rub products. If there are inadequate data to meet the proposed requirements and the proposed rule becomes final, then continued marketing of consumer antiseptic rubs containing the affected active ingredients would require that manufacturers obtain an NDA. Alternatively, current manufacturers of consumer antiseptic rub products could comply with the final rule by reformulating those products to remove the antiseptic active ingredients and market them as antiseptic-free cleansers in compliance with the relevant requirements related to cosmetic products.

The proposed rule explains that certain active ingredients, including benzethonium chloride, polyhexamethylene biguanide, and triclosan, do not have evidence to establish their eligibility to be considered GRAS/E under the OTC Drug Review for use in consumer antiseptic rub products. While these other active ingredients are not discussed further in the proposed rule, as we discuss in greater detail below, we include the costs and benefits associated with the removal of the ingredients that are still found in currently marketed consumer antiseptic rub products. If finalized as proposed, this rule would require manufacturers of drug products containing these ineligible ingredients to obtain NDA approval to continue marketing as a consumer antiseptic rub product.

If there are antiseptic active ingredients found to be GRAS/E in the final rule, manufacturers producing consumer rubs containing ineligible antiseptic active ingredients could reformulate their products to contain those ingredients. Individuals who were using products containing ineligible antiseptic active ingredients would then be able to substitute those products with products containing active ingredients that are found to be GRAS/E under the final rule. Manufacturers of consumer rubs containing ineligible antiseptic active ingredients could also choose to exit the market if the costs to comply with the rule exceed the benefits of continued production. Discontinuation of products containing ineligible active ingredients is not expected to adversely affect a substantial number of manufacturers. Available market data provided by AC Nielsen, as discussed below, indicate that a small fraction of consumer rubs contain ineligible antiseptic ingredients

D. Baseline Conditions

Data from AC Nielsen, which provides nationally representative product sales information, is used to estimate the baseline or the state of the world in the absence of the proposed regulatory action. Baseline conditions are characterized by describing the marketplace in terms of sales and aggregate exposure to antiseptic active ingredients associated with the use of such products. The most recent data available is for the 52 weeks ending in September 5, 2009. The baseline analysis is restricted to products for which there were positive sales over this period.

1. Active Ingredients in Currently Marketed OTC Consumer Antiseptic Rub Products

There are three ingredients that are eligible for evaluation under the OTC Drug Review for use in a consumer antiseptic rub: benzalkonium chloride, alcohol, and isopropyl alcohol. All three ingredients require additional testing to determine whether they are GRAS/E. Conditional on being demonstrated to be GRAS/E, if the rule is finalized as proposed, these are the only antiseptic active ingredients that will be permitted to be used in OTC consumer antiseptic rub products marketed under the monograph. Conversely, OTC consumer antiseptic rub products containing any of these three antiseptic active ingredients that are not demonstrated to be GRAS/E

will be considered nonmonograph in a final rule. Moreover, if this rule is finalized as proposed, sponsors of consumer antiseptic rub products containing ineligible antiseptic active ingredients will be required to obtain an approved NDA to continue marketing these products as consumer antiseptic rubs.

As a first step in characterizing the consumer rub product market, for each antiseptic active ingredient, we estimated the fraction of universal product codes (UPCs) and total equivalent (16 oz.) units currently on the market. In Table 1, we show the distribution of active ingredients in consumer antiseptic rub products by dosage form. At this time, alcohol or benzalkonium chloride are the two most widely used active ingredients in consumer antiseptic rub products. Alcohol, in particular, accounts for a substantial share of active ingredients in currently marketed UPCs in both dosage form categories. For example, it accounts for 92% of rubs that are consumed as liquids, gels, or foams (hereafter referred to as "liquids"), and 100% of rubs that are consumed as single-use wipes or towelettes (hereafter referred to as "non-liquids"). Among liquid consumer rub products, other used antiseptic active ingredients include benzalkonium chloride, benzethonium chloride, polyhexamethylene biguanide and triclosan. Alcohol is the only ingredient found in non-liquids. Over this period, no consumer rub product contained isopropyl alcohol as an antiseptic active ingredient. Using total equivalent units sold, alcohol is the most commonly used antiseptic active ingredient in the consumer rub product market.

The data indicate that 97 percent of consumer rub products contain alcohol or benzalkonium chloride. The remaining 3 percent of products contain other antiseptic active ingredients that the rule proposes are ineligible for GRAS/GRAE consideration under the OTC Drug Review for use in consumer antiseptic rub products. These other antiseptic active ingredients are benzethonium chloride, polyhexamethylene biguanide, and triclosan. A.C. Nielsen data indicate that manufacturers stopped selling consumer rub products containing polyhexamethylene biguanide as their active antiseptic ingredient. An extensive internet search also indicates that retailers and pharmacies continue to market consumer rubs containing benzethonium chloride, but that they stopped marketing consumer rubs containing triclosan. Hence, among these other antiseptic active ingredients, the proposed rule is only expected to affect consumer rub products containing benzethonium chloride.

To summarize, available market data indicate that the proposed rule, if finalized as proposed, would only affect consumer rub products containing alcohol, benzalkonium chloride, and benzethonium chloride because consumer rub manufacturers have already stopped using the other antiseptic active ingredients potentially affected by this rule.

