



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. FDA-2016-N-0124 (formerly part of Docket No. FDA-1975-N-0012)]

RIN 0910-AF69

Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or Agency) is issuing this proposed rule to amend the 1994 tentative final monograph or proposed rule (the 1994 TFM) for over-the-counter (OTC) antiseptic drug products. In this proposed rule, we are proposing to establish conditions under which OTC consumer antiseptic products intended for use without water (referred to throughout as consumer antiseptic rubs or consumer rubs) are generally recognized as safe and generally recognized as effective (GRAS/GRAE). In the 1994 TFM, certain antiseptic active ingredients were proposed as being GRAS for antiseptic rub use by consumers based on safety data evaluated by FDA as part of its ongoing review of OTC antiseptic drug products. However, in light of more recent scientific developments and changes in the use patterns of these products, we are now proposing that additional safety data are necessary to support the safety of antiseptic active ingredients for this use. We also are proposing that all consumer antiseptic rub active ingredients have in vitro data characterizing the ingredient's

antimicrobial properties and in vivo clinical simulation studies showing that specified log reductions in the amount of certain bacteria are achieved using the ingredient.

DATES: Submit electronic or written comments by [INSERT DATE 180 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. See section IX of this document for the proposed effective date of a final rule based on this proposed rule.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions"). We note however, that the OTC drug monograph process is a public process; and, the Agency intends to consider only non-confidential material that is submitted to the docket for this

rulemaking or that is otherwise publicly available in evaluating if a relevant ingredient is GRAS/GRAE.

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-N-0124 for "Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its

consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Anita Kumar, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5445, Silver Spring, MD 20993, 301-796-1032.

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I. Executive Summary

A. Purpose of the Regulatory Action

FDA is proposing to amend the 1994 TFM for OTC antiseptic drug products that published in the Federal Register of June 17, 1994 (59 FR 31402). The 1994 TFM is part of FDA's ongoing rulemaking to evaluate the safety and effectiveness of OTC drug products marketed in the United States on or before May 1972 (OTC Drug Review).

FDA is proposing to establish new conditions under which active ingredients used in OTC consumer antiseptic products intended to be used without water are GRAS/GRAE based on FDA's reevaluation of the safety and effectiveness data requirements proposed in the 1994 TFM

for what were then referred to as antiseptic hand washes (which included the products we refer to in this document as consumer antiseptic rubs or consumer rubs). We are conducting this reevaluation based on the comments received, input from subsequent public meetings, and our independent evaluation of other relevant scientific information we have identified and placed in the docket. This proposed rule applies to active ingredients used in consumer antiseptic rub products that are sometimes referred to as rubs, leave-on products, or hand "sanitizers," as well as to consumer antiseptic wipes. These products are intended to be used when soap and water are not available, and are left on and not rinsed off with water. We will refer to them here as consumer antiseptic rubs or consumer rubs. In separate rulemakings (78 FR 76444, December 17, 2013; 80 FR 25166, May 1, 2015), we proposed conditions under which OTC consumer antiseptic washes and OTC antiseptics intended for use by health care professionals in a hospital setting or other health care situation outside the hospital are GRAS/GRAE. Those antiseptic products are not addressed in this proposed rule.

B. Summary of the Major Provisions of the Regulatory Action in Question

We are proposing that additional safety and effectiveness data are necessary to support a GRAS/GRAE determination for OTC antiseptic rub active ingredients intended for use by consumers. The effectiveness data, the safety data, and the effect on the previously proposed classification of active ingredients are described briefly in this summary. Because no ingredients currently meet the criteria for a GRAS/GRAE determination in this proposed rule, this rulemaking does not specifically address requirements for anticipated final formulation testing (i.e., testing the mixture of both active and inactive ingredients proposed for marketing) or labeling. Final formulation testing could potentially involve both efficacy testing and safety testing to determine absorption. It is anticipated that if a final rule includes any GRAS/GRAE

ingredients, labeling will be addressed as part of the final rule and may include elements related to application volume and safety labeling for children, including a warning to keep out of reach of children. We anticipate that specific effectiveness claims in labeling will reflect the testing performed in support of these claims. Effectiveness testing using surrogate endpoints as described in this proposed rule is designed to support antibacterial claims.

C. Effectiveness

A determination that a drug product containing a particular active ingredient would be GRAE for a particular intended use requires consideration of the benefit-to-risk ratio for the drug under the specified conditions of use. New information on potential risks posed by the use of certain consumer antiseptic products, as well as input from the Nonprescription Drugs Advisory Committee (NDAC) that met in March 2005 (the March 2005 NDAC) and October 2005 (the October 2005 NDAC), has prompted us to reevaluate the data needed for classifying active ingredients used in consumer rubs as GRAE. The reevaluation of effectiveness will help to ensure that the level of effectiveness achieved is adequate to offset newly identified safety concerns (see new information described in the safety section of this executive summary). We continue to propose the use of surrogate endpoints (bacterial log reductions) as a demonstration of effectiveness for consumer antiseptic rubs combined with in vitro testing to characterize the antimicrobial activity of the ingredient. However, the log reductions required for the demonstration of effectiveness for consumer rubs have been revised based on the recommendations of the March 2005 and October 2005 NDAC meetings, comments received after the 1994 TFM, and other information we reviewed.

We have evaluated the available literature, the data, and other information that were submitted to the rulemaking on the effectiveness of consumer rub active ingredients, as well as

the recommendations from the public meetings held by the Agency on antiseptics. We propose that the record contain additional log reduction data to demonstrate the effectiveness of consumer rub active ingredients. We are also asking for data and information to be submitted about the impact of product use factors (such as volume of product per application) on efficacy to help inform labeling and requirements for final formulation testing.

D. Safety

Several important scientific developments that affect the safety evaluation of consumer rub active ingredients have occurred since FDA's 1994 evaluation of the safety of these 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 rub ingredients, systemic exposure is higher than previously thought (Refs. 1 through 5), and new information is available about the potential risks from systemic absorption and long-term exposure. These data are particularly important given the increased use of consumer antiseptic rubs since the publication of the 1994 TFM. New safety information also suggests that widespread antiseptic use could have an impact on the development of bacterial resistance. Currently, the significance of this new information is not known and we are unaware of any information that would lead us to conclude that any consumer antiseptic rub active ingredient is unsafe (other than those that we proposed to be Category II in the 1994 TFM). 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.

The previously proposed GRAS determinations were based on safety principles that have since evolved significantly because of advances in technology, development of new test

methods, and experience with performing test methods. The standard battery of tests that were used to determine the safety of drugs has changed over time to incorporate improvements in safety testing. To ensure that consumer antiseptic rub active ingredients are GRAS, data that meet current safety standards are needed.

Based on these developments, we are now proposing that additional safety data are needed for each consumer antiseptic rub active ingredient to support a GRAS classification. The data described in this proposed rule are the minimum data necessary to establish the safety of antiseptic active ingredients used in consumer antiseptic rub products in light of the new safety information. Consumers may use antiseptic rubs on a daily, long-term (i.e., chronic) basis. The data we propose, which are needed to demonstrate safety for all consumer antiseptic rub active ingredients, fall into two broad categories: (1) Human safety studies and (2) nonclinical safety studies. For one of the consumer antiseptic rub active ingredients (benzalkonium chloride), data to evaluate the development of antimicrobial resistance also is required to demonstrate its safety.

E. Active Ingredients

Three active ingredients are being evaluated for use as a consumer antiseptic rub in this proposed rule: Alcohol (ethanol or ethyl alcohol), isopropyl alcohol, and benzalkonium chloride (sometimes referred to as ADBAC). As part of this proposed rule, FDA evaluated new data submitted after publication of the 1994 TFM for each of these three ingredients.

In the 1994 TFM (59 FR 31402 at 31435), alcohol (60 to 95 percent) was proposed to be classified as GRAS/GRAE (59 FR 31402 at 31435 to 31436) for use as what was then called an antiseptic hand wash (a use which included both products intended to be rinsed off (washes) and those intended to be left on (rubs)). Isopropyl alcohol (70 to 91.3 percent) was proposed to be categorized in Category III in the 1994 TFM because of a lack of adequate effectiveness data for

use as an antiseptic hand wash (59 FR 31402 at 31435 to 31436). However, we now propose that both alcohol and isopropyl alcohol need additional safety and effectiveness data to support a classification of GRAS/GRAE for consumer antiseptic rub use. Our detailed evaluation of the effectiveness and safety of the active ingredients for which data were submitted can be found in sections VII.A and VIII.D.

In the 1994 TFM, FDA categorized benzalkonium chloride in Category III because of a lack of adequate safety and effectiveness data for its use as an antiseptic hand wash (59 FR 31402 at 31435). We have evaluated safety data received in response to the 1994 TFM and the consumer antiseptic wash proposed rule published in the Federal Register of December 17, 2013 (78 FR 76444) (2013 Consumer Wash Proposed Rule (PR)) (see section VIII.D). In this proposed rule, we propose that benzalkonium chloride needs additional safety and effectiveness data to support a classification of GRAS/GRAE for consumer antiseptic rub use.

If we do not receive sufficient data to support monograph conditions for consumer antiseptic rub products containing these active ingredients, these active ingredients may not be included in the future OTC consumer antiseptic rub final monograph. Any consumer antiseptic rub product containing the active ingredients being considered under this rulemaking that are not included in a future final monograph could seek approval to market by submitting new drug applications (NDAs) under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355). After a final monograph is established, NDA deviations might be submitted for these products in accordance with 21 CFR 330.11, limiting the scope of review necessary to obtain approval.

F. Costs and Benefits

The impact of the proposed rule on the OTC consumer antiseptic rub product industry will depend on the outcome of tests to determine whether three antiseptic ingredients--alcohol, isopropyl alcohol, and benzalkonium chloride--are GRAS/GRAE. It is possible that none, one, two, or all three of the ingredients will be determined to be GRAS/GRAE. We consider two extreme scenarios to capture the entire range of total costs: (1) All three ingredients are deemed to be GRAS/GRAE or (2) none of the ingredients is deemed to be GRAS/GRAE.

The range of estimated costs is wide because the number of products that would need to be reformulated and relabeled depends on whether or not an antiseptic ingredient is deemed to be GRAS/GRAE. A small number of products contain active ingredients which FDA has determined are not eligible for use in consumer antiseptic rubs and these products will need to be reformulated and relabeled (scenario 1). However, in scenario 2 (and intermediate scenarios), the resulting costs are higher because a greater number of products will need to be reformulated and relabeled as a result of tests failing to show GRAS/GRAE status.

The total upfront costs of the proposed regulation--which include the expenditures to reformulate and relabel products that contain nonmonograph ingredients--are estimated to range from \$0.34 million to \$1.02 million for scenario 1 and from \$15.99 million to \$47.09 million for scenario 2. 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 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. We assume that health risk falls with reduced exposure to potentially unsafe or ineffective antiseptic ingredients in consumer antiseptic rubs. We estimate that the proposed rule will reduce exposure to potentially unsafe or ineffective antiseptic ingredients in consumer antiseptic rubs by between 110 and 67,272,847 pounds.¹

Summary of Costs and Benefits of the Proposed Rule	Total Reduction in Antiseptic Ingredient Exposure (in pounds)	Total Costs Annualized Over 10 Years (in millions)	Total One-Time Costs (in millions)
Total.....	110 and 67,272,847	\$0.04 to \$5.52 (3%) \$0.05 to \$6.70 (7%)	\$0.34 and \$47.09

II. Introduction

In the following sections, we provide a brief description of terminology used in the OTC Drug Review regulations and an overview of OTC topical antiseptic drug products, and then describe in more detail the OTC consumer antiseptic rubs that are the subject of this proposed rule.

A. Terminology Used in the OTC Drug Review Regulations

1. Proposed, Tentative Final, and Final Monographs

To conform to terminology used in the OTC Drug Review regulations (§ 330.10 (21 CFR 330.10)), the September 1974 advance notice of proposed rulemaking (39 FR 33103, September 13, 1974) (1974 ANPR) was designated as a "proposed monograph." Similarly, the notices of proposed rulemaking, which were published in the Federal Register of January 6, 1978 (43 FR 1210) (the 1978 TFM), and in the Federal Register of June 17, 1994 (59 FR 31402) (the 1994

¹ As was the case with estimated costs, there is a great disparity in the estimated reductions in exposure to antiseptic ingredients. The lower bound (110 pounds) represents the estimated reduction in exposure to ingredients which FDA has determined are not GRAS/GRAE for use in consumer antiseptic rubs and few products contain such GRAS/GRAE ingredients.

TFM), were each designated as a "tentative final monograph" (see table 1 in section III.A). The present proposed rule, which is a proposal to amend the 1994 TFM with respect to consumer antiseptic rub drug products, is also designated as a "tentative final monograph."

2. Category I, II, and III Classifications

The OTC drug procedural regulations in § 330.10 use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required). Section 330.10 provides that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph (i.e., a final rule or regulation). Therefore, this proposed rule (the tentative final monograph stage) retains the concepts of Categories I, II, and III.

