

(A) Drain the engine oil and disconnect the F723-1 line assembly from the tank fitting at the firewall, using as reference Figure 1 of Robinson Helicopter Company R66 Service Bulletin SB-21A, Revision A, dated June 6, 2017.

(B) Pinch the flanges of G805-1 angle at the minimum required to enable insertion, and insert the angle in the oil tank outlet fitting until the angle snaps in place.

(C) Connect the F723-1 line assembly to the tank fitting. Special torque nut to 675 in.-lb. Torque stripe the fitting.

(i) If the identification ink stamp is followed by a revision letter J, determine if there is a yellow dot near the ink stamp. A yellow dot indicates that the angle has been pre-installed and that no further action is required by this AD. If there is not a yellow dot near the ink stamp, install a G805-1 angle by following the procedures in paragraphs (e)(2)(i)(A) through (e)(2)(i)(C) of this AD.

(iii) If the identification ink stamp is followed by a revision letter K, no further action is required by this AD.

(f) Alternative Methods of Compliance (AMOCs)

(1) The Manager, Los Angeles ACO Branch, FAA, may approve AMOCs for this AD. Send your proposal to: Danny Nguyen, Aerospace Engineer, Los Angeles ACO Branch, Compliance and Airworthiness Division, FAA, 3960 Paramount Blvd., Lakewood, California 90712; telephone (562) 627-5247; email 9-ANM-LAACO-AMOC-REQUESTS@faa.gov.

(2) For operations conducted under a 14 CFR part 119 operating certificate or under 14 CFR part 91, subpart K, we suggest that you notify your principal inspector, or lacking a principal inspector, the manager of the local flight standards district office or certificate holding district office before operating any aircraft complying with this AD through an AMOC.

(g) Subject

Joint Aircraft Service Component (JASC) Code: 7910, Engine Oil Storage (Airframe Furnished).

(h) Material Incorporated by Reference

(1) The Director of the Federal Register approved the incorporation by reference of the service information listed in this paragraph under 5 U.S.C. 552(a) and 1 CFR part 51.

(2) You must use this service information as applicable to do the actions required by this AD, unless the AD specifies otherwise.

(i) Robinson Helicopter Company R66 Service Bulletin SB-21A, Revision A, dated June 6, 2017.

(ii) [Reserved]

(3) For Robinson Helicopter Company service information identified in this AD, contact Robinson Helicopter Company, 2901 Airport Drive, Torrance, CA 90505; telephone (310) 539-0508; fax (310) 539-5198; or at <http://www.robinsonheli.com/serve/lib.htm>.

(4) You may view this service information at FAA, Office of the Regional Counsel, Southwest Region, 10101 Hillwood Pkwy., Room 6N-321, Fort Worth, TX 76177. For

information on the availability of this material at the FAA, call (817) 222-5110.

(5) You may view this service information that is incorporated by reference at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call (202) 741-6030, or go to: <http://www.archives.gov/federal-register/cfr/ibr-locations.html>.

Issued in Fort Worth, Texas, on March 26, 2019.

Lance T. Gant,

Director, Compliance & Airworthiness Division, Aircraft Certification Service.

[FR Doc. 2019-07177 Filed 4-11-19; 8:45 am]

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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-AH97

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; finding of ineligibility for inclusion in final monograph.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing this final action establishing that certain active ingredients used in nonprescription (also known as over-the-counter (OTC)) consumer antiseptic products intended for use without water (referred to throughout as consumer antiseptic rubs or consumer rubs) are not eligible for evaluation under the OTC Drug Review for use in consumer antiseptic rubs. Drug products containing these ineligible active ingredients will require approval under a new drug application (NDA) or abbreviated new drug application (ANDA) prior to marketing. FDA is issuing this final action after considering the recommendations of the Nonprescription Drugs Advisory Committee (NDAC), public comments on the Agency's notices of proposed rulemaking, and all data and information on OTC consumer antiseptic rub products that have come to the Agency's attention. This final action finalizes the 1994 tentative final monograph (TFM) for OTC consumer antiseptic rub drug products that

published in the **Federal Register** of June 17, 1994 (the 1994 TFM), as amended by the proposed rule published in the **Federal Register** (FR) of June 30, 2016 (2016 Consumer Antiseptic Rub proposed rule).

DATES: Effective April 13, 2020.

ADDRESSES: For access to the docket to read background documents or comments received, go to <https://www.regulations.gov> and insert the docket number found in brackets in the heading of this final rule, into the "Search" box and follow the prompts, and/or go to the Dockets Management Staff, 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 20993-0002, 301-796-1032.