Table 1: Estimated Distribution of Active Ingredients in Consumer Rub Products for 52 Weeks Ending in September 5, 2009, by Dosage Form

Antiseptic Active Ingredient	Liquid, Gel, and Foam		Wipes and Towelettes	
	Percent of UPCs	Percent of Total Equivalent (16 oz.) Units Sold	Percent of UPCs	Percent of Total Equivalent (16 oz.) Units Sold
Benzalkonium Chloride	5.2	0.3	0.0	0.00
Alcohol	91.8	99.1	100.0	100.0
Isopropyl Alcohol	0.0	0.0	0.0	0.00
Benzethonium Chloride	1.8	0.3	0.0	0.00
Polyhexamethylene Biguanide	0.5	0.0	0.0	0.00
Triclosan	0.7	0.3	0.0	0.00
Total	100.0	100.0	100.0	100.0

2. Number of Affected Products and Product Sales in the Current Market for OTC Consumer Antiseptic Rubs

In a recent internet search of consumer rub products, we could not find any currently marketed products containing isopropyl alcohol, polyhexamethylene biguanide or triclosan as an antiseptic active ingredient. Thus, the analysis below focuses on the other ingredients (alcohol, benzalkonium chloride, and benzethonium chloride). As a complement to the characterization of the consumer antiseptic rub product market using total equivalent unit sales, Table 2 shows the dollar sales of products by active ingredient and dosage form. The total number of UPCs and sales over the 52-week period ending in September 5, 2009 amounted to 460 and $116.8 million (in 2014 dollars), respectively. Nielsen data include product and sales information derived from purchases made in supermarkets, drug stores, and mass merchandisers (excluding Walmart). In July 2015, IBIS World estimated revenue in the hand sanitizer manufacturing industry to be $238 million, of which 81% derived from purchases outside the health care setting (Ref. 14). To

account for underrepresentation of product and sales information, we apply an adjustment factor of 1.65 (0.81*238/116.8) to UPC counts, formulas, annual unit sales, and annual dollar sales to obtain estimates representing the entire market of affected products. Table 2 provides our estimated product counts and dollar sales by active ingredient and dosage form. In the aggregate, we estimate that there are a total of 760 products that will be affected by this proposed rule, and sales of these products amounted to $191.2 million. As in Table 1, consumer antiseptic rub products that contain alcohol account for the vast majority of sales.

Table 2: Number of Products and Dollar Sales (in millions) for 52 Weeks Ending in September 5, 2009, by Active Ingredient and Dosage Form

Antiseptic Active Ingredient	Liquid, Gel, and Foam		Wipes and Towelettes	
	Number of Products	Dollar Sales (in Millions)	Number of Products	Dollar Sales (in Millions)
Benzalkonium Chloride	38	$1.2	0	$0.0
Alcohol	668	$181.3	41	$7.3
Isopropyl Alcohol	0	$0.0	0	$0.0
Benzethonium Chloride	13	$1.5	0	$0.0
Total	719	$183.9	41	7.3

3. Antiseptic Active Ingredient Usage in Consumer Rub Products

FDA lacks the necessary data to estimate the short- and long-term health risks associated with using consumer rub products containing antiseptic active ingredients. Absent information on the change in health risks associated with a one unit increase in exposure to each antiseptic active ingredient in consumer rub products, we are unable to translate the aggregate exposure figures into monetized benefits.

As an intermediate measure of the baseline risk resulting from the use of consumer antiseptic rub products, we estimate the annual consumption of antiseptic active ingredients and then use estimated concentration levels for each active ingredient to calculate annual exposure. We begin by standardizing sales units to estimate the consumption of consumer rub products by antiseptic active ingredient and dosage form. Table 3 shows that, in the 52 weeks leading up to September 5, 2009, about 30.1 million and 62.6 million equivalent units liquid and non-liquid

rub products were sold, respectively. Also, as before, rub products containing alcohol, account for most of unit sales.

Table 3: Total Equivalent Unit (16 oz.) Sales for 52 Weeks Ending in September 5, 2009, by Active Ingredient and Dosage Form		
Antiseptic Active Ingredient	**Liquid, Gel, and Foam**	**Wipes and Towelettes**
Benzalkonium Chloride	96,454	0
Alcohol	29,791,212	62,356,553
Isopropyl Alcohol	0	0
Benzethonium Chloride	81,013	0
Total	30,068,301	62,580,387

In Table 4, we express the estimated consumption of liquid (non-liquid) consumer hand rub products in volume (weight). For example, we estimate that about 14.2 million liters (or 29.8 million 16 oz. units x 0.473 liters per 16 oz.) of liquid consumer hand rub products containing alcohol are consumed per year.

Table 4: Estimated Annual Consumption of Antiseptic Rub Products, by Active Ingredient and Dosage Form		
Antiseptic Active Ingredient	**Liquid, Gel, and Foam (In Liters)**	**Wipes and Towelettes (In Pounds)**
Benzalkonium Chloride	45,640	0
Alcohol	14,096,487	62,356,553
Isopropyl Alcohol	0	0
Benzethonium Chloride	38,334	0
Total	14,180,460	62,356,553

Next, we translate the annual consumption of consumer antiseptic rub products into annual usage of antiseptic active ingredients. The FDA National Drug Code Directory is used to obtain ranges of concentration levels of each antiseptic active ingredient. In some cases, we are unable to provide a range because we do not have sufficiently reliable information. Concentration level is expressed as weight per unit of volume (w/v) for liquids and weight per unit of weight (w/w) for non-liquids. We find a wide range for alcohol (between 14% and 72%), and much narrower ranges for the other antiseptic active ingredients.

Table 5: Estimated Concentration Level (in w/v or w/w), by Active Ingredient			
Antiseptic Active Ingredient	**Low**	**Midpoint**	**High**
Benzalkonium Chloride	0.10%	0.13%	0.15%

Alcohol	14.0%	43.0%	72.0%
Isopropyl Alcohol	No Information to estimate		
Benzethonium Chloride	0.13%	0.22%	0.30%

Finally, we use the estimated concentration level ranges in Table 5 to estimate annual exposure to antiseptic active ingredients in consumer antiseptic rub products. The values for each antiseptic active ingredient are expressed in weight for ease of interpretation. In the aggregate, as shown in Table 6, we estimate that consumers are exposed to between 13.1 million and 67.3 million pounds of antiseptic active ingredients every year. Alcohol accounts for the vast majority of the exposure to antiseptic active ingredients through the use of consumer antiseptic rub products.