At the final monograph stage, FDA does not use the terms "Category I," "Category II," and "Category III." In place of Category I, the term "monograph conditions" is used; in place of Categories II and III, the term "nonmonograph conditions" is used.

B. Topical Antiseptics

The OTC topical antimicrobial rulemaking has had a broad scope, encompassing drug products that may contain the same active ingredients, but that are labeled and marketed for different intended uses. In 1974, the Agency published an ANPR for topical antimicrobial products that encompassed products for both health care and consumer use. The 1974 ANPR covered seven different intended uses for these products: (1) Antimicrobial soap; (2) health care personnel hand wash; (3) patient preoperative skin preparation; (4) skin antiseptic; (5) skin

wound cleanser; (6) skin wound protectant; and (7) surgical hand scrub (39 FR 33103 at 33140). FDA subsequently identified skin antiseptics, skin wound cleansers, and skin wound protectants as antiseptics used primarily by consumers for first aid use and referred to them collectively as "first aid antiseptics." We published a separate TFM covering the first aid antiseptics in the Federal Register of July 22, 1991 (56 FR 33644) (1991 First Aid TFM). Thus, first aid antiseptics are not discussed further in this document.

The four remaining categories of topical antimicrobials were addressed in the 1994 TFM. The 1994 TFM covered: (1) Antiseptic hand wash (i.e., consumer hand wash); (2) health care personnel hand wash; (3) patient preoperative skin preparation; and (4) surgical hand scrub (59 FR 31402 at 31442). In the 1994 TFM, FDA also identified a new category of antiseptics for use by the food industry and requested relevant data and information (59 FR 31402 at 31440). Antiseptics for use by the food industry are not discussed further in this document.

In the 1974 ANPR, we distinguished antimicrobial soaps used by consumers from professional use antiseptics, such as health care personnel hand washes. (See section II.C about the term "antimicrobial soaps.") In contrast, in the 1994 TFM, we proposed that both antiseptic hand washes (i.e., consumer antiseptic washes) and health care personnel hand washes should have the same effectiveness testing and performance criteria. In response to the 1994 TFM, we received submissions from the public arguing that consumer products serve a different purpose and should continue to be distinct from health care antiseptics. We agreed, and in the 2013 Consumer Wash PR and in the health care antiseptic proposed rule published in the Federal Register of May 1, 2015 (80 FR 25166) (2015 Health Care Antiseptic PR), our evaluation of OTC antiseptic drug products has been further subdivided into consumer antiseptics and health care antiseptics, which are used by health care professionals in a hospital setting or other health

care situations outside the hospital. We believe that these categories are distinct based on the proposed-use setting, target population, and the fact that each setting presents a different level of risk for infection. For example, in health care settings, the patient population is generally more susceptible to infection than the general U.S. consumer population (i.e., the population who use consumer antiseptic rubs or washes). Furthermore, the purpose of use is generally different; health care antiseptics are primarily used to protect the patient (rather than just the user), whereas consumer antiseptics are generally applied to protect the user. In the health care setting, the potential for spread of infection and the potential for serious outcomes of infection may be relatively higher than in the U.S. consumer setting. Therefore, the safety and effectiveness should be evaluated separately for each intended use to support a GRAS/GRAE determination.

As we did in the 2013 Consumer Wash PR, we refer to the group of products covered by this proposed rule as "consumer antiseptics." Consumer antiseptic drug products addressed by this proposal include consumer antiseptic hand rubs (commonly called hand sanitizers) and antiseptic wipes. These products may be used by consumers for personal use on a frequent basis, even multiple times per day. These products do not include personal care products intended to be used with water, such as antibacterial soaps, hand washes, and body washes.

C. This Proposed Rule Covers Only Consumer Antiseptic Rubs

In this proposed rule, FDA proposes the establishment of a monograph for OTC consumer antiseptics that are intended for use as an antiseptic rub, but that are not identified as "first aid antiseptics" in the 1991 First Aid TFM. When the 1994 TFM was published, the term for daily consumer use antiseptics was changed to "antiseptic hand wash." In response to this change, we received comments that the term "antiseptic hand wash" did not include all of the consumer products on the market, such as hand rubs and body washes. Therefore, in this

proposed rule, we use the term "consumer antiseptic," which is a broad term and meant to include all of the types of antiseptic products used on a frequent or daily basis by consumers. However, this proposed rule covers only consumer antiseptic rubs and does not include consumer antiseptic hand washes or body washes.

The 1994 TFM did not distinguish between products that we are now calling "antiseptic washes" and products we are now calling "antiseptic rubs." Washes are rinsed off with water, and include consumer hand washes and body washes, and health care personnel hand washes and surgical hand scrubs. Rubs are sometimes referred to as "leave-on products" and are not rinsed off after use. They are intended to be used when soap and water are not available. Consumer antiseptic rubs include "hand sanitizers" and wipes. The 1994 TFM also did not distinguish between consumer antiseptic washes and rubs, and health care hand washes and rubs. This proposed rule covers only consumer antiseptic rubs. Completion of the monograph for consumer antiseptic rubs and certain other monographs for the active ingredient triclosan are subject to a Consent Decree entered by the U.S. District Court for the Southern District of New York on November 21, 2013, in Natural Resources Defense Council, Inc. v. United States Food and Drug Administration, et al., 10 Civ. 5690 (S.D.N.Y.).

D. Comment Period

Because of the complexity of this proposed rule, we are providing a comment period of 180 days. Moreover, new data or information may be submitted to the docket via <http://www.regulations.gov> (see ADDRESSES) within 12 months of publication, and comments on any new data or information may then be submitted to the docket for an additional 60 days (see § 330.10(a)(7)(iii) and (iv)). In addition, FDA will also consider requests to defer further rulemaking with respect to a specific active ingredient for use as a consumer antiseptic rub to

allow the submission of new safety or effectiveness data to the record if these requests are submitted to the docket within the initial 180-day comment period. FDA will review all data and information submitted to the record in conjunction with all timely and complete requests to defer rulemaking. In assessing whether to defer further rulemaking for a particular active ingredient to allow for additional time for studies to generate new data and information, FDA will consider the data already in the docket, along with any information that is provided in any requests. FDA will determine whether the sum of the data, if submitted in a timely fashion, is likely to be adequate to provide all the data that are necessary to make a GRAS/GRAE determination.

We note that the OTC Drug Review is a public process and any data submitted is public. There is no requirement or expectation that more than one set of data will be submitted to the docket for a particular active ingredient, and it does not matter who submits the data. In addition, data and other information for a single active ingredient may be submitted by any interested party and not all data for an ingredient must be submitted by a single party.

III. Background

In this section, we describe the significant rulemakings and public meetings relevant to this proposed rule, and how we are responding to comments received in response to the 1994 TFM.

A. Significant Rulemakings Relevant to This Proposed Rule

A summary of the significant Federal Register publications relevant to this proposed rule is provided in table 1. Other publications relevant to this proposed rule are available at <http://www.regulations.gov> in FDA Docket No. 1975-N-0012.

Table 1.--Significant Rulemaking Publications Related To Consumer Antiseptic Drug Products¹

Federal Register Notice	Information in Notice
1974 ANPR (September 13, 1974, 39 FR 33103)	We published an ANPR to establish a monograph for OTC topical antimicrobial drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Antimicrobial I Drug Products (Antimicrobial I Panel or Panel),

	which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class.
1978 Antimicrobial TFM (January 6, 1978, 43 FR 1210)	We published our tentative conclusions and proposed effectiveness testing for the drug product categories evaluated by the Panel. The 1978 TFM reflects our evaluation of the recommendations of the Panel and comments and data submitted in response to the Panel's recommendations.
1982 Alcohol ANPR (May 21, 1982, 47 FR 22324)	We published an ANPR to establish a monograph for alcohol drug products for topical antimicrobial use, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class.
1991 First Aid TFM (July 22, 1991, 56 FR 33644)	We amended the 1978 TFM to establish a separate monograph for OTC first aid antiseptic products. In the 1991 First Aid TFM, we proposed that first aid antiseptic drug products be indicated for the prevention of skin infections in minor cuts, scrapes, and burns.
1994 Health Care Antiseptic TFM (June 17, 1994, 59 FR 31402)	We amended the 1978 TFM to establish a separate monograph for the group of products that were referred to as OTC topical health care antiseptic drug products. These antiseptics are generally intended for use by health care professionals. In that proposed rule, we also recognized the need for antibacterial personal cleansing products for consumers to help prevent cross-contamination from one person to another and proposed a new antiseptic category for consumer use: Antiseptic hand wash.
2013 Consumer Antiseptic Wash TFM (December 17, 2013, 78 FR 76444)	We issued a proposed rule to amend the 1994 TFM and to establish data standards for determining whether OTC consumer antiseptic washes are GRAS/GRAE. In that proposed rule, we proposed that additional safety and effectiveness data are necessary to support the safety and effectiveness of consumer antiseptic wash active ingredients.
2015 Health Care Antiseptics TFM (May 1, 2015, 80 FR 25166)	We issued a proposed rule to amend the 1994 TFM and to establish data standards for determining whether OTC health care antiseptics are GRAS/GRAE. In that proposed rule, we proposed that additional safety and effectiveness data are necessary to support the safety and effectiveness of health care antiseptic active ingredients.

¹The publications listed in table 1 can be found at the FDA's "Status of OTC Rulemakings" Web site available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm070821.htm>. The publications dated after 1993 can also be found in the Federal Register at <https://www.federalregister.gov>.

B. Public Meetings Relevant to This Proposed Rule

In addition to the Federal Register publications listed in table 1, there have been four meetings of the NDAC and one public feedback meeting that are relevant to the discussion of consumer antiseptic rub safety and effectiveness. These meetings are summarized in table 2.

Table 2.--Relevant Public Meetings

Date and Type of Meeting	Topic of Discussion
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January 1997 NDAC Meeting (Joint meeting with the Anti-Infective Drugs Advisory Committee) (January 6, 1997, 62 FR 764)	Antiseptic and antibiotic resistance in relation to an industry proposal for consumer and health care antiseptic effectiveness testing (Health Care Continuum Model) (Refs. 6, 7)
March 2005 NDAC Meeting (February 18, 2005, 70 FR 8376)	The use of surrogate endpoints and study design issues for the in vivo testing of health care antiseptics (Ref. 8)
October 2005 NDAC Meeting (September 15, 2005, 70 FR 54560)	Benefits and risks of consumer antiseptics. NDAC expressed concern about the pervasive use of consumer antiseptic washes where there are potential risks and no demonstrable benefit. To demonstrate a clinical benefit, NDAC recommended clinical outcome studies to show that antiseptic washes are superior to nonantibacterial soap and water (Ref. 9)
November 2008 Public Feedback Meeting	Demonstration of the effectiveness of consumer antiseptics (Ref. 10)
September 2014 NDAC Meeting (July 29, 2014, 79 FR 44042)	Safety testing framework for health care antiseptic active ingredients (Ref. 11)

C. Comments Received by FDA

In response to the 1994 TFM, FDA received approximately 160 comments from drug manufacturers, trade associations, academia, testing laboratories, consumers, health professionals, and law firms. In response to the 2013 Consumer Wash PR, we received safety data regarding benzalkonium chloride that is relevant to this ingredient's use in a consumer rub and these data are evaluated in section VIII.D.2. Copies of the comments received are on public display at <http://www.regulations.gov> (see ADDRESSES). Because only consumer antiseptic rubs are discussed in this proposed rule, only those comments and data received in response to the 1994 TFM that are related to consumer antiseptic rub active ingredients are addressed. We also received comments related to final formulation testing and labeling conditions proposed in the 1994 TFM. If in the future we determine that there are monograph consumer antiseptic rub active ingredients that are GRAS/GRAE, we will address these comments. We invite further comment on the final formulation testing and labeling conditions proposed in the 1994 TFM, particularly in light of the data proposed in this proposed rule as necessary to support a GRAS/GRAE determination. Comments that were received in response to the 1994 TFM regarding other intended uses of the active ingredients are addressed in the 2013 Consumer Wash

PR (78 FR 76444), or the 2015 Health Care Antiseptic PR (80 FR 25166), or will be addressed in future documents related to those other uses.

This proposed rule constitutes FDA's evaluation of submissions made in response to the 1994 TFM to support the safety and effectiveness of OTC consumer antiseptic rub active ingredients (Ref. 12). We reviewed the available literature and data and the comments submitted to the rulemaking and are proposing that adequate data for a determination of safety and effectiveness are not yet available for the consumer antiseptic rub active ingredients.

IV. Active Ingredients With Insufficient Evidence of Eligibility for the OTC Drug Review

In this section of the proposed rule, we describe the requirements for eligibility for the OTC Drug Review and the ingredients submitted to the OTC Drug Review that lack adequate evidence of eligibility for evaluation as consumer antiseptic rub products.