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I. Executive Summary

A. Purpose of the Final Rule

This document finalizes the 2016 Consumer Antiseptic Rub proposed rule. This final 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 response to several requests submitted to the 2016 Consumer Antiseptic Rub proposed rule, FDA has deferred further rulemaking on three active ingredients used in OTC consumer antiseptic rub products to allow for the development and submission to the record of new safety and effectiveness data for these ingredients. The deferred active ingredients are benzalkonium chloride, alcohol (also referred to as ethanol or ethyl alcohol), and isopropyl alcohol. Accordingly, FDA does not make a generally recognized as safe and effective (GRAS/GRAE) determination in this document for these three active ingredients for use in OTC consumer antiseptic rubs. The monograph or non-monograph status of these three ingredients will be addressed, either after completion and analysis of studies to address the safety and effectiveness data gaps of these ingredients or at another time, if these studies are not completed. As discussed below, this document describes the studies necessary as a scientific matter for the Agency to determine whether an active ingredient is GRAS/GRAE for use in consumer rubs.

The three deferred active ingredients—benzalkonium chloride, ethyl alcohol, and isopropyl alcohol—are the only active ingredients determined to be eligible for evaluation under the OTC Drug Review for use in OTC consumer antiseptic rub products. With respect to the 28 ineligible active ingredients identified in the 2016 Consumer Antiseptic Rub proposed

rule, we have not received any new information since the publication of the 2016 Consumer Antiseptic Rub proposed rule demonstrating that the active ingredients we previously proposed to be ineligible should be considered eligible for evaluation under the OTC Drug Review for inclusion in the OTC consumer antiseptic rub monograph. Accordingly, consumer antiseptic rub drug products containing any of these ineligible active ingredients require approval under an NDA or ANDA prior to marketing.

This document covers only OTC consumer antiseptic rubs that are intended for use without water. This document does not cover consumer antiseptic washes (78 FR 76444, 81 FR 61106); healthcare antiseptics (80 FR 25166, 82 FR 60474); antiseptics identified as “first aid antiseptics” in the 1991 First Aid tentative final monograph (TFM) (56 FR 33644); or antiseptics used by the food industry.

B. Summary of the Major Provisions of the Final Rule

This document finalizes the ineligibility status of the 28 active ingredients listed in section IV.C.2. No additional information was submitted demonstrating that any of the 28 ineligible active ingredients identified in the 2016 Consumer Antiseptic Rub proposed rule are eligible for evaluation under the OTC Drug Review for use in an OTC consumer antiseptic rub, and thus, these ineligible ingredients are not included in the OTC Consumer Antiseptic Rub monograph at this time. OTC consumer antiseptic rub products containing these ineligible ingredients are new drugs for which approved NDAs or ANDAs are required prior to marketing.

Requests were made that benzalkonium chloride, ethyl alcohol, and isopropyl alcohol be deferred from consideration in this consumer antiseptic rub document to allow more time for interested parties to complete necessary studies to fill the safety and effectiveness data gaps identified in the 2016 Consumer Antiseptic Rub proposed rule for these ingredients. In October 2017, we agreed to defer

rulemaking on these three ingredients (see Docket No. FDA–2016–N–0124 at <https://www.regulations.gov> and also <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm538131.htm>).

C. Costs and Benefits

This document defers regulatory action for three consumer antiseptic rub active ingredients (ethyl alcohol, isopropyl alcohol, and benzalkonium chloride) that are eligible for evaluation under the OTC Drug Review for use in OTC consumer antiseptic rub products, while establishing that all other consumer rub active ingredients are ineligible for evaluation under the OTC Drug Review and OTC consumer antiseptic rubs containing these ineligible active ingredients require approval under an NDA or ANDA prior to marketing. The costs of this document are associated with the reformulation and relabeling of consumer rub products that currently contain ineligible active ingredients. The benefits of this document include consumers’ reduced exposure to potentially unsafe consumer antiseptic rub products, as well as avoiding the deadweight loss associated with reduced consumption of ineffective products. FDA is only able to monetize the costs of this document. We estimate that the present value of the one-time costs associated with compliance range from \$1.07 million to \$2.50 million with a primary estimate of \$1.87 million. Annualizing upfront costs over a 10-year period at a discount rate of 3 percent, the costs of this document are estimated to be between \$0.13 million and \$0.29 million per year; the corresponding estimated cost at a discount rate of 7 percent is between \$0.15 million and \$0.36 million per year.