Table 6: Estimated Exposure to Consumer Antiseptic Active Ingredients (in Pounds per Year), by Active Ingredient

Antiseptic Active Ingredient	**Low**	**Midpoint**	**High**
Benzalkonium Chloride	101	126	151
Alcohol	13,080,753	40,176,598	67,272,443
Isopropyl Alcohol	No Information to estimate		
Benzethonium Chloride	110	182	254
Total	13,080,963	40,176,905	67,272,847

E. Benefits of the Proposed Rule

If finalized as proposed, the rule would prevent continued marketing of consumer antiseptic rub products that contain active ingredients that have not been determined to be GRAS/E without an approved NDA. Because results from tests to determine the GRAS/E status of benzalkonium chloride, alcohol, and isopropyl alcohol are not available currently, we consider two extreme scenarios to capture the possible range of the reduction in aggregate exposure to antiseptic active ingredients: (1) all three ingredients are determined to be GRAS/E or (2) none of the ingredients is determined to be GRAS/E (and none of the manufacturers of these products seek approval under an NDA). It is possible that one ingredient or two ingredients are determined to be GRAS/E while the other(s) are not. The reduction in exposure in these intermediate scenarios lies within our two extreme scenarios. As we describe below, the reduction in aggregate exposure to antiseptic active ingredients in consumer antiseptic rub products depends on the outcome of testing and a determination of GRAS/E status of the three ingredients being tested.

It is important to note that the benefits of the proposed rule depend on a currently uncertain state of the world. For example, suppose exposure to antiseptic ingredient X through the use of consumer rubs is hazardous to health and testing leads FDA to determine that ingredient X is not GRAS. In this state of the world, active ingredient X will no longer be found in consumer antiseptic rub products and decreased exposure to it may result in health benefits. However, if ingredient X is not hazardous to health, the optimal outcome is that testing leads FDA to determine that ingredient X is GRAS. If in this state of the world, the FDA determination is that ingredient X is not GRAS or it is not GRAE, then decreased exposure to ingredient X may or may not result in health benefits. More specifically, this rule, if finalized as proposed, would yield health benefits for consumers of ingredient X if the following conditions hold: X is not effective (regardless of whether it is safe) or X is somewhat effective, but less so than expected substitute(s), and is either not safe or not found GRAS/E due to no entity finding it sufficiently profitable to conduct the necessary testing to establish GRAS/E status.[2] If X is both safe and more effective than expected substitute(s), but is not found GRAS/E due to no entity finding it sufficiently profitable to conduct the necessary testing to establish GRAS/E status, then the rule yields net harms to health. If X is not safe but is more effective than expected substitute(s), then the rule's health impact is ambiguous without further evidence; it depends on the relative magnitudes of the benefits of avoided safety risks and the harms of reduced effectiveness due to switching to less-effective antimicrobials. Finally, if X is both safe and effective and GRAS/E status is established, the rule may still have important health benefits if the additional data results in labeling changes to improve safe use.

As discussed above, one or more of the tested ingredients may be determined to be not GRAS, not GRAE, or neither GRAS nor GRAE. This would prevent the continued marketing under the topical antimicrobial monograph of consumer antiseptic rub products containing non-GRAS or non-GRAE ingredients. The removal of these products may result in a benefit for consumers who thought these products were either safer or more effective than the tests indicate. On the one hand, if consumers' value for such products—in light of the new information on

[2] Presumably, two of the most common choices in situations of unavailability of consumer antimicrobial hand rubs are: washing with soap and water, which has some effectiveness against illness but entails time costs, and doing without any antimicrobial intervention, which does not.

safety and efficacy—were reduced to close to zero, there would be a net gain as consumers would benefit from a cost savings that would more than offset the lost value of the products they can no longer buy. On the other hand, if some consumers still value the products even after learning about the results of tests on efficacy and safety, then removal of these products might result in a net loss. We do not have information to allow us to quantify these two potential effects of the proposed rule, but they run in counterbalancing directions.

Data linking consumer exposure to antiseptic active ingredients and the resulting short- and long-run health impacts are unavailable. Thus, we are unable to monetize the reductions in aggregate exposure to antiseptic active ingredient associated with the proposed rule. However, if the proposed rule is finalized, any health risks associated with the use of products that are not determined to be GRAS/E are expected to decline along with the decreased exposure to antiseptic ingredients once these products are removed from the marketplace.

1. Reduction in Exposure to Antiseptics

Scenario 1: All Ingredients are Determined to be GRAS/E

If each of benzalkonium chloride, alcohol, and isopropyl alcohol are determined to be GRAS/E, then the products containing these ingredients could continue to be marketed under consumer antiseptic rub labels pursuant to the topical antimicrobial monograph. A potential consequence of this determination is a substitution from nonmonograph toward monograph ingredients. Any health risk associated with exposure to nonmonograph ingredients is expected to fall as a result of this substitution. Among the active ingredients whose usage we can quantify, we estimate that the substitution toward monograph ingredients would reduce exposure to nonmonograph ingredients by between 110 pounds to 254 pounds per year.

Scenario 2: None of the Ingredients is Determined to be GRAS/E

If none of benzalkonium chloride, alcohol, and isopropyl alcohol is determined to be GRAS/E, then the proposed rule would prevent products containing these ingredients from continuing to be marketed under consumer antiseptic rub labels pursuant to the topical antimicrobial monograph. FDA has determined that there are antiseptic-free products on the market that are intended to serve as a substitute for wiping hands when soap and water are not readily available. For example, pre-moistened disposable wipes are currently available on the market for use when soap and water are not available, and these wipes do not contain any antiseptic active ingredients (Ref. 16). A potential consequence of this scenario is that manufacturers of products marketed under consumer antiseptic rub labels will produce similar products that are not marketed under such labels. We assume that consumers will substitute toward such antiseptic-free products. Among the active ingredients whose usage we can quantify, we estimate that this substitution would reduce exposure to nonmonograph ingredients by between 13,080,963 and 67,272,847 pounds per year.