A. Eligibility for the OTC Drug Review

An OTC drug is covered by the OTC Drug Review if its conditions of use existed in the OTC drug marketplace on or before May 11, 1972 (37 FR 9464) (Ref. 13).² Conditions of use include, among other things, active ingredient, dosage form and strength, route of administration, and specific OTC use or indication of the product (see § 330.14(a)). To determine eligibility for the OTC Drug Review, FDA typically must have actual product labeling or a facsimile of labeling that documents the conditions of marketing of a product prior to May 1972 (see § 330.10(a)(2)). FDA considers a drug that is ineligible for inclusion in the OTC monograph system to be a new drug that will require FDA approval through the NDA process. Ineligibility

² Also, note that drugs initially marketed in the United States after the OTC Drug Review began in 1972 and drugs without any U.S. marketing experience can be considered in the OTC monograph system based on submission of a Time and Extent Application. (See § 330.14).

for use as a consumer antiseptic rub does not affect eligibility under any other OTC drug monograph.

B. Eligibility of Certain Active Ingredients for the OTC Drug Review

The following list includes those active ingredients that were addressed in the 1994 TFM for use as an antiseptic hand wash or health care personnel hand wash, and which currently do not have adequate evidence of eligibility for evaluation under the OTC Drug Review for use in a consumer antiseptic rub. Our review of the labeling submitted to the Panel or to FDA at a later time did not identify evidence demonstrating eligibility for the following active ingredients:

- Benzethonium chloride
- Chloroxylenol
- Chlorhexidine gluconate³
- Cloflucarban
- Fluorosalan
- Hexachlorophene
- Hexylresorcinol
- Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
- Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
- Methylbenzethonium chloride
- Nonylphenoxypoly (ethyleneoxy) ethaniodine
- Phenol (less than 1.5 percent)

³ Chlorhexidine gluconate 4 percent aqueous solution was found to be ineligible for inclusion in the monograph for any health care antiseptic use and was not included in the 1994 TFM (59 FR 31402 at 31413). We have not received any new information since the 1994 TFM demonstrating that this active ingredient is eligible for the topical antimicrobial monograph.

- Phenol (greater than 1.5 percent)
- Poloxamer iodine complex
- Povidone-iodine 5 to 10 percent
- Secondary amyltr cresols
- Sodium oxychlorosene
- Tribromsalan
- Triclocarban
- Triclosan
- Triple dye
- Undecoylium chloride iodine complex

Following the publication of the 1994 TFM, FDA received submissions for the first time requesting that the following compounds be added to the monograph (Refs. 14 through 20):

- Polyhexamethylene biguanide
- Benzalkonium cetyl phosphate
- Cetylpyridinium chloride
- Calicylic acid, sodium hypochlorite
- Tea tree oil
- Combination of potassium vegetable oil solution, phosphate sequestering agent, and triethanolamine

These compounds were not addressed in prior FDA documents related to the monograph and were not evaluated for antiseptic hand wash use by the Antimicrobial I Panel. The submissions received by the Agency to date do not include documentation demonstrating the

eligibility of any of these compounds for inclusion in the topical antimicrobial monograph (Ref. 21). Because of their lack of eligibility, effectiveness and safety information that has been submitted to the rulemaking for these consumer antiseptic rub active ingredients are not discussed in this proposed rule for such use. However, if documentation of the type described in section IV.A is submitted, these active ingredients could be determined to be eligible for evaluation for use as a consumer antiseptic rub.

V. Ingredients Previously Proposed as Not Generally Recognized as Safe and Effective

FDA may determine that an active ingredient is not GRAS/GRAE for a given OTC use (i.e., nonmonograph) because of lack of evidence of effectiveness, lack of evidence of safety, or both. In the 1994 TFM (59 FR 31402 at 31435), FDA proposed that the active ingredients fluorosalan, hexachlorophene, phenol (greater than 1.5 percent), and tribromsalan be found not GRAS/GRAE for the uses referred to in the 1994 TFM as antiseptic hand wash and health care personnel hand wash. None of these ingredients currently have adequate evidence of eligibility for use in a consumer antiseptic rub (see section IV.B). Consequently, effectiveness and safety information that has been submitted to the rulemaking for these consumer antiseptic rub active ingredients are not discussed in this proposed rule for such use. However, if documentation of the type described in section IV.A is submitted, these active ingredients could be determined to be eligible for evaluation for use as a consumer antiseptic rub.

VI. Summary of Proposed Classifications of OTC Consumer Antiseptic Rub Active Ingredients

Table 3 lists the OTC consumer antiseptic active ingredients eligible for evaluation under the OTC Drug Review for use in consumer rubs, the classification proposed in the 1994 TFM, and the classification being proposed in this rulemaking. For each active ingredient, data that have been submitted to the public docket (for the topical antimicrobial rulemaking) and

evaluated by FDA and the description of data still lacking in the administrative record are described in detail in section VIII.

Table 3.--Classification of OTC Consumer Antiseptic Rub Active Ingredients in the 1994 TFM and in This Proposed Rule

Active Ingredient	1994 TFM Proposal ¹	This Proposed Rule
Alcohol 60 to 95 percent	I ²	IIISE ³
Isopropyl alcohol 70 to 91.3 percent	IIIE	IIISE
Benzalkonium chloride	IIISE	IIISE

¹ Because the 1994 TFM did not describe antiseptic hand washes and rubs separately, the 1994 TFM classification was for use as an antiseptic hand wash or health care antiseptic hand wash.

² "I" denotes a classification that an active ingredient has been shown to be safe and effective.

³ "III" denotes a classification that additional data are needed. "S" denotes safety data needed. "E" denotes effectiveness data needed.

In the 1994 TFM, alcohol was classified as Category I, isopropyl alcohol was classified as Category IIIE, and benzalkonium chloride was classified as Category IIISE for use as an antiseptic hand wash or health care personnel hand wash. However, in this proposed rule, we are proposing to classify all three ingredients as Category IIISE for use as a consumer antiseptic rub because additional effectiveness and safety data are needed to classify each ingredient as GRAS/GRAE for this use.

VII. Effectiveness (Generally Recognized as Effective) Determination

OTC regulations (§§ 330.10(a)(4)(ii) and 314.126(b) (21 CFR 330.10(a)(4)(ii) and 314.126(b))) define the standards for establishing that an OTC drug containing a particular active ingredient would be GRAE for its intended use. These regulations provide that supporting investigations must be adequate and well-controlled, and able to distinguish the effect of a drug from other influences such as a spontaneous change in the course of the disease, placebo effect, or biased observation. In general, such investigations include controls that are adequate to provide an assessment of drug effect, are adequate measures to minimize bias, and use adequate analytical methods to demonstrate effectiveness. For active ingredients being evaluated in the OTC Drug Review, this means that a demonstration of the contribution of the active ingredient to

any effectiveness observed is required before an ingredient can be determined to be GRAE for OTC drug use.

In the 1994 TFM, we continued to apply a log reduction standard (a clinical simulation standard) for establishing effectiveness of consumer antiseptics originally proposed in the 1978 TFM (59 FR 31402 at 31412) for the proposed intended use of decreasing bacteria on the skin. The 1994 TFM log reduction standard for effectiveness is based on a surrogate endpoint (i.e., number of bacteria removed from the skin), rather than a clinical outcome (e.g., reduction in the number of infections). Although the test methods proposed in the 1994 TFM are intended to evaluate the effectiveness of antiseptic final formulations, this type of clinical simulation testing, when adequately controlled, can also be used to demonstrate that an active ingredient is GRAE for use in a consumer antiseptic rub product. As reflected by the recommendations of some public health agencies, FDA believes that consumer antiseptic rubs are generally used when hands are not visibly soiled, and soap and water are not readily available (Refs. 22, 23), for example, in settings such as school classrooms, childcare facilities, outdoors and various other public places (Ref. 24). However, as discussed in section VII.A, data from adequately controlled studies demonstrating the impact of consumer antiseptic rubs on infection rates are not available. In contrast to consumer washes, for which we are asking for clinical outcome data to support the benefit of these products, given the easily available alternative of washing with soap and water, there is no similar readily available alternative for consumer antiseptic rubs. A clinical outcome trial comparing the use of consumer antiseptic rubs to standard hand washing with soap and water has less applicability given that consumer antiseptic rubs are not generally used in situations in which soap and water are a readily available alternative. Therefore, we are

currently recommending the use of clinical simulation studies because they are a practical means to assess the general effectiveness of consumer antiseptic rubs.

FDA has already relied on clinical simulation studies as a standard for evaluating effectiveness of hand antiseptic drug products approved under NDAs, which are proven to be an effective measure to lower the surgical site infection rate (Refs. 25 through 27). In addition, in our recently revised standards for evaluating the effectiveness of health care antiseptics published in May 2015 (80 FR 25166), we relied on clinical simulation studies based on the recommendations of the March 2005 NDAC. In contrast, in the 2013 Consumer Wash PR, we proposed an efficacy standard for consumer antiseptic washes that relies on clinical outcome trials, also based on NDAC recommendations. As noted previously, consumer antiseptic rub products are generally used when soap and water are not available, so consumers lack a readily available alternative. As such, we continue to propose a log reduction standard to demonstrate the general recognition of effectiveness for consumer antiseptic rubs in accordance with our standards for health care antiseptics, which contain the same active ingredients (i.e., alcohol, isopropyl alcohol, and benzalkonium chloride). Details of our current proposed log reduction standard are outlined in section VII.B.

As discussed in section VII.A, we have evaluated the available effectiveness studies that were submitted to the OTC Drug Review or retrieved through the published literature to support the effectiveness for consumer antiseptic rubs using the log reduction criteria most recently proposed in the 1994 TFM (59 FR 31402 at 31448) (Refs. 28 and 29). We found that the available studies are not adequate to support a GRAE determination for any consumer antiseptic rub active ingredient under either the final formulation effectiveness testing criteria proposed in the 1994 TFM or under the GRAE criteria proposed in this proposed rule (see table 4).

We have also evaluated all the studies that were submitted to the OTC Drug Review and have searched the published literature for studies performed in consumer use settings that would provide the direct evidence of a clinical benefit from the use of consumer antiseptic rubs (Ref. 24). We are defining a clinical benefit here as a reduction in the number of infections in a population that uses the consumer antiseptic rubs. Although a definitive link between consumer antiseptic rubs and reduced infection rates has not been established, some public health agencies recommend the use of consumer antiseptic rubs when soap and water are not available (Refs. 22, 23).

A. Evaluation of Effectiveness Data

1. Clinical Simulation Studies

Most of the available data to support the effectiveness of consumer antiseptic rubs are based on clinical simulation studies, such as the ones described in the 1994 TFM (59 FR 31402 at 31444). The premise behind these studies as described in the 1994 TFM is that bacterial reductions translate to a reduced risk for infection. However, currently, there are no clinical data that demonstrate that the specific bacterial log reductions that we have relied upon as a demonstration of effectiveness lead to a specific reduction in infections. In our view, although a lower number of bacteria on hands may not directly translate into a reduced chance of infection, a reduced bacterial load does decrease the opportunity for infection when used in situations with no other options for hand cleansing. In this case, rather than comparing using consumer antiseptic rubs to hand washing with soap and water, we are comparing them to the alternative of not cleaning the hands. In addition, because we believe that the consumer antiseptic rubs are intended to provide immediate reduction of bacteria rather than a persistent benefit, we are

proposing that log reductions be measured after a single bacterial challenge (see table 4), rather than after repeated contamination.

We have evaluated all clinical simulation studies that were submitted to the OTC Drug Review for evidence of the effectiveness of consumer antiseptic rub active ingredients under the log reduction criteria proposed in the 1994 TFM (59 FR 31402 at 31448) (Refs. 28 through 30). We also searched the published literature for clinical simulation studies that assess consumer antiseptic rubs' effectiveness using the log reduction criteria in the 1994 TFM (Refs. 28 and 29).

Overall, the studies used a variety of study designs, including nonstandard study designs. In some cases, data submitted to the OTC Drug Review were in the form of technical reports or published articles without any study details. There is insufficient information to evaluate the scientific merit of studies described in abstracts and technical reports. Most importantly, none of the evaluated studies were adequately controlled to demonstrate the contribution of the active ingredient to the effectiveness observed in the studies (43 FR 1210 at 1240) and, therefore, cannot be used to demonstrate that the active ingredient tested is GRAE.

In general, the evaluated studies also had at least one of the following deficiencies:

- Some studies that were described as using a standardized method (American Society for Testing and Materials (ASTM)⁴ or 1994 TFM) varied from these methods without explanation or validation, and the majority of studies did not provide sufficient information about critical aspects of the study conduct.
- Many studies did not include appropriate controls; for example, most studies did not include a vehicle control or an active control (59 FR 31402 at 31448), and some studies

⁴ General information about ASTM can be found at <https://www.astm.org/>.

that included an active control failed to use the control product according to its labeled directions (59 FR 31402 at 31448).

- Many studies did not provide sufficient detail concerning neutralizer use (43 FR 1210 at 1244) or validation of neutralizer effectiveness.
- The studies evaluated a small number of subjects (59 FR 31402 at 31449).
- Some studies did not sample all of the time points specified by the test method (59 FR 31402 at 31448).

FDA's detailed evaluation of the data is filed in Docket No. FDA-2016-N-0124, available at <http://www.regulations.gov>.