The full discussion of economic impacts is available in Docket No. FDA–2016–N–0124 and at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation	What it means
ANDA	Abbreviated New Drug Application.
ANPR	Advanced Notice of Proposed Rulemaking.
ASTM	American Society for Testing and Materials International.
ATCC	American Type Culture Collection.
ATE	Average Treatment Effect.
CFR	Code of Federal Regulations.
FDA	Food and Drug Administration.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FR	Federal Register.

Abbreviation	What it means
GRAS/GRAE	Generally Recognized as Safe/Generally Recognized as Effective.
MBC	Minimum Bactericidal Concentration.
MIC	Minimum Inhibitory Concentration.
MUsT	Maximal Usage Trial.
NDA	New Drug Application.
NDAC	Nonprescription Drugs Advisory Committee.
OTC	Over-the-counter.
PBPK	Physiologically based pharmacokinetic.
PK	Pharmacokinetic.
RIA	Regulatory Impact Analysis.
TFM	Tentative Final Monograph.
U.S.C	United States Code.

III. Introduction

In the following sections, we provide a brief description of terminology used in the OTC Drug Review regulations, an overview of OTC topical antiseptic drug products, and a more detailed description of the OTC consumer antiseptic rub active ingredients that are the subject of this document.

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 advanced notice of proposed rulemaking (ANPR) that was published in the **Federal Register** of September 13, 1974 (39 FR 33103) (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) (1978 TFM); the **Federal Register** of June 17, 1994 (59 FR 31402) (1994 TFM); the **Federal Register** of December 17, 2013 (78 FR 76444) (2013 Consumer Antiseptic Wash proposed rule); the **Federal Register** of May 1, 2015 (80 FR 25166) (2015 Health Care Antiseptic proposed rule); and the **Federal Register** of June 30, 2016 (81 FR 42912) (2016 Consumer Antiseptic Rub proposed rule) were each designated as a TFM (see table 1 in section IV.A.).

2. Category I, II, and III Classifications

The OTC drug 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 generally recognized as safe and effective, and further testing is necessary). Section 330.10 provides that any testing necessary to resolve the safety or effectiveness issues that resulted in an initial 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, the proposed rules (at the tentative final monograph stage) used 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.” Instead, the term “monograph conditions” is used in place of Category I, and “nonmonograph conditions” is used in place of Categories II and III.

B. Topical Antiseptics and Scope of Document

The OTC topical antimicrobial rulemaking encompasses a range of drug products that contain a number of active ingredients and are labeled and marketed for a variety of intended uses. The 1974 ANPR for topical antimicrobial products encompassed products for both healthcare and consumer use (39 FR 33103). The 1974 ANPR covered seven different intended uses for these products: (1) Antimicrobial soap; (2) healthcare 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 antiseptic drug products.” We published a separate TFM covering first aid antiseptics in the **Federal Register** of July 22, 1991 (56 FR 33644). We do not discuss first aid antiseptics further in this document, and this document does not address the status of first aid antiseptics.

The four remaining categories of topical antimicrobials were addressed in the 1994 TFM (59 FR 31402). The 1994 TFM covered: (1) Antiseptic hand wash (*i.e.*, consumer hand wash); (2)

healthcare 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). We do not discuss food handler antiseptics further in this document, and this document does not address the status of antiseptics for food industry use.

The 1994 TFM did not distinguish between consumer antiseptic washes and rubs and healthcare antiseptic washes and rubs. In the 2013 Consumer Antiseptic Wash proposed rule, we proposed that our evaluation of OTC antiseptic drug products be further subdivided into healthcare antiseptics and consumer antiseptics (78 FR 76444 at 76446). 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. In the 2013 Consumer Antiseptic Wash proposed rule (78 FR 76444 at 76446 to 76447) and the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912 at 42915 to 42916), we proposed that our evaluation of OTC consumer antiseptic drug products be further subdivided into consumer washes (products that are rinsed off with water, including hand washes and body washes) and consumer rubs (products that are not rinsed off after use, including hand rubs and antibacterial wipes). This document does not address the status of OTC consumer antiseptic wash or healthcare antiseptic products.

This document covers only OTC 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.).

IV. Background

In this section, we describe the significant rulemakings and public meetings relevant to this document and discuss our response to comments

received on the 2016 Consumer Antiseptic Rub proposed rule.