F. Costs of the Proposed Rule

If the rule is finalized as proposed, there are two primary costs associated with compliance, relabeling and product reformulation costs. It is important to note that, to demonstrate that an antiseptic active ingredient is GRAS/E, some antiseptic active ingredient manufacturers will also incur additional costs associated with safety and effectiveness testing. We do not attribute these testing costs to this proposed rule because these costs are expected to be realized if manufacturers comply with the proposed rule for health care antiseptics (80 FR 25166) which precedes this rule. As mentioned above, the test results that determine the GRAS/E status of benzalkonium chloride, alcohol, and isopropyl alcohol are still unknown, so we consider two extreme scenarios to capture the possible range of total costs: (1) all three ingredients are determined to be GRAS/E or (2) none of the ingredients is determined to be GRAS/E.

It is also important to note that the safety and effectiveness data required for GRAS/E determination are similar to those required for an approved NDA. In FY 2016, manufacturers that decide to submit an NDA will be required to pay approximately $2.4 million in user fee

costs for each application requiring clinical data. Manufacturers of an approved NDA would, however, benefit from a period of marketing exclusivity, which increases the potential for recovery of NDA-related costs. In addition to the cost to manufacturers of preparing and submitting an NDA, the submission of an NDA would also generate incremental review costs to FDA. The most recent available data on standard costs associated with review of human drug applications (including rent, overhead, and centrally funded costs) published by FDA indicate that in FY 2013 the average cost to FDA for reviewing an NDA with clinical data for a non-new molecular entity is approximately $1.5 million. Because we lack sufficient information to be able to estimate the number of manufacturers that would opt to submit NDAs, we are unable to estimate NDA-related costs of the proposed rule. Because the safety and effectiveness data required to gain approval for an NDA would likely be similar to the requirements proposed under this rule, we do not expect many, if any, manufacturers to submit an NDA because, if they were unable to submit the safety and effectiveness data for OTC use, it is highly unlikely that they would meet the NDA safety and efficacy standards necessary to gain approval.

We re-emphasize that we do not attribute the safety and effectiveness testing costs to this proposed rule because these costs are expected to be realized if manufacturers comply with the proposed rule for health care antiseptics (80 FR 25166) which precedes this proposed rule. However, these costs would be attributed to this rule if this rule (80 FR 25166) is finalized before the health care antiseptics rule or if manufacturers conduct the testing for the three ingredients discussed in this rule, but do not conduct the testing for these ingredients as discussed in the health antiseptic proposed rule. Although neither case is expected, we estimate these testing costs in this analysis to promote transparency. We only estimate testing costs for alcohol and benzalkonium chloride because these are the only two of the three ingredients that are currently marketed.

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. 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) and thus $3.2 million to conduct one set of efficacy tests on each of the two active antiseptic ingredients that are marketed.

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) for the consumer washes antiseptic proposed rule. That analysis also calculates the average costs associated with each safety study. These results indicate that these costs are as follows:

- Human Pharmacokinetic (MUsT): $0.5 million;
- Animal Pharmacokinetic (ADME): $1.40 million;
- Oral Carcinogenicity: $3.12 million;
- Dermal Carcinogenicity: $3.12 million;
- Developmental and Reproductive Toxicity: $4.03 million;
- Potential Hormonal Effects: $1.2 million
- Bacterial Resistance: No available data.

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.

The proposed rule indicates that some manufacturers have already submitted adequate data for certain tests. The results indicate that the following antiseptic active ingredients have adequate data for:

- Benzalkonium Chloride: oral carcinogenicity, developmental and reproductive toxicity (DART), and potential hormonal effects;
- Alcohol: animal pharmacokinetic (ADME), oral and dermal carcinogenicity, developmental and reproductive toxicity (DART), potential hormonal effects, and bacterial resistance;

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: $5.0 million (=$0.5 million per human pharmacokinetic study + $1.4 million per animal pharmacokinetic study + $3.1 million per dermal carcinogenicity study). Benzalkonium Chloride 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.
- Ethyl Alcohol: Ethyl alcohol only requires one human pharmacokinetic study. We estimate these costs to approximately equal $0.5 million.

To summarize, total efficacy and safety testing costs (not including potential bacterial resistance testing) are expected to equal $8.7 million (= $3.2 million to demonstrate GRAE and $5.5 million to demonstrate GRAS). We emphasize that we attribute these costs to the health care antiseptics proposed rule (80 FR 25166), which precedes this proposed rule, and that we do

not expect to finalize this rule before the health care antiseptics proposed rule. However, we re-estimate these costs in this analysis to promote transparency.

1. Relabeling Costs

If the proposed rule is finalized as currently proposed, the costs associated with compliance will depend on the response of manufacturers. A two-fold reaction to the proposed rule is plausible. If a manufacturer's product is affected by the rule, then a likely response is that it will choose to reformulate the affected product to contain an antiseptic active ingredient under the monograph or reformulate the affected product as a non-antimicrobial consumer rub by removing the antiseptic active ingredient, and relabeling the product to reflect the change in the product's ingredient list. The latter cost, relabeling costs, will be a function of the type of printing method, number of color changes, whether the products are nationally branded or private label, and the compliance period for implementing such label changes.

To estimate relabeling costs, we use a model developed by one of our contractors, RTI International (RTI). The model includes the costs associated with labor inputs, material inputs, and discarded inventory. We consider that any label changes required by the proposed rule will be major, as they will likely involve multiple color changes that require redesigning of labels. In Table 7, we show estimates of the affected UPCs by brand and coordination type. Because some manufacturers will be able to coordinate regulatory label changes with routine voluntary label changes, compliance costs in such cases will be lower than uncoordinated changes. For a compliance period of 12 months, the RTI relabeling model assumes that 96% and 97% of branded and private-label products, respectively, cannot be coordinated with planned label changes, which explains the smaller estimated number of coordinated label changes.

Table 7: Number of UPCs, by Brand and Coordination Type

Brand Type	Uncoordinated	Coordinated	Total
Branded	566	24	589
Private	166	5	171
Total	732	28	760

In Table 8, we show estimates of the relabeling costs per UPC, by brand and coordination type. For uncoordinated changes, we estimate that the relabeling costs for nationally branded products will be between $8,145 and $24,210 per UPC; the corresponding range for private-label products is $11,651 and $30,053 per UPC. The difference in costs for branded and private-label products stems from the fact that private labelers incur higher costs associated with discarded inventories. For both branded and private-label products, the estimated relabeling costs range between $353 and $2,843 per coordinated UPC change.