2. Clinical Outcome Studies

Although we are not currently proposing to require clinical outcome studies to support a GRAE determination in this proposed rule, FDA identified and evaluated clinical outcome studies from the published literature that could potentially provide evidence of effectiveness for the use of consumer antiseptic rubs (Ref. 24). In our view, clinical outcome studies evaluating the effectiveness of consumer rubs should be adequately controlled and include a placebo or negative control arm to show the effect of an active ingredient. Among the reviewed studies and published literature, there are only a few studies that use these specified parameters for evaluating the effectiveness of consumer antiseptic rubs (Ref. 25). Overall, most of the studies were confounded, underpowered, and/or not properly controlled.

Our detailed review of consumer hand rubs studies is available in Docket No. FDA-2016-N-0124 (Ref. 24). None of the alcohol-based hand rub studies demonstrating benefit were adequately controlled, thus they could not demonstrate the contribution of the antiseptic active

ingredient to the observed clinical outcome of reduced infection rates. In general, the studies had the following design flaws:

- No comparison to vehicle
- Small sample size
- Lack of randomization, blinding, or both
- Inadequate statistical power and, in some cases, a failure to analyze results for statistical significance
- Inadequate description of methodology and data collection methods
- Failure to observe and document hand rub application technique

One clinical outcome study was identified that was randomized, blinded, and placebo-controlled and was well designed to evaluate the effectiveness of a particular antiseptic active ingredient (Ref. 31). Although it had several significant limitations that prevent it from being sufficient to establish effectiveness for use of the active ingredient in a consumer antiseptic rub, this study is the best among the available studies that evaluate the impact of consumer antiseptic rubs on infections.

This clinical outcome study performed in Sweden compared the effectiveness of a 70-percent alcohol-containing consumer antiseptic rub as an adjunct to hand washing with plain soap and water in childcare centers (Ref. 31). The study included 60 childcare centers (30 matched pairs) from 10 counties with a mean number of 50 children in each center. One childcare center from each matched pair was randomized to the intervention group, with the other serving as the control group. The intervention groups were provided instructions (verbal and written), and children and staff were asked to wash hands with plain soap and water, then rub with a 70-percent alcohol-containing consumer antiseptic rub. Control groups followed the

same hand-washing protocol without the hand rub. The primary outcome was the rate of illness absenteeism. Parents were asked to report every episode when the child was absent from childcare because of illness, including the dates of absence, symptoms, and any medical treatment. There were 0.37 absences per 100 child hours in the control group, compared to 0.33 in the intervention group. The effect of the intervention was a 12-percent reduction in absenteeism. Based on the amount of hand rub used during the study, the estimated frequency of hand rub use by each child was two to six times per day. Although the study is well designed, there are several significant limitations, such as the following:

- No clinical or microbiological evaluation of illness
- No specific infection was studied
- Children kept home based on parent choice not addressed in the statistical analysis
- Degree of illness and symptoms to keep child home varied among parents

B. Current Standards: Studies Needed to Support a Generally Recognized as Effective Determination

In the 1994 TFM, we proposed that the effectiveness of antiseptic active ingredients could be supported by a combination of in vitro studies and in vivo clinical simulation testing as described in 21 CFR 333.470 (59 FR 31402 at 31444). In vitro studies are designed to demonstrate the product's spectrum and kinetics of antimicrobial activity, as well as the potential for the development of resistance associated with product use. In vivo test methods and evaluation criteria are based on the premise that bacterial reductions can be adequately demonstrated using tests that simulate conditions of actual use for OTC consumer antiseptic rub products and that those reductions are reflective of bacterial reductions that would be achieved during use. For the use of antiseptic rubs, some public health agencies (Ref. 22) recommend

their use when soap and water are not available, and when there is no other reasonably available alternative for the consumer.

In addition to the standards described in section VII.B, the effectiveness of consumer antiseptic rubs can be affected by a variety of other factors related to product formulation and use. Section VII.C discusses these factors, which includes the number of times per day a product is used and the volume used in each use.

1. In Vitro Studies

The 1994 TFM proposed that the in vitro antimicrobial activity of an active ingredient could be demonstrated by a determination of the in vitro spectrum of antimicrobial activity, minimum inhibitory concentration (MIC) testing against 25 fresh clinical isolates and 25 laboratory strains, and time-kill testing against 23 laboratory strains (59 FR 31402 at 31444). Comments received in response to the 1994 TFM objected to the proposed in vitro testing requirements, stating that they were overly burdensome (Ref. 32). Submissions of in vitro data submitted to support the effectiveness of antiseptic active ingredients were far less extensive than what was proposed in the 1994 TFM (Ref. 33). Although we agree that the in vitro testing proposed in the 1994 TFM is not warranted for testing every final formulation of an antiseptic product that contains a GRAE ingredient, we believe that a GRAE determination for a consumer antiseptic active ingredient should be supported by adequate in vitro characterization of the antimicrobial activity of the ingredient. In addition, we now propose the option of assessing the minimum bactericidal concentration (MBC) as an alternative to testing the MIC to demonstrate the broad spectrum activity of the antiseptic. The ability of an antiseptic to kill microorganisms, rather than inhibit them, is more relevant for a topical product. Because GRAE status is a very broad determination that can apply to many different formulations of an active ingredient, we

continue to propose that an evaluation of the spectrum and kinetics of antimicrobial activity of a consumer antiseptic rub active ingredient should be evaluated by the following testing:

- A determination of the in vitro spectrum of antimicrobial activity against potential pathogens (listed in this section) that may be encountered in consumer use settings where soap and water are not readily available. MIC or MBC testing of 25 representative clinical isolates and 25 reference (e.g., American Type Culture Collection (ATCC)) strains of each of the microorganisms listed in this section.
- Time-kill testing of each of the following ATCC strains to assess how rapidly the antiseptic active ingredient produces its effect. The dilutions and time points tested should be relevant to the actual use pattern of the final product.

Gram-negative organisms

- Haemophilus influenzae
- Bacteroides fragilis
- Enterobacter species
- Burkholderia cepacia (ATCC 25416 and ATCC 25608)
- Escherichia coli (ATCC 11775 and ATCC 25922)
- Klebsiella pneumoniae (ATCC 13883 and ATCC 27736)
- Pseudomonas aeruginosa (ATCC 15442 and ATCC 27853)
- Serratia marcescens (ATCC 8100 and ATCC 14756)
- Campylobacter jejuni (ATCC 33291 and ATCC 49943)
- Salmonella enterica Serovar Enteritidis (ATCC 13076) and Serovar Typhimurium (ATCC 14028). Serovar refers to the subspecies classification of a group of microorganisms based on cell surface antigens.

- Shigella sonnei (ATCC 9290 and ATCC 25931)

Gram-positive organisms

- Enterococcus faecalis (ATCC 19433 and ATCC 29212)
- Staphylococcus aureus (ATCC 6538 and ATCC 29213) and methicillin-resistant Staphylococcus aureus (ATCC 33591 and ATCC 33592)
- Streptococcus pyogenes (ATCC 14289 and ATCC 19615)
- Listeria monocytogenes (ATCC 7644 and ATCC 19115)
- Streptococcus pneumoniae (ATCC 6303 and ATCC 49619)

We propose that a consumer antiseptic rub active ingredient be considered bactericidal at the concentration and contact time that demonstrates a 3- \log_{10} (99.9 percent) or greater reduction in bacterial viability for all the tested strains. This is the same performance criterion used by the Clinical and Laboratory Standards Institute (NCCLS, "Methods for Determining Bactericidal Activity of Antimicrobial Agents; Approved Guideline," NCCLS document M26-A, 1999).

Despite the fact that the in vitro data submitted to support the effectiveness of antiseptic active ingredients were far less extensive than proposed in the 1994 TFM, manufacturers may have data of this type on file from their own product development programs that have not been submitted to the rulemaking. Furthermore, published data may be available that would satisfy some or all these data requirement. Data from these in vitro studies, as well as data from the literature, may be used to inform labeling, in particular, if there are specific organisms for which an active ingredient does not have significant activity. It is anticipated that if data supporting use of a consumer antiseptic demonstrate lack of activity against a particular organism that requires labeling, that labeling would also be relevant in the health care setting.

2. In Vivo Studies

Based on the recommendations of the March 2005 NDAC meeting for health care antiseptic products, we continue to propose the use of bacterial log reductions as a means of demonstrating that consumer antiseptic rubs are GRAE (Ref. 8). The 1994 TFM also proposed final formulation testing for antiseptic hand washes (59 FR 31402 at 31448). We are not discussing the final formulation testing here because we are not proposing that any of the ingredients are GRAS/GRAE. Although, as previously noted, these proposed test methods are intended to evaluate the effectiveness of antiseptic final formulations, this type of clinical simulation testing when adequately controlled can also be used to demonstrate that an active ingredient is GRAE for use in a consumer antiseptic rub product. Based on our experience with the approval of NDA antiseptic products, and input from the March 2005 and October 2005 NDAC meetings, we recommend that the bacterial log reduction studies used to demonstrate that an active ingredient is GRAE for use in consumer antiseptic rub drug products include the following:

- A vehicle control to show the contribution of the active ingredient to effectiveness. The test product should be statistically superior to the vehicle control for the clinical simulation to be considered successful at showing that the test product is effective for use in consumer antiseptic rub products. Products with vehicles that have antimicrobial activity should consider using a negative control, such as saline, rather than a vehicle control.
- An active control to validate the study conduct, to assure that the expected results are produced. For the results to be valid, the active control should meet the appropriate log reduction criteria.

- A sample size large enough to show statistically significant differences from the results achieved using the vehicle, and meeting the threshold of at least a 70-percent success rate for the test product, including justification that the number of subjects tested is adequate for the test.
- Use of an appropriate neutralizer in all recovery media (i.e., sampling solution, dilution fluid, and plating media) and a demonstration of neutralizer validation. The neutralizer is used to halt the antimicrobial activity of the antiseptic after product exposure so that a continued effect through subsequent dilution steps and culturing thereby does not create inflated log reductions. The purpose of neutralizer validation is to show that the neutralizer used in the study is effective against the test and control products, and that it is not toxic to the test microorganisms. If a test product can be neutralized through dilution, this should be demonstrated in the neutralizer validation study.
- An analysis of the proportion of subjects who meet the log reduction criteria based on a two-sided statistical test for superiority to vehicle and a 95-percent confidence interval approach.

To establish that a particular active ingredient is GRAE for use in consumer antiseptic rubs, clinical simulation studies using the parameters described in this section should be evaluated using log reduction criteria similar to those proposed in the 1994 TFM (59 FR 31402 at 31448). Our current criteria are laid out in table 4. We have revised the log reduction criteria proposed for consumer antiseptic rubs based on the recommendations of the March 2005 NDAC and comments to the 1994 TFM, which argued that the demonstration of a cumulative antiseptic effect for these products is unnecessary. We agree that the critical element of the effectiveness is that a product must be effective after the first application because that represents the way in

which consumer antiseptic rub products are used (59 FR 31402 at 31442). For these reasons, log reduction criteria are proposed only for a single application of the test product rather than multiple applications. Given that we are no longer requiring a cumulative antiseptic effect, the log reduction criteria were revised to reflect this single application and fall between the log reductions previously proposed for the first and last applications. The GRAE criteria proposed for consumer antiseptic rubs are based on log reductions achieved by antiseptics as shown in the published literature (Refs. 28 and 29) as well as those evaluated under the NDA process. Table 4 shows the log reductions that we would expect an effective consumer antiseptic rub active ingredient to meet to show that it is GRAE.

Table 4.--Clinical Simulation Testing Bacterial Log Reduction Effectiveness Criteria in this Proposed Rule and in the 1994 TFM

Indication	1994 TFM	This Proposed Rule
Antiseptic hand wash/Consumer antiseptic rub	(1) Reduction of 2 log ₁₀ on each hand within 5 minutes after the first wash and (2) Reduction of 3 log ₁₀ on each hand within 5 minutes after the tenth wash.	(1) Reduction of 2.5 log ₁₀ on each hand within 5 minutes after a single rub.

C. Impact of Application Parameters on Efficacy

Establishing GRAE status of active ingredients is one important aspect of ensuring the efficacy of OTC consumer antiseptic rub products. The standards for a GRAE determination for consumer antiseptic rubs have been described (see section VII.B). These standards will help determine final monograph active ingredients, as well as their permitted concentrations and the skin application time needed for the active ingredient to achieve adequate bacterial reduction. However, the efficacy of any particular final formulation of a consumer antiseptic rub appears to be affected by a variety of other factors related to product formulation and use.