A. Significant Rulemakings Relevant to This Document

A summary of the significant **Federal Register** publications relevant to this document is provided in table 1. Other

publications relevant to this document are available at <https://www.regulations.gov> in FDA Docket No. 1975–N–0012 (formerly Docket No. 1975–N–0183H and Docket No. FDA–2015–N–0101).

TABLE 1—SIGNIFICANT RULEMAKING PUBLICATIONS RELATED TO CONSUMER ANTISEPTIC DRUG PRODUCTS ¹

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 (the 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, reflecting our evaluation of the Panel's recommendations and comments and data submitted in response to the Panel's recommendations.
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 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 referred to as OTC topical healthcare antiseptic drug products. These antiseptics are generally intended for use by healthcare professionals. In the 1994 TFM, 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 the 2013 Consumer Antiseptic Wash TFM, 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 Antiseptic 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 healthcare antiseptics are GRAS/GRAE. In the 2015 Health Care Antiseptic TFM, we proposed that additional data are necessary to support the safety and effectiveness of healthcare antiseptic active ingredients.
2016 Consumer Antiseptic Rub TFM (June 30, 2016, 81 FR 42912).	We issued a proposed rule to amend the 1994 TFM and to establish data standards for determining whether OTC consumer antiseptic rubs are GRAS/GRAE. In the 2016 Consumer Antiseptic Rub TFM, we proposed that additional safety and effectiveness data are necessary to support the safety and effectiveness of consumer antiseptic rub active ingredients.
2016 Consumer Antiseptic Wash Final Monograph (September 6, 2016, 81 FR 61106).	We issued a final rule finding that certain active ingredients used in OTC consumer antiseptic wash products are not GRAS/GRAE. We deferred further rulemaking on three specific active ingredients (benzalkonium chloride, benzethonium chloride, and chloroxylenol) used in OTC consumer antiseptic wash products to allow for the development and submission of new safety and effectiveness data to the record for those ingredients.
2017 Health Care Antiseptic Final Monograph (December 20, 2017, 82 FR 60474).	We issued a final rule finding that certain active ingredients used in OTC healthcare antiseptic products are not GRAS/GRAE. We deferred further rulemaking on six specific active ingredients (benzalkonium chloride, benzethonium chloride, chloroxylenol, ethyl alcohol, isopropyl alcohol and povidone iodine) used in OTC healthcare antiseptic products to allow for the development and submission of new safety and effectiveness data to the record for those ingredients.

¹ The publications listed in table 1 can be found at FDA's "Status of OTC Rulemakings" website available at <https://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 Document

In addition to the **Federal Register** publications listed in table 1, there have

been four meetings of the NDAC that are relevant to the discussion of OTC consumer antiseptic rubs' safety and

effectiveness. These meetings are summarized in table 2.

TABLE 2—PUBLIC MEETINGS RELEVANT TO CONSUMER ANTISEPTIC RUBS

Date and type of meeting	Topic of discussion
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 healthcare antiseptic effectiveness testing (Health Care Continuum Model) (Refs. 1 and 2).
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 healthcare antiseptics (Ref. 3).

TABLE 2—PUBLIC MEETINGS RELEVANT TO CONSUMER ANTISEPTIC RUBS—Continued

Date and type of meeting	Topic of discussion
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. 4).
November 2008; Public Feedback Meeting	Demonstration of the effectiveness of consumer antiseptics (Ref. 5).
September 2014; NDAC Meeting (July 29, 2014, 79 FR 44042)	Safety testing framework for healthcare antiseptic active ingredients (Ref. 6).

C. 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).¹ 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 21 CFR 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 before 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 requires FDA approval of an NDA or ANDA prior to marketing. The ineligibility of an active ingredient for evaluation under the OTC Drug Review for use in an OTC consumer antiseptic rub does not affect eligibility of that

active ingredient under any other OTC drug monograph.

1. Eligible Active Ingredients

Table 3 lists the active ingredients eligible for evaluation under the OTC Drug Review for use in OTC consumer antiseptic rubs and provides the classification proposed in the 1994 TFM and the classification proposed in the 2016 Consumer Antiseptic Rub proposed rule.

TABLE 3—CLASSIFICATION OF OTC CONSUMER ANTISEPTIC RUB ACTIVE INGREDIENTS IN THE 1994 TFM AND IN THE 2016 PROPOSED RULE

Active ingredient	1994 TFM proposal ¹	2016 Proposed rule
Alcohol 60 to 95 percent	I ²	IIISE ³ .
Isopropyl alcohol 70 to 91.3 percent	IIIE	IIIE.
Benzalkonium chloride	IIISE	IIIE.