Table 8: Estimated Labeling Change Costs per UPC, by Brand and Coordination Type

	Costs per Uncoordinated UPC		
Brand Type	**Low**	**Medium**	**High**
Branded	$8,145	$14,425	$24,210
Private	$11,651	$19,100	$30,053
	Costs per Coordinated UPC		
Brand Type	**Low**	**Medium**	**High**
Branded	$353	$1,231	$2,843
Private	$353	$1,231	$2,843

2. Reformulation Costs

A manufacturer's decision to reformulate will depend on the difference between the expected return to reformulating its product to meet the conditions set forth by the proposed rule and the expected return to not reformulating. The expected return to product reformulation, or the difference between the expected revenue and cost streams generated by reformulating a product, will be a function of consumer market demand conditions. It is difficult to know how consumers will react to changes in market offerings or the composition of products in the market for consumer antiseptic rubs. We account for this uncertainty by presenting ranges for reformulation costs.

Depending on the outcome of tests for the three ingredients that are being tested, manufacturers will have more than one reformulation option. For example, in the case of all three ingredients being determined to be GRAS/E, only manufacturers that produce a product containing other active ingredients will need to reformulate if they want to continue marketing

their product under consumer antiseptic rub labels pursuant to the topical antimicrobial monograph. However, if none of the ingredients is determined to be GRAS/E, no products will be able to continue marketing under the topical antimicrobial monograph under consumer antiseptic rub labels. An internet search of products has revealed that there are rubs on the market that do not contain antiseptic ingredients that are intended for cleansing or moisturizing the skin when rinsing hands with soap and water is not practical. Manufacturers may choose to reformulate their products so that they are free of antiseptic ingredients if the final rule prevents continued marketing of all products under consumer antiseptic rub labels and continued marketing of such products would require the submission and approval of an NDA.

We assume that within a brand, products containing the same antiseptic ingredient and possessing the same concentration and dosage form share the same formulation. Of the affected UPCs, we estimate that there are 201 unique formulations. Previously published estimates of the reformulation cost of OTC cough-cold combination drug products (67 FR 78158) ranged from $100,000 to $500,000. We inflate these values by 87% to reflect the increase in the Producer Price Index for pharmaceutical preparation manufacturing between 2002 and 2014 to arrive at an estimated range of between $187,634 and $938,170. We use the lower end of this range as the estimated per-UPC cost to reformulate consumer antiseptic rub products, which was also used in the economic analyses in proposed rules for consumer antiseptic washes (78 FR 76443) and health care antiseptics (80 FR 25166).

3. Costs by Scenario

Scenario 1: All Ingredients are Determined to be GRAS/E

If each of benzalkonium chloride, alcohol, and isopropyl alcohol are demonstrated to be GRAS/E, then sponsors will be able to continue marketing products containing these ingredients pursuant to the topical antimicrobial monograph under consumer antiseptic rub labels. If benzethonium chloride remains ineligible for OTC Drug Review, then manufacturers using benzethonium chloride in consumer antiseptic rub products would have to reformulate using a GRAS/E consumer rub active ingredient and relabel their products if they wish to continue their

presence in the market for products with consumer antiseptic rub labels or else seek NDA approval for their products. The fraction of manufacturers that will choose to reformulate and relabel their products is unknown, and thus estimating the fraction of products that will be affected by the resulting regulation-induced changes is difficult. We show ranges to capture this uncertainty.

The total estimated cost of labeling changes is obtained by multiplying the number of uncoordinated (coordinated) UPCs in a given scenario with the per-UPC cost for uncoordinated (coordinated) UPC changes. Tables 9 and 10 contain the range of estimated costs of labeling changes and reformulation, respectively. In this scenario, relabeling costs are estimated to range between $112,033 and $320,901; the corresponding range for reformulation costs is between $232,197 and $696,591.

Table 9: Estimated Costs of Labeling Changes (Assuming All Ingredients are Determined to be GRAS/E), by Brand Type

Brand Type	Low	Medium	High
Branded	$78,957	$140,084	$235,422
Private	$33,076	$54,277	$85,480
Total	$112,033	$194,360	$320,901

Table 10: Estimated Reformulation Costs (Assuming All Ingredients Are Determined to be GRAS/E)

Estimate	Percent of Products Reformulated		
	25	50	75
Estimated Cost of Reformulation per Product	$187,634	$187,634	$187,634
Estimated Number of Reformulations	1	2	4
Estimated Total Reformulation Costs	$232,197	$464,394	$696,591

Scenario 2: None of the Ingredients is Determined to be GRAS/E

If none of benzalkonium chloride, alcohol, and isopropyl alcohol is demonstrated to be GRAS/E, then the proposed rule would prevent manufacturers from marketing products containing these ingredients under consumer antiseptic rub labels pursuant to the topical antimicrobial monograph. In this scenario, no products that are currently in the marketplace will be allowed to be marketed under consumer antiseptic rub labels (and no manufacturers seek approval of their products under an NDA). Manufacturers have the option of exiting the market entirely or removing the antiseptic active ingredient in their product. FDA is aware of rubs that do not contain antiseptic ingredients that are intended for cleansing or moisturizing the skin when rinsing hands with soap and water is not practical.[3] A plausible action taken by manufacturers in the hand sanitizer and cleaner industry is to remove the antiseptic active ingredient in their products and market non-antimicrobial consumer rub products.

Tables 11 and 12 contain the estimated cost ranges of labeling changes and reformulation, respectively. The total cost of relabeling is estimated to range between $6,549,620 and $18,760,395, and the total reformulation cost is estimated to range between $9,442,677 and $28,328,030. The costs in this scenario are much larger than in the previously discussed scenario because many more products will be affected if the three ingredients that require testing are not demonstrated to be GRAS/E.