These factors include the number of times per day a product is used and the volume used in each use. The number of times per day that a consumer antiseptic rub product is applied has been shown to be positively correlated with a reduction in illness-related absenteeism in a

kindergarten school (Ref. 34). In addition, more specific measures of application parameters have been assessed. The volume of product applied and the skin coverage achieved by the applied volume appear to have an impact on efficacy of antiseptic rub products containing alcohol. In comparing five different application volumes of 70 percent ethanol gel with 85 percent ethanol gel and 70 percent ethanol foam, Kampf et al. (2013) demonstrated that the label recommended volume of 1.1 milliliters (mL) for the 70 percent ethanol products was not sufficient to achieve efficacy in in vivo efficacy testing according to ASTM methods (Ref. 35). The recommended application of 2 mL of 85 percent gel, as well as higher than recommended volumes of the 70 percent products, met efficacy criteria under ASTM E 2755-10 and ASTM E 1174-06 methods used in this study. In the same study, insufficient skin coverage with lower application volumes (1.1 mL) was suggested as the reason for failure to achieve efficacy. Failure to achieve effectiveness with the lower volume was based on observation of gaps in skin coverage after volunteers applied products containing fluorescent dye to their hands. In a similar study, Kampf (2008) assessed the efficacy and coverage of four hand rub products (foam or gel formulation unspecified) containing 85 percent, 62 percent, 61 percent, or 60 percent ethanol (Ref. 36). At an application volume of 2.4 mL, the 60 percent and 61 percent ethanol formulations failed to meet in vivo ASTM efficacy criteria while 2.4 mL application volumes of 62 percent and 85 percent ethanol formulations met the criteria. Application volumes of 3.6 mL met efficacy criteria for all ethanol concentrations tested (Ref. 36).

Given that the applied volume of product may have consequences for product efficacy, the factors that may affect application volume are of interest. Variability has been demonstrated in the output of both gel and foam antiseptic rub dispensers. Macinga et al. (2013) measured output from a single wall-mounted dispenser and among wall-dispensers from different

manufacturers (Ref. 37). In dispensing five different gel formulations containing varying percentages of ethanol or isopropanol, dispensers from five different manufacturers had outputs that ranged from 0.9 to 1.3 mL per actuation. In dispensing three different foam formulations each containing 70 percent ethanol, foam dispensers from three different manufacturers ranged from 0.6 to 1.1 mL per actuation. Furthermore, the volume of product that individuals choose to apply may be affected, independent of labeled instruction, by factors such as the time it takes hands to dry after application. Kampf et al. (2010) assessed four foam formulations, each containing 62 percent ethanol, and found that the amount (weight) of foam applied was significantly correlated with the perceived drying time (Ref. 38). There is also evidence that final formulation affects efficacy. Different products containing the same concentration of active ingredient have been shown to perform differently when tested by in vivo bacterial reduction testing (ASTM 1174) (Ref. 39). One "novel" gel formulation and one "novel" foam formulation, each containing 70 percent ethanol, were both shown to be statistically superior after both 1 and 10 applications compared to two marketed formulations, one gel and one foam, both containing 70 percent ethanol. All formulations were applied in equal volumes. The two "novel" formulations also demonstrated some evidence of improved performance relative to a marketed gel containing 90 percent ethanol.

Understanding the impact of product-related parameters, such as formulation, dose applied, and application volume, to be used according to the labeling is imperative. We also need to understand the extent to which variability in product-related parameters must be reduced to ensure that products achieve the results expected based on their use of GRAE ingredients. Given the data demonstrating that efficacy varies with dose, application volume, and formulation, final formulation efficacy testing will be necessary for consumer antiseptic rub

products in order to confirm effectiveness and label the product appropriately for use. However, because no ingredient has sufficient data to support GRAS/GRAE status in this rulemaking, we are not proposing specific final formulation testing or labeling at this time. Instead, we are requesting data to allow the assessment of the impact of various application parameters on efficacy and the interaction among them (e.g., how does formulation affect application volume requirements) to inform final formulation testing and labeling requirements.

VIII. Safety (Generally Recognized as Safe) Determination

In the 1994 TFM, 11 active ingredients were proposed to be classified as GRAS for antiseptic hand wash use, which includes 2 active ingredients (alcohol and isopropyl alcohol) that are eligible for consumer antiseptic rub use (59 FR 31402 at 31435). As described in section II.C, consumer antiseptic hand rubs were not addressed separately from antiseptic hand washes in the 1994 TFM. There have since been a number of important scientific developments affecting our evaluation of the safety of the active ingredients in consumer antiseptic rubs, causing us to reassess the data necessary to support a GRAS determination. There is now new information regarding systemic exposure to antiseptic active ingredients (Refs. 1 through 5). The potential for widespread antiseptic use to promote the development of antibiotic-resistant bacteria also needs to be evaluated. Furthermore, additional experience with, and knowledge about, safety testing has led to improved testing methods. Improvements include study designs that are more capable of detecting potential safety risks. Based on our reassessment, we are proposing new GRAS data standards for consumer antiseptic rub active ingredients. To fully address these new safety concerns, additional safety data will be necessary to support a GRAS determination for all consumer antiseptic rub active ingredients.

Many of the safety considerations for consumer antiseptic rubs are based on FDA's view that the use of consumer antiseptic rubs is a "chronic" use as that term is defined by the International Council on Harmonisation (ICH).⁵ As defined by the ICH, a use is considered chronic if the drug will be used for a period of at least 6 months over the user's lifetime, including repeated, intermittent use (Ref. 40). We believe that consumer antiseptic rubs are often used on a daily basis and sometimes repeatedly over the course of the day.

⁵ FDA is a member of the ICH Steering Committee, the governing body that oversees the harmonization activities, and contributes to the development of ICH guidelines.

A. New Issues

Since the 1994 TFM was published, new data have become available indicating that systemic exposure to topical antiseptic active ingredients may be greater than previously thought. Systemic exposure refers to the presence of antiseptic active ingredients inside and throughout the body. Because of advances in technology, our ability to detect antiseptic active ingredients in body fluids such as serum and urine is greater than it was in 1994. For example, studies have shown detectable blood alcohol levels after use of alcohol-containing hand rubs (Refs. 1, 4, and 5). We believe that any consequences of this systemic exposure should be identified and assessed to support our risk-benefit analysis for consumer antiseptic use.

Given the frequent repeated use of consumer antiseptic rubs, systemic exposure may occur. Although some systemic exposure data exist for all three consumer antiseptic rub active ingredients, data on systemic absorption after maximal use are lacking. Currently, there is also a lack of data to assess the impact of important drug use factors that can influence systemic exposure such as dose, application frequency and method, duration of exposure, product formulation, skin condition, and age. Depending on the systemic absorption of the ingredient, variability in absorption anticipated between formulations, and the safety margin for toxic effects, final formulation safety testing for particular ingredients may be needed to assure that substantially different absorption that might significantly change the margin of safety is not anticipated for a new formulation. FDA does not address final formulation testing in this rulemaking because no ingredients have been proposed as GRAS/GRAE. However, FDA recently described final formulation safety testing for another class of OTC dermal products regulated under the OTC drug monograph (Ref. 41).

The evaluation of the safety of drug products involves correlating findings from animal toxicity studies to the level of drug exposure obtained from pharmacokinetic studies in animals and humans. Our administrative record lacks the data necessary to define a margin of safety for the potential chronic use of consumer antiseptic rub active ingredients. Thus, we are continuing to propose that both animal and human pharmacokinetic (PK) data are necessary for consumer antiseptic rub active ingredients. This information will help identify any potential safety concerns and help determine the safety margin for OTC human use.

One potential effect of systemic exposure to consumer antiseptic active ingredients that has come to our attention since publication of the 1994 TFM is data suggesting that some antiseptic active ingredients have hormonal effects. Ingredients in topical antiseptic products can cause alterations in the thyroid of neonatal and adolescent animals (Refs. 42 through 51). Hormonally active compounds have been shown to affect not only the exposed organism, but also subsequent generations (Ref. 52). These effects may not be related to direct deoxyribonucleic acid (DNA) mutation, but rather to alterations in factors that regulate gene expression (Ref. 53).

A hormonally active compound that causes reproductive system disruption in the fetus or infant may have effects that are not apparent until many years after initial exposure. There are also critical times in fetal development when a change in hormonal balance that would not cause any lasting effect in an adult could cause a permanent developmental abnormality in a child. For example, untreated hypothyroidism during pregnancy has been associated with cognitive impairment in the offspring (Refs. 54 through 56).

Because consumer antiseptic rubs are used chronically and are likely to be used by sensitive populations such as children and pregnant women, evaluation of the potential for

chronic toxicity and effects on reproduction and development should be included in the safety assessment. The designs of general toxicity and reproductive/developmental studies are often sufficient to identify developmental effects that can be caused by hormonally active compounds through the use of currently accepted endpoints and standard good laboratory practice toxicology study designs. As followup in some cases, additional study endpoints may be needed to fully characterize the potential effects of drug exposure on the exposed individuals.

B. Antimicrobial Resistance

In the 2013 Consumer Wash PR and 2015 Health Care Antiseptic PR, FDA raised the concern of the development of antiseptic resistance and its potential impact on the development of antibiotic resistance (78 FR 76444 at 76454 and 80 FR 25166 at 25180). This concern was based on numerous reports of laboratory studies demonstrating the development of reduced susceptibility to certain antiseptic active ingredients and antibiotics after growth in nonlethal amounts of the antiseptic (i.e., low-to-moderate concentrations of antiseptic) and reports of the persistence of low levels of some antiseptic active ingredients in the environment (78 FR 76444 at 76454 and 80 FR 25166 at 25180). FDA concluded in both of these proposed rules that, given the increasing evidence of the magnitude of the antibiotic resistance problem and the speed with which new antibiotic resistant organisms are emerging, it is important to assess this potential consequence of antiseptic use and requested data to address the concern (78 FR 76444 at 76454 and 80 FR 25166 at 25180). However, in its evaluation of the available data on the development of resistance to alcohol and isopropyl alcohol in the proposed rule for health care antiseptics, FDA cited a number of factors (speed of action, multiple nonspecific toxic effects, and lack of a residue) that made the development of resistance to these alcohols as a result of health care antiseptic use unlikely. Based on these factors, FDA concluded that no additional data relevant

to this issue were necessary to support a GRAS determination for these ingredients for health care antiseptics (80 FR 25166 at 25184, 25187, and 25192). Consistent with FDA's findings for alcohol and isopropyl alcohol in its proposed rule for health care antiseptic, we have also tentatively concluded that no further data on the development of resistance to alcohol and isopropyl alcohol as a result of their use in consumer antiseptic rub products are needed. This is not the case for benzalkonium chloride for which additional laboratory studies will assist in more clearly defining the potential for the development of resistance. (See section VIII.D.2).

C. Studies to Support a Generally Recognized as Safe Determination

A GRAS determination for consumer antiseptic rub active ingredients must be supported by both nonclinical (animal) and clinical (human) studies.⁶ To issue a final monograph for these products, this safety data must be in the docket.⁷

To assist manufacturers or others who wish to provide us with the information we expect will establish GRAS status for these active ingredients, we are including specific information, based in part on existing FDA guidance, about the other kinds of studies to consider conducting and submitting. We have published guidance documents describing the nonclinical safety studies that a manufacturer should perform when seeking to market a drug product under an NDA (Refs. 40, 57 through 63). These guidance documents also provide relevant guidance for performing the nonclinical studies necessary to determine GRAS status for a consumer antiseptic rub active ingredient. Because consumer antiseptic rubs may be used repeatedly and in sensitive populations, we propose that consumer antiseptic rub active ingredients will need to be tested for

⁶ We encourage sponsors to consult with us on non-animal testing methods they believe may be suitable, adequate, validated, and feasible. We are willing to consider if alternative methods could be assessed for equivalency to an animal test method.

⁷ The Agency intends to consider only non-confidential material that is submitted to the docket for this rulemaking or that is otherwise publicly available in its evaluation of the GRAS/GRAE status of a relevant ingredient. Information about how to submit this data or information to the docket is set forth in this document in the ADDRESSES section.

carcinogenic potential, developmental and reproductive toxicity (DART), and other potential effects as described in more detail in this section.

1. FDA Guidances Describing Safety Studies

The safety studies that are described in the existing FDA guidances (Refs. 40, 57 through 63) provide a framework for the types of studies that are needed for FDA to assess the safety of each consumer rub active ingredient according to modern scientific standards and make a GRAS determination. A description of each type of study and how we would use this information to improve our understanding of the safety of consumer antiseptic rub active ingredients is provided in table 5.