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 healthcare antiseptic hand wash.

² "I" denotes a classification that an active ingredient is GRAS/GRAE and not misbranded.

³ "III" denotes a classification that the available data are insufficient to classify the active ingredient as GRAS/GRAE. "S" denotes safety data needed. "E" denotes effectiveness data needed.

In the 1994 TFM, alcohol was proposed to be classified as Category I, isopropyl alcohol was proposed to be classified as Category IIIE, and benzalkonium chloride was proposed to be classified as Category IIISE for use in an antiseptic hand wash or healthcare personnel hand wash. However, in the 2016 Consumer Antiseptic Rub proposed rule, we proposed to classify all three ingredients as Category IIISE for use in a consumer antiseptic rub because additional effectiveness and safety data are needed to classify each ingredient as GRAS/GRAE for this use.

FDA has deferred further rulemaking on these three active ingredients for use in OTC consumer antiseptic rubs to allow for the development and submission to the record of new safety

and effectiveness data for these three ingredients. Therefore, we do not make a GRAS/GRAE determination for these three active ingredients in this document. The monograph or nonmonograph status of these three ingredients will be addressed, either after completion and analysis of studies to address the safety and effectiveness data gaps of these ingredients or at another time, if these studies are not completed. As discussed below, this document describes the studies necessary as a scientific matter for the Agency to determine whether an active ingredient is GRAS/GRAE for use in consumer antiseptic rubs.

2. Ineligible Active Ingredients

The following list includes those active ingredients addressed in the 1994 TFM for use in antiseptic hand washes or healthcare personnel hand washes and identified in the 2016 Consumer Antiseptic Rub proposed rule as having inadequate evidence of eligibility for evaluation under the OTC Drug Review for use in an OTC consumer antiseptic rub:

- Benzethonium chloride
- Chloroxylenol
- Chlorhexidine gluconate²
- Cloflucarban
- Fluorosalan
- Hexachlorophene
- Hexylresorcinol

¹ 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 under the OTC Drug

Review based on submission of a time and extent application. (See 21 CFR 330.14.)

² Chlorhexidine gluconate 4 percent aqueous solution was also found to be ineligible for inclusion in the monograph for any healthcare

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.

- Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
- Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
- Methylbenzethonium chloride
- Nonylphenoxypoly (ethyleneoxy) ethanoliiodine
- Phenol (equal to or less than 1.5 percent or greater than 1.5 percent)
- Poloxamer iodine complex
- Povidone-iodine 5 to 10 percent
- Secondary amylicresols
- Sodium oxychlorosene
- Tribromsalan
- Triclocarban
- Triclosan
- Triple dye
- Undecoylium chloride iodine complex

In addition, as previously described in the 2016 Consumer Antiseptic Rub proposed rule, FDA received several submissions in response to the 1994 TFM requesting that the compounds identified below be included in the monograph:

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

These compounds were not addressed prior to the 1994 TFM in FDA documents related to the topical antimicrobial monograph and were not evaluated for antiseptic hand wash use by the Advisory Review Panel on OTC Topical Antimicrobial I Drug Products (Antimicrobial I Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class.

In addition, 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 classified as not GRAS/GRAE for the uses referred to in the 1994 TFM as antiseptic hand wash and healthcare personnel hand wash. In the 2016 Consumer Antiseptic Rub proposed rule, FDA explained that it would not discuss the efficacy and safety information regarding these ingredients that had been submitted to the rulemaking because none of the four active ingredients had adequate evidence of eligibility for evaluation under the OTC Drug Review for use in an OTC consumer antiseptic rub (81 FR 42912 at 42918).

FDA also explained in the 2016 Consumer Antiseptic Rub proposed rule

that if appropriate documentation was submitted for a proposed ineligible active ingredient, we could determine that the active ingredient was eligible for evaluation under the OTC Drug Review for use in an OTC consumer antiseptic rub. We have not received any information or documentation for the 28 active ingredients identified as ineligible in the 2016 Consumer Antiseptic Rub proposed rule since the proposed rule's publication demonstrating that these active ingredients are eligible for evaluation under the OTC Drug Review for inclusion in the OTC consumer antiseptic rub monograph. Accordingly, OTC consumer antiseptic rub drug products containing any of these ineligible active ingredients are new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(p)) for which approved applications under section 505 of the FD&C Act (21 U.S.C. 355) and part 314 (21 CFR part 314) of the regulations are required for marketing and which may be misbranded under section 502 of the FD&C Act (21 U.S.C. 352).