Table 11: Estimated Costs of Labeling Changes (Assuming None of the Ingredients are Determined to be GRAS/E), by Brand Type

Brand Type	Low	Medium	High
Branded	$4,615,965	$8,189,515	$13,763,125
Private	$1,933,655	$3,173,096	$4,997,270
Total	$6,549,620	$11,362,612	$18,760,395

Table 12: Estimated Reformulation Costs (Assuming None of the Ingredients is Determined to be GRAS/E)

Estimate	Percent of Products Reformulated		
	25	50	75
Estimated Cost of Reformulation per Product	$187,634	$187,634	$187,634

[3] For example, an online retailer sells disposable wet wipes that are intended to wipe hands after meals (Ref. 16).

Estimated Number of Reformulations	50	101	151
Estimated Total Reformulation Costs	$9,442,677	$18,885,354	$28,328,030

4. Summary of Total Costs

A summary of the total one-time costs and annualized costs over a 10-year period is shown in Table 13, by scenario. If benzalkonium chloride, alcohol, and isopropyl alcohol are demonstrated to be GRAS/E, the total one-time costs of relabeling and reformulation range from $0.34 million to $1.02 million. If none of them is demonstrated to be GRAS/E, the corresponding total one-time costs range from $15.99 million to $47.09 million. This value does not include testing costs, which we estimated to approximately equal an additional $8.7 million. We do not include testing costs to this rule's total costs because the health care antiseptics (80 FR 25166), which precedes this rule, proposes the same costs and is expected to be finalized prior to this rule. However, in the unlikely event that this rule is finalized before the healthcare antiseptics rule or if manufacturers conduct the testing for the three ingredients discussed in this rule, but do not conduct the testing for these ingredients as discussed in the health antiseptic proposed rule, these additional $8.7 million in testing costs would be attributed to this rule, resulting in total one-time costs ranging from $9.04 million to $55.79 million.

If we assume that all three ingredients will be demonstrated to be GRAS/E, the annualized cost over 10 years is estimated to range from $0.04 million and $0.12 per year at a 3 percent discount rate and from $0.05 million and $0.14 per year at a 7 percent discount rate. The corresponding annualized cost is estimated to range from $1.87 million and $5.52 million per year at a 3 percent discount rate and from $2.28 million and $6.70 million per year at a 7 percent discount rate, if we instead assume that none of the ingredients will be demonstrated to be GRAS/E.

Table 13: Estimated Total Costs (in millions), by Scenario			
	One-Time Costs	**Annualized Costs Over a 10-Year Period**	
Cost		3% Discount Rate	7% Discount Rate

Category	Low	Med.	High	Low	Med.	High	Low	Med.	High
Scenario 1: Assuming All Ingredients are Determined to be GRAS/E									
Relabeling Costs	$0.11	$0.19	$0.32	$0.01	$0.02	$0.04	$0.02	$0.03	$0.05
Reformulation Costs	$0.23	$0.46	$0.70	$0.03	$0.05	$0.08	$0.03	$0.07	$0.10
Total Costs	$0.34	$0.66	$1.02	$0.04	$0.08	$0.12	$0.05	$0.09	$0.14
Scenario 2: Assuming None of the Ingredients is Determined to be GRAS/E									
Relabeling Costs	$6.55	$11.36	$18.76	$0.77	$1.33	$2.20	$0.93	$1.62	$2.67
Reformulation Costs	$9.44	$18.89	$28.33	$1.11	$2.21	$3.32	$1.34	$2.69	$4.03
Total Costs	$15.99	$30.25	$47.09	$1.87	$3.55	$5.52	$2.28	$4.31	$6.70
Range of Total Costs Under Both Scenarios									
Relabeling Costs	$0.11	$9.44	$18.76	$0.01	$1.11	$2.20	$0.02	$1.34	$2.67
Reformulation Costs	$0.23	$14.28	$28.33	$0.03	$1.67	$3.32	$0.03	$2.03	$4.03
Total Costs	$0.34	$23.72	$47.09	$0.04	$2.78	$5.52	$0.05	$3.38	$6.70

G. Analysis of Regulatory Alternatives

We have estimated the costs of the proposed rule by assuming a 12-month compliance period. We now examine how the costs of the proposed rule would change if the compliance period were shortened or lengthened by 6 months. These otherwise identical rules would change total costs through changes in relabeling costs because a shorter (or longer) compliance period would allow for fewer (or more) coordinated labeling changes. While the RTI Relabeling Cost Model assumes that 3-4% of changes can be coordinated with planned changes if the compliance period is 12 months, the assumed percentage falls to 0% and increases to 9-12% if the compliance period is instead 6 months and 18 months, respectively. In Table 14, we show the estimated costs for each regulatory alternative by scenario. In both scenarios, reducing (or increasing) the compliance period would cause total costs to increase (or decrease). For example, if benzalkonium chloride, alcohol, and isopropyl alcohol are demonstrated to be GRAS/E, requiring a 6-month compliance period would increase one-time total costs by between $50,000

and $300,000 relative to the costs of the proposed rule; if, instead, an 18-month compliance period were required, one-time total costs would decrease by between $40,000 and $110,000.