Table 5.--FDA Guidance Documents Related to Requested Safety Data and Rationale for Studies

Type of Study	Study Conditions	What the Data Tell Us	How the Data Are Used
Animal pharmacokinetic absorption, distribution, metabolism, and excretion (ADME) (Refs. 58 and 64)	Both oral and dermal administration	Allows identification of the dose at which the toxic effects of an active ingredient are observed as a result of systemic exposure of the drug. ADME data provide: The rate and extent an active ingredient is absorbed into the body (e.g., AUC, Cmax, Tmax) ¹ ; where the active ingredient is distributed in the body; whether metabolism of the active ingredient by the body has taken place; information on the presence of metabolites; and how the body eliminates the original active ingredient (parent) and its metabolites (e.g., T _{1/2}). ²	Used as a surrogate to identify toxic systemic exposure levels that can then be correlated to potential human exposure via dermal pharmacokinetic study findings. Adverse event data related to particular doses and drug levels (exposure) in animals are used to help formulate a safety picture of the possible risk to humans.
Human pharmacokinetics (MUsT) (Ref. 62)	Dermal administration using multiple formulations under maximum use conditions	Helps determine how much of the active ingredient penetrates the skin, leading to measurable systemic exposure.	Used to relate the potential human exposure to toxic drug levels identified in animal studies.
Carcinogenicity (ICH S1A, S1B, and S1C) (Refs. 40, 57, and 60)	Minimum of one oral and one dermal study for topical products ³	Provides a direct measure of the potential for active ingredients to cause tumor formation (tumorigenesis) in the exposed animals.	Identifies the systemic and dermal risks associated with drug active ingredients. Taken together, these studies are used to identify the type(s) of

Type of Study	Study Conditions	What the Data Tell Us	How the Data Are Used
Developmental toxicity (ICH S5) (Ref. 59)	Oral administration	Evaluates the effects of a drug on the developing offspring throughout gestation and postnatally until sexual maturation.	toxicity, the level of exposure that produces these toxicities, and the highest level of exposure at which no adverse effects occur, referred to as the "no observed adverse effect level" (NOAEL). The NOAEL is used to determine a safety margin for human exposure.
Reproductive toxicity (ICH S5) (Ref. 59)	Oral administration	Assesses the effects of a drug on the reproductive competence of sexually mature male and female animals.	
Hormonal effects (Ref. 63)	Oral administration	Assesses the drug's potential to interfere with the endocrine system.	Used in hazard assessment to determine whether the drug has the capacity to induce a harmful effect at any exposure level without regard to actual human exposures.

¹ "AUC" denotes the area under the concentration-time curve, a measure of total exposure or the extent of absorption. "Cmax" denotes the maximum concentration, which is peak exposure. "Tmax" denotes the time to reach the maximum concentration, which aids in determining the rate of exposure.

² "T½" denotes the half-life, which is the amount of time it takes to eliminate half the drug from the body or decrease the concentration of the drug in plasma by 50 percent.

³ Assessment of dermal carcinogenicity is considered important because the intended clinical route of administration is dermal, and skin exposure could be high. In addition, dermal exposure can result in systemic exposure to parent and metabolites that may differ from other routes. When substantial nonclinical information is already available for an active ingredient, the need for a dermal carcinogenicity study could be reconsidered based on available information such as negative systemic carcinogenicity information and lack of preneoplastic effects in chronic nonrodent dermal toxicity studies.

These studies represent FDA's current thinking on the data needed to support a GRAS determination for an OTC antiseptic active ingredient and are similar to those recommended by the Antimicrobial I Panel (described in the ANPR (39 FR 33103 at 33135)) as updated by the recommendations of the 2014 NDAC. However, even before the September 2014 NDAC meeting, the Panel's recommendations for data to support the safety of an OTC topical antimicrobial active ingredient included studies to characterize the following:

- Degree of absorption through intact and abraded skin and mucous membranes
- Tissue distribution, metabolic rates, metabolic fates, and rates and routes of elimination
- Teratogenic and reproductive effects
- Mutagenic and carcinogenic effects

2. Studies to Characterize Maximal Human Exposure

Because the available data indicate that some dermal products, including at least some antiseptic active ingredients, are absorbed after topical application in humans and animals, it is necessary to assess the effects of long-term dermal and systemic exposure to these ingredients. This is particularly important for populations, such as pregnant women (and fetuses), lactating women, and children, who may have greater potential to experience deleterious developmental effects from drug exposure. Human exposure data can then be compared to drug levels in animals known to produce adverse effects in order to calculate a safety margin.

Based on input from the September 2014 NDAC meeting, the Agency has also determined that results from a human PK maximal usage trial (MUSt) are needed to support a GRAS determination. This trial design is also referred to as a maximal use PK trial and is described in FDA's 2005 draft guidance for industry on developing drugs for treatment of acne vulgaris (Ref. 62). The purpose of the MUSt is to evaluate systemic exposure under conditions that would maximize the potential for drug absorption in a manner consistent with possible "worst-case" real world use of the product. In a MUSt, the collected plasma samples are analyzed, and the resulting in vivo data could be used to estimate a safety margin based on animal toxicity studies.

A MUSt to support a determination that an active ingredient is GRAS for use in consumer antiseptics is conducted by obtaining an adequate number of PK samples following administration of the active ingredient. For studies of active ingredients to be used in topically applied products like these, for which there is less information available and for which crossover designs are not feasible, a larger number of subjects are required compared to studies of orally

administered drug products. A MUsT using 50 to 75 subjects per cohort should be sufficient to get estimates of the PK parameters from a topically applied consumer antiseptic.

The MUsT should attempt to maximize the potential for drug absorption to occur by considering the following design elements (Ref. 65):

- Adequate number of subjects (steps should be taken to ensure that the target population (for example, age, gender, race) is properly represented)
- Frequency of dosing (e.g., number of rub applications during the study)
- Duration of dosing
- Use of highest proposed strength (e.g., 95 percent alcohol)
- Total involved surface area to be treated at one time (e.g., hands)
- Amount applied per square centimeter
- Method of application (e.g., rub)
- Sensitive and validated analytical methods

It also is important that the MUsT reflect maximal use conditions of consumer antiseptic rubs using different formulations to fully characterize the active ingredient's potential for dermal penetration. There are very limited data on the maximal number of uses of antiseptic rubs in consumer settings. Consumer antiseptic rubs used in institutional settings, such as daycare centers, schools, and office buildings, would be used (as per label directions) at higher rates than in domestic households, and thus would represent maximal use. Kinnula et al. (2009) surveyed workers in child daycare centers in Finland to determine how commonly alcohol-containing hand rub gels were applied daily (Ref. 66). The respondents (n = 128) reported applying the alcohol hand rub gels up to 50 times per day. Using the upper limit of applications per day of antiseptic

hand rubs from this study, FDA is considering 50 times per day as the maximal use of consumer hand rubs in a consumer setting.

It should be noted that a systemic carcinogenicity study will not be required for an ingredient if a MUSt results in a steady state blood level less than 0.5 nanograms (ng)/mL, and an adequately conducted toxicology program demonstrates that there are no other signals for the ingredient or any known structurally similar compound indicating the potential for adverse effects at lower levels. The threshold value of 0.5 ng/mL is based on the principle that the level would approximate the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100,000 after a single dose.

The lack of absorption in a MuST does not alleviate the need to assess dermal carcinogenicity because the magnitude of exposure to the skin can be much higher than would be covered by systemic studies. In addition, systemic exposure to the parent compound and metabolites can differ significantly for a dermally applied product because the skin has metabolic capability and first-pass metabolism is bypassed via this route of administration.

To fulfill the maximum human exposure requirement, the MUSt study should meet appropriate design standards using the highest concentration sought under this proposed rule in formulations expected to produce the highest in vivo absorption. The assay used in the MUSt should be properly validated according to current Good Laboratory Practices and consistent with FDA guidance for industry: "Bioanalytical Method Validation" (Ref. 67).

We expect that the 0.5 ng/mL concentration will be sufficiently above the assay's limit of quantitation-limit of detection to allow a signal: noise ratio that assures confidence in the derived concentrations (in the case of "exaggerated" values) or lack of concentrations.

3. Studies to Characterize Hormonal Effects

We propose that data are also needed to assess whether consumer antiseptic rub active ingredients have hormonal effects that could produce developmental or reproductive toxicity. There are several factors common to antiseptic products that make it necessary to assess their full safety profile prior to classifying an antiseptic active ingredient as GRAS for use in consumer antiseptic rub products. These factors are as follows:

- Evidence of systemic exposure to several of the antiseptic active ingredients
- Exposure to multiple sources of antiseptic active ingredients that may be hormonally active compounds
- Exposure to antiseptic active ingredients may be long term for some users

According to FDA's 2015 guidance on nonclinical evaluation of endocrine-related drug toxicity (Ref. 63), endocrine effects may be identified from the standard battery of toxicity tests conducted during drug development and may not require additional separate studies.

4. Studies to Evaluate the Potential Impact of Antiseptic Active Ingredients on the Development of Resistance

Since the 1994 TFM published, the issue of antiseptic resistance and whether bacteria that exhibit antiseptic resistance have the potential for antibiotic cross-resistance has been the subject of much study and scrutiny. One of the major mechanisms of antiseptic and antibiotic cross-resistance is changes in bacterial efflux activity at nonlethal concentrations of the antiseptic (Refs. 68 through 73). Efflux pumps are an important nonspecific bacterial defense mechanism that can confer resistance to a number of substances toxic to the cell, including antibiotics (Refs. 74 and 75). The development of bacteria that are resistant to antibiotics is an important public health issue, and additional data may tell us whether use of antiseptics in consumer settings may

contribute to the selection of bacteria that are less susceptible to both antiseptics and antibiotics. Therefore, we are requesting additional data and information to address this issue for ingredients other than alcohol or isopropyl alcohol (see section VIII.D).

FDA believes that a tiered approach is an efficient means of developing data to address this issue. Laboratory studies in conjunction with a literature review are a feasible first step in evaluating the impact of exposure to nonlethal amounts of antiseptic active ingredients on antiseptic and antibiotic bacterial susceptibilities. However, only limited data exist on the effects of antiseptic exposure on the bacteria that are predominant in the oral cavity, gut, skin flora, and the environment (Ref. 76). These organisms represent pools of resistance determinants that are potentially transferable to human pathogens (Refs. 77 and 78). Thus, broader laboratory testing of consumer antiseptic active ingredients would more clearly define the scope of the impact of antiseptic active ingredients on the development of antibiotic resistance and may be able to identify those antiseptic active ingredients for which the development of resistance is not a concern. Laboratory studies evaluating the antiseptic and antibiotic susceptibilities of bacteria grown in the presence of sublethal concentrations of antiseptic active ingredients could help support a GRAS determination for antiseptic active ingredients intended for use in OTC consumer antiseptic drug products. The following types of organisms should be evaluated:

- Human bacterial pathogens
- Nonpathogenic organisms, opportunistic pathogens, and obligate anaerobic bacteria that make up the resident microflora of the human skin, gut, and oral cavity
- Food-related bacteria such as Listeria, Lactobacillus, and Enterococcus
- Nonpathogenic organisms and opportunistic pathogens from relevant environmental sources (e.g., soil)

If the results of these studies show no evidence of changes in antiseptic or antibiotic susceptibility, no further studies addressing the development of resistance would be needed to support a GRAS determination.

For antiseptic active ingredients that demonstrate an effect on antiseptic and antibiotic susceptibilities, additional data will be necessary to help assess the likelihood that similar effects would occur in the consumer setting. Several types of data could be used to assess whether or not ingredients with positive laboratory findings pose a public health risk, and the type of data needed would depend on what is already known about the antiseptic active ingredient's mechanism of action and persistence in the environment. We do not anticipate that it will be necessary to obtain data from multiple types of studies for each active ingredient to adequately assess its potential to affect resistance. Such types of data could include, but are not limited to, the following:

- Information about the mechanism(s) of antiseptic action (for example, membrane destabilization or inhibition of fatty acid synthesis), and whether there is a change in the mechanism of action with changes in antiseptic concentration.
- Information clarifying the bacteria's mechanism(s) for the development of resistance or reduced susceptibility to the antiseptic active ingredient (for example, efflux mechanisms).
- Data characterizing the potential for reduced antiseptic susceptibility caused by the antiseptic active ingredient to be transferred to other bacteria that are still sensitive to the antiseptic.

- Data characterizing the concentrations and antimicrobial activity of the antiseptic active ingredient in biological and environmental compartments (for example, bacteria found on human skin, in the gut, and in environmental matrices).
- Data characterizing the antiseptic and antibiotic susceptibility levels of environmental isolates of bacteria in areas of prevalent antiseptic use, such as in the home or in schools.

Data from the types of testing described previously, as well as from testing of antiseptic and antibiotic susceptibilities of bacteria in settings where consumer topical antiseptic rub use is prevalent can help demonstrate whether or not changes in susceptibility are occurring with actual use. Because actual use concentrations of consumer antiseptics are much higher than the MICs for these active ingredients, data from compartments where sublethal concentrations of biologically active antiseptic active ingredients may occur (e.g., environmental compartments) can give us a sense of the potential for change in antimicrobial susceptibilities in these compartments (Refs. 79 through 81). FDA recognizes, however, that methods of evaluating this issue are an evolving science and that there may be other data appropriate to evaluate the impact of consumer antiseptic active ingredients on the development of resistance. For this reason, FDA encourages interested parties to consult with the Agency on the specific studies appropriate to address this issue for a particular active ingredient.

D. Review of Available Data for Each Antiseptic Active Ingredient

We have identified for each consumer antiseptic rub active ingredient whether the studies outlined in section VIII.C are publicly available. Table 6 lists the types of studies available for each antiseptic active ingredient eligible for use as a consumer rub proposed as Category I or Category III in the 1994 TFM and indicates whether the currently available data are adequate to serve as the basis of a GRAS determination. Although we have some data from submissions to

the rulemaking and from information we have identified in the literature, our administrative record is incomplete for at least some types of safety studies for each of the active ingredients (see table 6). As noted previously, only information that is part of the administrative record for this rulemaking can form the basis of a GRAS/GRAE determination.