D. Updated Statistical Analysis for Efficacy

In the 1994 TFM, FDA recommended that the general effectiveness of antiseptics be assessed in several ways, including by conducting clinical simulation studies with the surrogate endpoint of the number of bacteria removed from the skin. In the 2015 Health Care Antiseptic proposed rule and the 2016 Consumer Antiseptic Rub proposed rule, FDA made revisions to the effectiveness criteria proposed in the 1994 TFM, while continuing to recommend that bacterial log reduction studies be used to demonstrate that an active ingredient is GRAE for use in a consumer antiseptic rub product. FDA recommended that these bacterial log reduction studies: (1) Include both a negative control (test product vehicle or saline solution) and an active control (an FDA-approved product); (2) have an adequate sample size to show that the test product is superior to its negative control; (3) incorporate the use of an appropriate neutralizer and a demonstration of neutralizer validation; and (4) include an analysis of the proportion of subjects who meet the recommended log reduction criteria based on a two-sided statistical test for superiority to negative control and a 95 percent confidence interval approach (81 FR 42912 at 42921 to 42922). FDA also recommended that the success rate or responder rate of the test product be significantly higher than 70 percent.

This meant that the lower bound of the 95 percent confidence interval for the proportion of subjects who met the log reduction criteria was expected to be at least 70 percent.

Consistent with the 1994 TFM, the 2015 Health Care Antiseptic proposed rule, the 2016 Consumer Antiseptic Rub proposed rule, and the 2017 Health Care Antiseptic FR, we find that bacterial log reduction studies should continue to be used to demonstrate that an active ingredient is effective for use in a consumer antiseptic rub product. Also, consistent with the 2015 Health Care Antiseptic proposed rule, the 2016 Consumer Antiseptic Rub proposed rule, and the 2017 Health Care Antiseptic final rule, subjects should be randomized to a three-arm study: Test, active control, and negative control (the test product's vehicle or saline solution). However, as outlined in the consumer antiseptic rub deferral letters (Ref. 7) and based on comments submitted on the 2015 Health Care Antiseptic proposed rule and the Agency's further evaluation of additional data, we have updated the statistical analysis related to the log reduction criteria for classifying consumer antiseptic rub active ingredients as GRAE. This updated statistical analysis is consistent with the statistical analysis set forth in the 2017 Health Care Antiseptic final rule.

Rather than using only a change in bacterial count from baseline, the updated analysis uses the average treatment effect (ATE), an estimated difference of the effect of two treatments correcting for baseline count. The ATE is estimated from a linear regression of post-treatment bacterial count (\log_{10} scale) on the additive effect of a treatment indicator and the baseline or pre-treatment measurement (\log_{10} scale). The updated analysis is designed to assess whether the ATEs across subjects meet specific conditions of superiority and non-inferiority, rather than whether the percentage of subjects who meet a specific threshold significantly exceeds 70 percent. Under the updated analysis, products must show non-inferiority of test product to active control by a margin of 0.5 (\log_{10} scale) and superiority of test product to negative control by a margin of 1.5 (\log_{10} scale). In the conditions below, the ATE of the test product compared to the negative control is defined as the contrast of treatment effect of negative control minus the treatment effect of the test drug in the linear regression. Likewise, the ATE of the active control compared to the test product is defined as the contrast of treatment effect of test product minus the treatment effect of

the active control in the linear regression.

Superiority to negative control by a specific margin is needed because our evaluation suggests that application of a negative control, whether the test product's vehicle or saline, may exhibit some minimal antimicrobial properties. Thus, using superiority to negative control by those margins will help ensure that we can appropriately assess the effectiveness of the antimicrobial products. The margins we identify in this section were derived from review and analysis of existing data and may be revised as data gaps on deferred antimicrobial products are filled.

Because of existing data gaps, we also require the deferred ingredient to show non-inferiority to active controls by a 0.5 margin (\log_{10} scale).

Accordingly, based on the updated analysis, the bacterial log reduction studies used to assess whether an active ingredient is effective for use in consumer antiseptic rubs should include the following:

- The test product should be non-inferior to an FDA-approved antiseptic rub as active control with a 0.5 margin (\log_{10} scale). That is, we expect the upper bound of the 95 percent confidence interval of the ATE of the active control compared to the test product to be less than 0.5 (\log_{10} scale). An active control is not intended to validate the study conduct or to show superiority of the test drug product but to show that the test drug product is not inferior to the control. Non-inferiority to active control should be met on each hand within 5 minutes after a single rub for the consumer antiseptic rub indication.