Table 14: Estimated Total Costs of Regulatory Alternatives (in millions), by Scenario									
Cost Category	**One-Time Costs**			**Annualized Costs Over a 10-Year Period**					
				3% Discount Rate			7% Discount Rate		
	Low	Med.	High	Low	Med.	High	Low	Med.	High
Scenario 1, Alternative 1: Assuming All Ingredients are Determined to be GRAS/E									
Relabeling Costs (6 Months)	$0.16	$0.31	$0.62	$0.02	$0.04	$0.07	$0.02	$0.04	$0.09
Reformulation Costs	$0.23	$0.46	$0.70	$0.03	$0.05	$0.08	$0.03	$0.07	$0.10
Total Costs	$0.39	$0.77	$1.32	$0.05	$0.09	$0.15	$0.06	$0.11	$0.19
Change from 12 Months	$0.05	$0.11	$0.30	$0.01	$0.01	$0.04	$0.01	$0.02	$0.04
Scenario 1, Alternative 2: Assuming All Ingredients are Determined to be GRAS/E									
Relabeling Costs (18 Months)	$0.07	$0.13	$0.21	$0.01	$0.02	$0.03	$0.01	$0.02	$0.03
Reformulation Costs	$0.23	$0.46	$0.70	$0.03	$0.05	$0.08	$0.03	$0.07	$0.10
Total Costs	$0.31	$0.59	$0.91	$0.04	$0.07	$0.11	$0.04	$0.08	$0.13
Change from 12 Months	-$0.04	-$0.07	-$0.11	$0.00	-$0.01	-$0.01	-$0.01	-$0.01	-$0.02
Scenario 2, Alternative 1: Assuming None of the Ingredients is Determined to be GRAS/E									
Relabeling Costs (6 Months)	$9.19	$17.99	$36.41	$1.08	$2.11	$4.27	$1.31	$2.56	$5.18
Reformulation Costs	$9.44	$18.89	$28.33	$1.11	$2.21	$3.32	$1.34	$2.69	$4.03
Total Costs	$18.63	$36.87	$64.74	$2.18	$4.32	$7.59	$2.65	$5.25	$9.22
Change from 12 Months	$2.64	$6.63	$17.65	$0.31	$0.78	$2.07	$0.38	$0.94	$2.51
Scenario 2, Alternative 2: Assuming None of the Ingredients is Determined to be GRAS/E									
Relabeling Costs (18 Months)	$4.30	$7.52	$12.48	$0.50	$0.88	$1.46	$0.61	$1.07	$1.78
Reformulation Costs	$9.44	$18.89	$28.33	$1.11	$2.21	$3.32	$1.34	$2.69	$4.03
Total Costs	$13.74	$26.40	$40.81	$1.61	$3.10	$4.78	$1.96	$3.76	$5.81
Change from 12 Months	-$2.25	-$3.85	-$6.28	-$0.26	-$0.45	-$0.74	-$0.32	-$0.55	-$0.89

H. Cost-Effectiveness

We assess the cost-effectiveness of the proposed rule and regulatory alternatives by examining the annualized costs over a 10-year period per pound of reduced exposure to potentially harmful nonmonograph ingredients at 3 percent and 7 percent discount rates. If benzalkonium chloride, alcohol, and isopropyl alcohol are demonstrated to be GRAS/E, the reduction in exposure to nonmonograph active ingredients will be small. As shown in Table 15, if the proposed rule is finalized, we estimate that reducing exposure to nonmonograph ingredients in scenario 1 will come at a cost of between $3,133 and $4,013 at a 3 percent discount rate. The range is nearly identical if a 7 percent discount rate is used. The estimated cost of reducing a pound of nonmonograph ingredients is smaller if none of the ingredients is demonstrated to be GRAS/E (scenario 2) because there will be a far greater reduction in exposure to nonmonograph ingredients relative to scenario 1.

It is important to note that the cost-effectiveness of the proposed rule and regulatory alternatives ultimately depends on the currently unknown underlying health risks associated with exposure to benzalkonium chloride, alcohol, and isopropyl alcohol in consumer antiseptic rub products. For example, suppose tests indicate that exposure to ingredient X in consumer antiseptic rub products is hazardous to health. In such a case, FDA's non-GRAS determination would lead to decreased exposure to ingredient X through the use of rubs and the corresponding health benefits would be realized. While the dollars per pound of reduced exposure figures vary substantially by scenario, the cost-effectiveness of the rule and regulatory alternatives are a function of test outcomes to determine the safety and effectiveness of benzalkonium chloride, alcohol, and isopropyl alcohol.

Table 15: Cost-Effectiveness, by Compliance Period (in Dollars per Pound of Reduced Exposure)

Compliance Period	3% Discount Rate			7% Discount Rate		
	Low	Medium	High	Low	Medium	High
	Scenario 1: Assuming All Ingredients are Determined to be GRAS/E					
6 Months	$3,544	$4,249	$5,204	$3,544	$4,249	$5,204
12 Months (Proposed Rule)	$3,133	$3,626	$4,013	$3,133	$3,626	$4,013
18 Months	$2,783	$3,264	$3,590	$2,783	$3,264	$3,590
	Scenario 2: Assuming None of the Ingredients is Determined to be GRAS/E					
6 Months	$1.42	$0.92	$0.96	$1.42	$0.92	$0.96

12 Months (Proposed Rule)	$1.22	$0.75	$0.70	$1.22	$0.75	$0.70
18 Months	$1.05	$0.66	$0.61	$1.05	$0.66	$0.61

III. Initial Regulatory Flexibility Analysis

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

A. Description and Number of Affected Small Entities

The proposed rule would affect firms in the toilet preparation manufacturing industry (NAICS code 325620). According to the 2007 Economic Census of Manufacturers, there are 854 manufacturers in this industry. The Economic Census does not provide entity counts for relabelers, repackers, and distributors. However, manufacturers of consumer antiseptic rub products are expected to incur the vast majority of product reformulation and relabeling costs. Table 16 shows the number of establishments and the average value of their shipments by total number of employees. According to the Small Business Administration, a business entity is considered small if it employs 500 or fewer individuals. Based on this size standard, about 97 percent of toilet preparation manufacturers are small entities, and the average value of their shipments range from $1,488,815 to $217,831,979. For small entities, the average value of shipments is $24,823,395 per small entity.

Table 16: Toilet Preparation Manufacturers by Total Number of Employees

Total Number of Employees	Number of Establishments	Average Value of Shipments (in millions)
0 to 4	315	$1.49

5 to 9	122	$6.50
10 to 19	90	$9.54
20 to 49	115	$10.75
50 to 99	82	$32.87
100 to 249	63	$88.43
250 to 499	41	$217.83
500 to 999	22	$952.40
1,000 to 2,499	4	$1,890.28
2,500 or more	0	—

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

Using the FDA Drug Product Registration Database, we estimate that about 69 percent of consumer antiseptic rub products are manufactured by small entities. We assume that the costs associated with the proposed rule that are incurred by small entities are proportional to the size of the small-entity product market. Table 17 shows the estimated total costs for small businesses by scenario. If benzalkonium chloride, alcohol, and isopropyl alcohol are demonstrated to be GRAS/E, one-time total costs for small businesses is estimated to range from $0.24 million and $0.70 million. This amounts to between $280 and $850 per small entity, which is 0.001-0.003 percent of the average value of shipments for a small business. If all of the three ingredients are not demonstrated to be GRAS/E, then costs are estimated to be between $13,300 and $39,300, or 0.05-0.16 percent of the average value of shipments for a small business.