We recognize that data and information submitted in response to the 2013 Consumer Wash PR or 2015 Health Care Antiseptic PR may be relevant to this proposed rule. At the time of publication of this proposed rule, FDA's review of all submissions made to the 2015 Health Care Antiseptic PR has not been completed. FDA requests that any information relevant to consumer antiseptic rub active ingredients be resubmitted under this docket (FDA-2016-N-0124).

Table 6.--Safety Studies Available for Consumer Antiseptic Hand Rub Active Ingredients¹

Active Ingredient	Human Pharmacokinetic (MUsT)	Animal Pharmacokinetic (ADME)	Oral Carcinogenicity	Dermal Carcinogenicity	Reproductive Toxicity (DART)	Potential Hormonal Effects	Resistance Potential
Alcohol	○	●	●	●	●	●	●
Benzalkonium chloride		○	●		●	●	○
Isopropyl alcohol	○	○		○	●	○	●

¹ Empty cell indicates no data available; "○" indicates incomplete data available; "●" indicates available data are sufficient to make a GRAS/GRAE determination.

In the remainder of this section, we discuss the existing data and data gaps for alcohol, benzalkonium chloride and isopropyl alcohol, the consumer antiseptic rub active ingredients that were proposed as GRAS in the 1994 TFM, and explain why these active ingredients are no longer proposed as GRAS for use in consumer antiseptic hand rubs (i.e., why they are now proposed as Category III). We also discuss benzalkonium chloride, which was proposed as Category III in the 1994 TFM and for which there are some new data available and explain why this ingredient is still Category III. These three ingredients are also used in health care antiseptic products, and the safety data gaps identified in the 2015 Health Care Antiseptic PR are similar to

those discussed in this proposed rule for each ingredient. The requirements for a GRAS determination for an ingredient are generally the same for either a health care or consumer antiseptic product, with the exception of higher maximal use for health care antiseptic products. Therefore, it is anticipated that ingredients fulfilling the requirements for a health care antiseptic GRAS determination would also meet the criteria for GRAS as a consumer antiseptic, if eligible for that indication.

1. Alcohol

In the 1994 TFM, FDA proposed to classify alcohol as GRAS for all health care antiseptic uses based on the recommendation of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel), which concluded that the topical application of alcohol is safe (59 FR 31402 at 31412). In the 2013 Consumer Wash PR, FDA proposed to separately evaluate the safety and effectiveness of the OTC antiseptic drug products by use setting, specifically health care and consumer antiseptic products. As defined in the 2013 Consumer Wash PR, consumer antiseptic products that are not rinsed off after use include hand rubs and antiseptic wipes. FDA is proposing to classify alcohol as Category III for use in consumer antiseptic rubs. Extensive studies have been conducted to characterize the metabolic and toxic effects of alcohol in animal models. Although the impetus for most of the studies has been to study the effects of alcohol exposure via the oral route of administration, some dermal toxicity studies are available and have shown that, although there is alcohol absorption through human skin, it is much lower than absorption via the oral route. Overall, there are adequate safety data to make a GRAS determination for alcohol, with the exception of human pharmacokinetic data under maximal use conditions.

a. Summary of alcohol safety data.

As discussed in more detail in the 2015 Health Care Antiseptic PR (80 FR 25166 at 25185 to 25187), FDA has reviewed the following and found them to be sufficient to characterize the safety of alcohol for use in consumer antiseptic rubs:

- Animal ADME data demonstrating absorption of alcohol both in vitro and in vivo (Refs. 82 through 86)
- Dermal and oral carcinogenicity data in animals and oral carcinogenicity data in humans (Refs. 87 through 93)
- DART human data (Refs. 94 and 95)
- Data on the hormonal effects of alcohol in animals and humans (Refs. 96 through 102)
- Data on the antimicrobial mechanism of alcohol (Refs. 103 through 106). Alcohol readily evaporates from the skin after topical application, and the resulting lack of antiseptic residue on the skin suggests that the topical application of alcohol is not likely to contribute to the development of antimicrobial resistance (Refs. 103, 105)

Alcohol human pharmacokinetic data. The 2015 Health Care Antiseptic PR described data that characterize the level of dermal absorption and expected systemic exposure in adults as a result of topical use of alcohol-containing antiseptics (80 FR 25166 at 25185-25186). These data do not cover maximal use of these products as detailed in section VIII.D.1.a.

A variety of alcohol-based hand rub product formulations and alcohol concentrations have been used in these studies. Based on the available data, which represents moderate hand rub use (7.5 to 40 hand rub applications per hour, studied for 30 to 240 minutes), the highest observed exposure was 1,500 milligrams (mg) of alcohol (Ref. 4), which is the equivalent of 10 percent of an alcohol-containing drink. See also the discussion of occupational exposure to

alcohol via the dermal route (Ref. 107) in the alcohol carcinogenicity section of the 2015 Health Care Antiseptic PR (80 FR 25166 at 25186).

Although these data do indicate absorption of alcohol does occur after topical administration of alcohol-containing antiseptic rubs, we did not find the exposure conditions of these studies comparable to exposure that are required by our current MUsT standards specified in section VIII.C.2. Consequently, human pharmacokinetic data under maximal use conditions as determined by a MUsT are needed to make a GRAS determination for the alcohol-containing consumer antiseptic rubs.

b. Alcohol safety data gap.

In summary, our administrative record for the safety of alcohol is incomplete with respect to the following:

- Human pharmacokinetic studies under maximal use conditions when applied topically (MUsT), including documentation of validation of the methods used to measure alcohol and its metabolites

2. Benzalkonium Chloride

In the 1994 TFM, FDA categorized benzalkonium chloride as Category III because of a lack of adequate safety data for its use as both a health care antiseptic and consumer antiseptic product (59 FR 31402 at 31435). FDA also is proposing to classify benzalkonium chloride as Category III for the indication of consumer antiseptic rubs. Thus, additional safety data are still needed to make a GRAS determination for benzalkonium chloride for use as a consumer antiseptic rub.

In the 2013 Consumer Wash PR, FDA identified the safety data needed to make a GRAS determination for benzalkonium chloride as an ingredient in consumer antiseptic wash products. The safety gaps listed were human and animal pharmacokinetic data, reproductive toxicity

studies, potential hormonal effects, carcinogenicity (oral and dermal) studies, and potential of the development of antimicrobial resistance to benzalkonium chloride. As was summarized in the 2015 Health Care Antiseptic PR, the safety of benzalkonium chloride has been reviewed and was determined to be safe for use in disinfectants and cosmetic products by the Environmental Protection Agency (EPA) and the Cosmetic Ingredient Review (an industry panel), respectively (Refs. 108 and 109). The data cited in both of these evaluations are proprietary and only summaries of the data are publicly available. Consequently, these studies are not available to FDA and FDA cannot conduct a complete evaluation of them. Safety assessments with study summaries do not constitute an adequate record on which to base a GRAS classification (§ 330.10(a)(4)(i)). For FDA to evaluate this data with respect to the safety of benzalkonium chloride for this rulemaking, the full study reports and data sets must be submitted to the rulemaking docket or otherwise be publicly available.

In response to the call for data in the 2013 Consumer Wash PR, a manufacturing consortium submitted the following studies to the 2013 Consumer Wash PR docket (Refs. 110 through 121):

- an embryofetal toxicity study in the rabbit;
- an embryofetal toxicity study in the rat;
- a 2-generation study in the rat;
- a 90 day subchronic dietary study in rats;
- a 90 day subchronic dermal toxicity study in rats;
- a 1-year chronic dietary toxicity study in dogs;
- an ADME study in rats;
- a rat oral carcinogenicity study; and

- a mouse oral carcinogenicity study.

All of these studies have been reviewed by FDA. Some of the data were found to be adequate to fill some of the safety data gaps for a GRAS determination for benzalkonium chloride. Data gaps remain for the following endpoints: Human pharmacokinetic data under maximal use condition, animal dermal carcinogenicity and animal ADME data, and data on antimicrobial resistance to benzalkonium chloride.

a. Summary of benzalkonium chloride safety data.

Benzalkonium chloride ADME data. ADME studies of ADBAC in rats of both sexes were conducted using the oral and the intravenous (IV) routes of administration. In the oral studies, rats were administered radiolabeled benzalkonium chloride using the following cohorts: A low-dose single oral administration study (10 mg/kilogram (kg)), a low-dose repeated oral administration study (10 mg/kg) and a high-dose single oral administration study (50 mg/kg) (Ref. 115). For the low-dose repeated oral administration study, rats were treated via freely available feed containing 100 parts per million (ppm) of non-radiolabeled benzalkonium chloride for 14 days, followed by administration of 10 mg/kg benzalkonium chloride by oral gavage. Benzalkonium chloride was found to be excreted mainly via the feces in rats after oral administration. In all of the treated groups, the average amount of radioactivity recovered was 87 to 99 percent in the feces and 5 to 8 percent in the urine.

In a separate group of animals tested in the same study, a single low-dose of 10 mg/kg benzalkonium chloride was administered to rats of both sexes. The average amount of radioactivity recovered following IV dosing was 45 to 55 percent in the feces and 20 to 30 percent in the urine. Tissue residues of radioactivity were less than 1 percent of the orally administered dose in all groups and 30 to 35 percent of the IV dose. No significant changes were

noted when comparing the ADME profile of high dose versus low dose-treated rats. Although the available ADME data from nondermal routes of exposure are sufficient to characterize the ADME profile of benzalkonium chloride following nondermal exposure, they are not sufficient to characterize the ADME profile after dermal exposure. Studies on animal ADME after dermal exposure to benzalkonium chloride will need to be submitted to FDA for review, in order to complete a GRAS determination for benzalkonium chloride.

Benzalkonium general toxicity data. Two subchronic 90-day toxicity studies in rats were submitted, one dermal and the other dietary (oral). A 1-year chronic oral toxicity study in dogs was also submitted. In the oral rat study, benzalkonium chloride was administered via feeding with concentrations ranging from 0 to 8,000 ppm (Ref. 111) for 13 weeks. Among rats treated with 4,000 and 8,000 ppm benzalkonium chloride, an increased incidence in mortality and overt toxicity was seen. A no adverse effect level (NOAEL) of 500 ppm was noted, which correlated with a mean daily dose of 31.2 mg/kg in males and 38.3 mg/kg in females.

A 1-year chronic oral toxicity study in dogs was also submitted. Dogs were chronically administered benzalkonium chloride via feeding in concentrations ranging from 0 to 1,200 ppm for 1 year (Ref. 114). Changes in body weight included reduced absolute body weight and reduced body weight gain in males and females in the highest group tested (1,200 ppm), which correlated with a reduction in food consumption. At 1,200 ppm, cholesterol levels were reduced by about 10 percent in both males and females ($p \leq 0.01$). No specific organ toxicity was identified. Based on the changes in body weight and food consumption at 1,200 ppm, a NOAEL of 400 ppm was determined, which corresponds to 13.1 and 14.6 mg/kg/day in males and females, respectively.

In the dermal toxicity study, rats were topically exposed to benzalkonium chloride in concentrations ranging from 0 (water) to 1.0 percent (which correspond to 0 to 20 mg/kg/day) over a 13-week treatment period (Ref. 113). Slight local irritation and hyperkeratosis (thickening of the epidermis) were observed in all treatment groups (including control) in both sexes. All findings were limited to the treatment site. Under the conditions of this study, the NOAEL was 20 mg/kg (1.0 percent). Toxicokinetic data were not collected; therefore, systemic exposure to benzalkonium chloride was not characterized. Consequently, dermal ADME (toxicokinetic) data is still needed to characterize benzalkonium chloride.

Benzalkonium chloride carcinogenicity data. Two oral carcinogenicity studies, one in the rat and another in the mouse, were submitted (Refs. 117 through 121). Both studies were conducted in the 1980's prior to the current ICH guidelines. They were conducted according to the OECD (Organisation for Economic Co-operation and Development) guidelines⁸ and designed to meet the requirements of EPA's regulations, which use a different type of exposure risk assessment analysis than is used by FDA for drug products.

A 78-week dietary carcinogenicity study was conducted in mice with benzalkonium chloride concentrations of 500, 1,000, and 1,500 ppm, corresponding to approximately 15, 73, and 229 mg/kg/day in males and 18, 92, 289 mg/kg/day in females (Refs. 120 and 121). Findings were limited to decreased body weight in both males and females treated with the highest dose compared to controls (7 percent and 5 percent at week 78 in males and females, respectively). There were no treatment-related increases in the incidence of neoplasms at any of the doses tested.

⁸ http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

A 2-year oral carcinogenicity study was conducted in rats with benzalkonium chloride concentrations of 300, 1,000, and 2,000 ppm, corresponding to 13, 44, and 88 mg/kg/day, respectively, in males, and to 17, 57, and 116 mg/kg/day, respectively, in females (Refs. 117 through 119). No treatment-related increases in the incidence of neoplasms were observed at any of the tested doses.