- The test product should be superior to the negative control by a margin of 1.5 (\log_{10} scale). That is, we expect the lower bound of the 95 percent confidence interval of the ATE of the test product compared to the negative control to be greater than 1.5 (\log_{10} scale). In cases where the vehicle cannot be used as a negative control, saline solution can be used. Based on our evaluation of the existing data, for the consumer antiseptic rub indication a superiority margin of 1.5 (\log_{10} scale) should be met on each hand within 5 minutes after a single rub.

- Include a minimum sample size of 100 subjects per treatment arm. The study can have a larger sample size in each treatment arm to meet criteria for non-inferiority and superiority after assessment of variability.

- Conduct two adequate and well-controlled clinical simulation pivotal studies for the consumer antiseptic rub indication at two separate independent

laboratory facilities by independent principal investigators.

V. Comments on the Proposed Rule and FDA Response

A. Introduction

In response to the 2016 Consumer Antiseptic Rub proposed rule, we received approximately 47 comments from an animal rights organization, healthcare professionals, a manufacturer, trade associations, and individuals. We also received additional data and information for certain deferred consumer antiseptic rub active ingredients.

We describe and respond to the comments in sections V.B. through V.E. We have numbered each comment to help distinguish among the different comments. We have grouped similar comments together under the same number, and in some cases, we have separated different issues discussed in the same comment and designated them as distinct comments for purposes of our responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value, importance, or the order in which comments were received.

B. General Comments on the Proposed Rule and FDA Response

1. Definition of Consumer Antiseptic Rubs

(Comment 1) We received comments asking FDA to revise the definition of consumer antiseptic rubs. In the 2016 Consumer Antiseptic Rub proposed rule, we stated that consumer antiseptic rubs are products that are intended to be used when soap and water are not available and are left on and not rinsed off with water (81 FR 42912 at 42913). These comments asked FDA to define consumer antiseptic rubs as products "that are intended for use when hands are not visibly soiled, or when soap and water are not practical or available and are not intended to be rinsed off with water."

(Response 1) We decline to revise the definition of consumer antiseptic rubs to add information about using or not using consumer antiseptic rubs when hands are visibly soiled. In general, information about when and how to use a drug product is contained in the product's label. In this case, the label is the appropriate place for information about using or not using consumer antiseptic rub products when hands are visibly soiled. Integrating information about such use into the definition of consumer antiseptic rubs could be problematic because whether a

consumer antiseptic rub product can be used when hands are visibly soiled could depend on the particular product's final formulation.

We also decline to incorporate the concept of practicality into the consumer antiseptic rub's definition. It is unclear what it means to say that soap and water are not "practical," or how not "practical" differs from not "available." We do not think that adding the word "practical" helps to define the category of consumer antiseptic rubs or to differentiate consumer antiseptic rubs from other products. For these reasons, we will continue to define consumer antiseptic rubs as products that are intended to be used when soap and water are not available and are left on and not rinsed off with water (81 FR 42912 at 42913).

2. GRAS/GRAE Classification of Alcohol

(Comment 2) Several comments requested that FDA reconsider its proposal in the 2016 Consumer Antiseptic Rub proposed rule to classify alcohol as a Category III (available data are insufficient to classify as safe and effective, and further testing is necessary) active ingredient. In the 1994 TFM, alcohol was proposed to be classified as a Category I (generally recognized as safe and effective and not misbranded) topical antiseptic ingredient for certain indications. Two comments argued that FDA has provided no data to indicate that there is a safety or efficacy concern or issue with alcohol. These comments noted that during the September 3, 2014, NDAC meeting, several NDAC members argued in favor of continuing to categorize alcohol as Category I while further testing is conducted to fill the data gaps about its safety.