Table 17: Estimated Total Costs for Small Businesses (in millions), by Scenario

Cost Category	**One-Time Costs**			**Annualized Costs Over a 10-Year Period**					
				3% Discount Rate			7% Discount Rate		
	Low	Med.	High	Low	Med.	High	Low	Med.	High
Scenario 1: Assuming All Ingredients are Determined to be GRAS/E									
Relabeling Costs	$0.08	$0.13	$0.22	$0.01	$0.02	$0.03	$0.01	$0.02	$0.03
Reformulation Costs	$0.16	$0.32	$0.48	$0.02	$0.04	$0.06	$0.02	$0.05	$0.07
Total Costs	$0.24	$0.45	$0.70	$0.03	$0.05	$0.08	$0.03	$0.06	$0.10
Scenario 2: Assuming None of the Ingredients is Determined to be GRAS/E									
Relabeling	$4.52	$7.84	$12.94	$0.53	$0.92	$1.52	$0.64	$1.12	$1.84

Costs									
Reformulation Costs	$6.52	$13.03	$19.55	$0.76	$1.53	$2.29	$0.93	$1.86	$2.78
Total Costs	$11.03	$20.87	$32.49	$1.29	$2.45	$3.81	$1.57	$2.97	$4.63

C. Alternatives to Minimize the Burden on Small Entities

1. Exemption for Small Businesses

If small businesses receive an exemption from the proposed rule, then 97 percent of the consumer antiseptic rub product industry will receive regulatory relief. The size of the regulatory relief depends on whether benzalkonium chloride, alcohol, and isopropyl alcohol are demonstrated to be GRAS/E. The burden on the industry would fall by between $280 and $850 per small business in scenario 1 and by between $13,300 and $39,300 in scenario 2. FDA believes that exempting small business would not be desirable. Since small businesses make up a substantial share of the consumer antiseptic rub product market, an exemption for small business would forgo most of potential benefits generated by the proposed rule.

2. Longer Compliance Period for Small Businesses

Extending the compliance period for small businesses is another alternative for regulatory relief. We examined the change in costs associated with lengthening the compliance period for small businesses to 18 months. It is important to note that approximately 69 percent of consumer antiseptic rub products are manufactured by small businesses, so extending the compliance period for small businesses would leave many products unchanged for 6 additional months after the proposed effective date. Also, extending the effective date for products containing antiseptic active ingredients not found to be GRAS/E would lead to continued exposure and delay the potential benefits of this rule.

As shown in Table 18, this would lead to a reduction in the costs borne by small businesses relative to the compliance period of 12 months in the proposed rule (Table 18). If

benzalkonium chloride, alcohol, and isopropyl alcohol are demonstrated to be GRAS/E, then the estimated one-time cost per small business ranges between $250 and $760. However, if they are not demonstrated to be GRAS/E, the corresponding estimated cost per small business ranges between $11,500 and $34,000.

Table 18: Estimated Total Costs for Small Businesses Under 18-Month Compliance Period (in millions), by Scenario

Cost Category	One-Time Costs			Annualized Costs Over a 10-Year Period					
				3% Discount Rate			7% Discount Rate		
	Low	Med.	High	Low	Med.	High	Low	Med.	High
	Scenario 1: Assuming All Ingredients are Determined to be GRAS/E								
Relabeling Costs (18 Months)	$0.05	$0.09	$0.15	$0.01	$0.01	$0.02	$0.01	$0.01	$0.02
Reformulation Costs	$0.16	$0.32	$0.48	$0.02	$0.04	$0.06	$0.02	$0.05	$0.07
Total Costs	$0.21	$0.41	$0.63	$0.02	$0.05	$0.07	$0.03	$0.06	$0.09
	Scenario 2: Assuming None of the Ingredients is Determined to be GRAS/E								
Relabeling Costs (18 Months)	$2.97	$5.19	$8.61	$0.35	$0.61	$1.01	$0.42	$0.74	$1.23
Reformulation Costs	$6.52	$13.03	$19.55	$0.76	$1.53	$2.29	$0.93	$1.86	$2.78
Total Costs	$9.48	$18.22	$28.16	$1.11	$2.14	$3.30	$1.35	$2.59	$4.01

IV. Appendix Table

Economic Data: Costs and Benefits Statement

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year				2014	7%	10 years	
					2014	3%	10 years	
	Annualized Quantified pounds/year	40,176,905	110	67,272,847				Reduction in antiseptic active ingredient exposure. Assumes that health risk falls with reduced exposure. Range of estimates captures uncertainty.
		40,176,905	110	67,272,847				
	Qualitative							
Costs	Annualized Monetized $millions/year	$3.38	$0.05	$6.70	2014	7%	10 years	Annualized costs of reformulation and relabeling products. Range of estimates captures uncertainty.
		$2.78	$0.04	$5.52	2014	3%	10 years	
	Annualized Quantified				2014	7%	10 years	
					2014	3%	10 years	
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year				2014	7%	10 years	Annual sales of products with active ingredients affected by this proposed rule are currently approx. $200 million. There will be changes
					2014	3%	10 years	
		From:			To:			
	Other Annualized Monetized $millions/year				2014	7%	10 years	
					2014	3%	10 years	
		From:			To:			

				in sales patterns to the degree that these products have their GRAS/E status revoked.
Effects	State, Local or Tribal Government: Not applicable Small Business: The estimated costs associated with potentially affected small entities range between 0.001 and 0.16 percent of their average value of shipments. Wages: Not applicable Growth: Not applicable			

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