There were no treatment-related neoplasms in either oral carcinogenicity study. Though the mouse study is suboptimal because of its relatively short duration (78 weeks), we believe these two studies are adequate to fill the oral carcinogenicity data gap for benzalkonium chloride.

No dermal carcinogenicity studies of benzalkonium chloride have been submitted to FDA. The available data are not adequate to assess the carcinogenic potential of benzalkonium chloride. We propose that dermal carcinogenicity studies are still needed to complete a GRAS determination for benzalkonium chloride.

Benzalkonium chloride DART data. A developmental toxicity study conducted in rabbits showed some increase (not dose-related) in the incidence of certain visceral and skeletal malformations among benzalkonium chloride-treated rabbits relative to concurrent controls (Ref. 110). None of the findings were considered significant. Some of the mated dams proved to be not pregnant; therefore, the total number of litters (13 to 15) is slightly less than the 16 to 20 recommended in the ICH S5 guideline, but further benzalkonium chloride DART data are not necessary to make a GRAS determination.

In a developmental toxicity study in rats, the animals were administered benzalkonium chloride (10, 30, and 100 mg/kg/day) (Ref. 112). There were no treatment-related differences in gestational parameters, including total number of embryonic implantations, number of viable and nonviable implants. There were also no treatment-related effects on fetal body weights per litter,

or on the incidences of external, visceral, or skeletal malformations/variations. Based on these findings, a NOAEL for maternal toxicity was considered to be 10 mg/kg/day and for developmental toxicity 100 mg/kg/day.

A two-generation reproduction and development study in rats was submitted for review. Rats were exposed to benzalkonium chloride in the feed (Ref. 116). The exposure to benzalkonium chloride up to the highest dose tested of 2,000 mg/kg did not result in parental toxicity. No treatment-related reproductive effects were observed in any of the treatment groups. Findings were limited to decreases in body weight accompanied by a decrease in food consumption among treated females at 2,000 mg/kg/day and a decrease in pup body weight. Based on these findings, a NOAEL for adults and offspring was considered to be 1000 ppm (62.5 mg/kg/day).

The submitted DART studies are adequate and no additional DART studies are needed for benzalkonium chloride.

Hormonal effects. Based on the negative findings in the carcinogenicity studies and the two-generation DART studies, no signal for hormonal effects was detected and no further testing on hormonal effects will be required for benzalkonium chloride.

Antimicrobial resistance. In addition to the summaries, as discussed in the 2013 Consumer Wash PR (78 FR 76444 at 76463), FDA has reviewed studies on resistance data and antibiotic susceptibility of certain bacteria related to the development of resistance to benzalkonium chloride (Refs. 122 through 129), and determined that the available studies have examined few bacterial species, provide no information on exposure levels, and are not adequate to define the potential for the development of resistance or cross resistance. Additional data are

needed to more clearly define the potential for the development of resistance to benzalkonium chloride.

b. Benzalkonium chloride safety data gaps.

In summary, our administrative record for the safety of benzalkonium chloride is incomplete with respect to the following:

- Human pharmacokinetic studies under maximal use conditions when applied topically (MUsT), including documentation of validation of the methods used to measure benzalkonium chloride and its metabolites;
- Animal dermal ADME;
- Dermal carcinogenicity; and
- Data from laboratory studies that assess the potential for the development of resistance to benzalkonium chloride and cross-resistance to antibiotics as discussed in section VIII.C.

3. Isopropyl Alcohol

In the 1994 TFM, FDA proposed to classify isopropyl alcohol (70 to 91.3 percent) as GRAS for all consumer antiseptic washes (59 FR 31402 at 31435). FDA is now proposing to classify isopropyl alcohol as Category III for use in consumer antiseptic rubs. The GRAS determination in the 1994 TFM was based on the recommendations of the Miscellaneous External Panel, which based its recommendations on human absorption data and blood isopropyl alcohol levels (47 FR 22324 at 22329). There was no comprehensive nonclinical review of the toxicity profile of isopropyl alcohol, nor was there a nonclinical safety evaluation of the topical use of isopropyl alcohol.

a. Summary of isopropyl alcohol safety data.

As discussed in more detail in the 2015 Health Care Antiseptic PR (80 FR 25166 at 25190-25193), FDA has reviewed the following data and found the data to be sufficient to characterize the safety of isopropyl alcohol:

- DART data (Refs. 130 through 135)
- Data on the antimicrobial mechanism of isopropyl alcohol (Refs. 103 through 106, 136 through 138). Isopropyl alcohol readily evaporates from the skin after topical application. The lack of antiseptic residue on the skin indicates that the topical application of isopropyl alcohol is not likely to contribute to the development of antimicrobial resistance (Refs. 103, 105). Additional data on the development of antimicrobial resistance are not needed to make a GRAS determination.

No new data has been made available to FDA since publication of the 1994 TFM that can fill any of the remaining safety data gaps for isopropyl alcohol. The following areas of safety assessment, which were identified in the 1994 TFM and discussed in detail in the 2015 Health Care Antiseptic PR (80 FR 25166 at 25190-25193), are being updated in this document:

- Human absorption data (Refs. 1, 139 through 142). However, the data submitted and found in the literature to date do not cover maximal use of these products in an institutional setting as detailed in section VIII.C.2.
- Animal ADME data following dermal and systemic exposure to isopropyl alcohol (Refs. 143 through 149). The available dermal exposure studies have demonstrated that there is some systemic exposure to isopropyl alcohol following dermal application. However, the extent of that exposure has not been fully characterized. Moreover, absorption data following dermal absorption in animals are still needed to determine the extent of

systemic exposure following maximal dermal exposure to isopropyl alcohol-containing consumer antiseptic rub products.

- Systemic and dermal carcinogenicity data in animal models. Available data for chronic exposure to isopropyl alcohol include inhalation carcinogenicity data in rodents (Refs. 150 and 151) and a chronic 1-year dermal toxicity study in mice (Ref. 149). However, these data are not adequate to assess the systemic or dermal carcinogenic potential of isopropyl alcohol.
- Data on the hormonal effects of isopropyl alcohol. The existing data are not adequate to characterize the potential for hormonal effects of isopropyl alcohol. However, additional studies may not be needed to assess the potential hormonal effects of isopropyl alcohol if assessment of potential hormonal activity can be derived from existing (reproductive and developmental studies; chronic general toxicity data) and additional pending isopropyl alcohol (systemic and dermal carcinogenicity and ADME data) nonclinical studies, provided the appropriate endpoints are assessed.

Thus, we believe the existing evaluations need to be supplemented to fully evaluate the safety of isopropyl alcohol. As described in more detail in the 2015 Health Care Antiseptic PR (80 FR 25166 at 25190-25193), we propose that human pharmacokinetic studies under maximal use conditions when applied topically (MUsT), animal ADME studies (dermal absorption), systemic and dermal carcinogenicity studies, and data on hormonal effects are still needed to complete a GRAS determination for isopropyl alcohol.

b. Isopropyl alcohol safety data gaps.

In summary, our administrative record for the safety of isopropyl alcohol is incomplete with respect to the following:

- Human pharmacokinetic studies under maximal use conditions when applied topically (MUsT), including documentation of validation of the methods used to measure isopropyl alcohol and its metabolites;
- animal ADME (dermal absorption);
- dermal carcinogenicity;
- systemic carcinogenicity (may be waived if the MUsT data do not show absorption); and
- hormonal effects (could be derived from other endpoints).

IX. Proposed Effective Date

Based on the currently available data, this proposed rule finds that additional data are necessary to establish the safety and effectiveness of consumer antiseptic rub active ingredients for use in OTC consumer antiseptic rub drug products. Accordingly, consumer antiseptic rub active ingredients would be nonmonograph in any final rule based on this proposed rule. We recognize, based on the scope of products subject to this monograph, that manufacturers will need time to comply with a final rule based on this proposed rule. However, because of the potential effectiveness and safety considerations raised by the data for some antiseptic active ingredients evaluated, we believe that an effective date later than 1 year after publication of the final rule would not be appropriate or necessary. Consequently, any final rule that results from this proposed rule will be effective 1 year after the date of the final rule's publication in the Federal Register. On or after that date, any OTC consumer antiseptic rub drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not GRAS/GRAE or to be misbranded, could not be introduced or delivered for introduction into interstate commerce unless it is the subject of an approved new drug application or abbreviated new drug application. Any OTC consumer antiseptic rub drug

product subject to the final rule that is repackaged or relabeled after the effective date of the final rule would be required to be in compliance with the final rule, regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce.

X. Economic Analysis of Impacts

A. Introduction

We have 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). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. We believe that this proposed rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the consumer antiseptic rub product industry is mainly composed of establishments with 500 or fewer employees, we tentatively conclude that the proposed rule may have a significant economic impact on a substantial number of small entities.

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

more (adjusted annually for inflation) in any 1 year." The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

There are three active ingredients being evaluated for use as a consumer antiseptic rub in this proposed rule: Alcohol (ethanol or ethyl alcohol), isopropyl alcohol, and benzalkonium chloride. The impact of the proposed rule on OTC consumer antiseptic rub product industry will depend on the outcome of tests to determine whether these three active antiseptic ingredients are GRAS/GRAE. It is possible that none, one, two, or all three of the ingredients will be determined to be GRAS/GRAE. We consider two extreme scenarios to capture the entire range of total costs: (1) All three ingredients are deemed to be GRAS/GRAE or (2) none of the ingredients is deemed to be GRAS/GRAE.

In table 7, 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 conduct the testing discussed in 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 manufacturers conduct the testing for the three ingredients discussed in this rule but do not conduct the testing for these

ingredients for the health care antiseptic proposed rule ~~or this rule is finalized but the health care antiseptics proposed rule is not.~~

In scenario 1, all three ingredients are determined to be GRAS/E and manufacturers of products containing other ingredients will no longer be able 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 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.

Table 7.--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
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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 the 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.

FDA also examined the economic implications of the rule as required by the Regulatory Flexibility Act. If a rule will 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. This proposed rule could impose a significant economic impact on a substantial number of small entities. For small entities, we estimate the rule's one-time costs to roughly range between 0.001 and 0.16 percent of average annual value of shipments for a small business. In the Initial Regulatory Flexibility Analysis, we assess regulatory options that would reduce the proposed rule's burden on small entities, such as extending relabeling compliance times to 18 months (rather than 12 months).

The full analysis of economic impacts is available in the docket for this proposed rule (Docket No. FDA-2016-N-0124) and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

XI. Paperwork Reduction Act of 1995

This proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

XII. Analysis of Environmental Impact

We have determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XIII. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to "construe ... a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." The sole statutory provision giving preemptive effect to this proposed rule is section 751 of the FD&C Act (21 U.S.C. 379r). We have complied with all of the applicable requirements under the Executive order and have determined that the preemptive effect of this proposed rule, if finalized, would be consistent with Executive Order 13132. Through publication of this proposed rule, we are providing notice and an opportunity for State and local officials to comment on this rulemaking.

XIV. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m. Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

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9. Transcript of the October 20, 2005, Meeting of the Nonprescription Drugs Advisory Committee, available at <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4184T1.pdf>.

10. Summary Minutes of the November 14, 2008, Feedback Meeting with Personal Care Products Council and Soap and Detergent Association, OTC Vol. 230002. Available in Docket No. FDA 2015-N-0101 at <http://www.regulations.gov>.

11. Transcript of the September 3, 2014, Meeting of the Nonprescription Drugs Advisory Committee, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM421121.pdf>, 2014.

12. Comments submitted in Docket No. FDA-1975-N-0012 available at <http://www.regulations.gov> with Comment Nos. FDA-1975-N-0012-0037, FDA-1975-N-0012-0049, FDA-1975-N-0012-0068, FDA-1975-N-0012-0071, FDA-1975-N-0012-0073, FDA-1975-N-0012-0075, FDA-1975-N-0012-0081, FDA-1975-N-0012-0082,

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List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310, as proposed to be amended December 17, 2013, at 78 FR 76444, and May 1, 2015, at 80 FR 25166, is proposed to be further amended as follows:

PART 310--NEW DRUGS

1. The authority citation for part 310 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 360hh-360ss, 361(a), 371, 374, 375, 379e, 379k-1; 42 U.S.C. 216, 241, 242(a), 262.

2. In § 310.545:

a. Add paragraph (a)(27)(v);

b. In paragraph (d) introductory text, remove "(d)(42)" and in its place add "(d)(43)"; and

c. Add paragraph (d)(43).

The additions to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC)

for certain uses.

(a) * * *

(27) * * *

(v) Consumer antiseptic rub drug products. Approved as of [DATE 1 YEAR AFTER DATE OF PUBLICATION OF THE FINAL RULE IN THE FEDERAL REGISTER]:

Alcohol (ethanol and ethyl alcohol)

Benzalkonium chloride

Isopropyl alcohol

* * * * *

(d) * * *

(43) [DATE 1 YEAR AFTER DATE OF PUBLICATION OF THE FINAL RULE IN THE FEDERAL REGISTER], for products subject to paragraph (a)(27)(v) of this section.

Dated: June 24, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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