(Response 2) As we explained in the 2017 Health Care Antiseptic final rule, we classify ingredients as Category I, Category II (not generally recognized as safe and effective or misbranded), and Category III until the final monograph stage, at which point we use the term "monograph conditions" in place of Category I, and the term "nonmonograph conditions" in place of Categories II and III (82 FR 60474 at 60482). In the 1994 TFM, alcohol was proposed to be classified as Category I for use in "antiseptic hand wash" products, which included consumer antiseptic rubs (59 FR 31402 at 31433). In the 2016 Consumer Antiseptic Rub proposed rule, we changed the proposed classification of alcohol for use in consumer antiseptic rubs from Category I to III, because we found that there were not enough data on alcohol to meet our proposed safety data requirements

(81 FR 42912 at 42918 to 42919, 42928). We explained that there had been many important scientific developments since 1994 that affected our evaluation of the safety of the active ingredients in consumer antiseptic rub products and that this, in turn, had caused us to reassess the data necessary to support a GRAS determination (81 FR 42912 at 42923). These developments include new information regarding systemic exposure to antiseptic active ingredients, the need to evaluate the potential for widespread antiseptic use to promote the development of antibiotic-resistant bacteria, and improved study designs that are more capable of detecting a potential safety risk. In the case of alcohol, we explained that the available data characterizing the level of dermal absorption and expected systemic exposure in adults as a result of topical use of alcohol-containing antiseptics do not cover maximal use of these products (81 FR 42912 at 42928). Therefore, we determined that the data regarding the safety of alcohol were insufficient to make a GRAS determination without human pharmacokinetic (PK) studies under maximal usage trial (MUsT) conditions when applied topically, including documentation of validation of the methods used to measure alcohol and its metabolites.

3. Requests for Deferrals of Final Rulemaking

(Comment 3) We received comments requesting that FDA defer rulemaking on the three active ingredients eligible for use in OTC consumer antiseptic rub products to allow for the development and submission to the record of new safety and effectiveness data for these active ingredients. One comment asserted that the studies FDA proposed could take several years to design, execute, analyze, and report, and requested that FDA defer rulemaking for alcohol and benzalkonium chloride. Another comment contended that the differences in the testing requirements between the 1994 TFM and the 2016 Consumer Antiseptic Rub proposed rule warrant an extension of time to determine essential studies that may be needed for isopropyl alcohol, protocols for those studies, review of any data generated, and submission of the data to FDA.

(Response 3) As explained earlier, in response to several requests submitted to the 2016 Consumer Antiseptic Rub proposed rule, FDA has deferred further rulemaking on the three active ingredients eligible for use in OTC consumer antiseptic rub products to allow for the development and

submission to the record of new safety and effectiveness data for these ingredients. The deferred active ingredients are benzalkonium chloride, alcohol (also referred to as ethanol or ethyl alcohol), and isopropyl alcohol. For each active ingredient, FDA has deferred rulemaking for 1 year, with the possibility of renewal, which allows the Agency to monitor the continued progress of the studies being conducted (Ref. 7).

4. Labeling

(Comment 4) One comment stated that the labeling of consumer antiseptic rub products should contain the established name of the drug and identify the product using “Antiseptic Rub,” “Antiseptic Hand Rub,” “Antimicrobial rub,” “Antimicrobial hand rub,” “Hand Sanitizer,” “Antiseptic Hand Sanitizer,” or “Antimicrobial Hand Sanitizer.” The comment contended that “Hand Sanitizer” is the term that is the most recognized and understood by consumers and that a change in terminology could cause confusion. The comment also recommended that FDA clarify that the Drug Facts label for consumer antiseptic rubs can use the header “Use/s” in place of “Indication,” since “Use” is more easily understood by consumers, and also recommended certain terminology to describe the products’ use. In addition, the comment proposed that the “Directions” section of the Drug Facts label for consumer antiseptic rubs reflect the parameters used when product efficacy was demonstrated. Other comments proposed that the Directions section include clear and specific instructions for proper use, such as the number of pumps required to adequately coat the hand, as well as information on products’ shelf lives.

(Response 4) As we explained in the 2016 Consumer Antiseptic Rub proposed rule, the labeling for consumer antiseptic rub products containing a particular active ingredient will be addressed as part of the final rule if FDA determines that the active ingredient is GRAS/GRAE (81 FR 42912 at 42913). Because all three of the active ingredients that are eligible for evaluation for use in consumer antiseptic rubs have been granted deferrals, and FDA has not yet made a GRAS/GRAE determination on these ingredients, we do not address their labeling in this document. If any of the three active ingredients are subsequently found to be GRAS/GRAE, we will address the labeling for products containing that active

ingredient in the applicable final monograph.

5. Implementation and Compliance

(Comment 5) We received comments stating that one benefit of the consumer antiseptic rub rulemaking is that consumer antiseptic rub products containing potentially harmful active ingredients will be removed from the market. One comment asked what steps FDA will take to remove “substandard” products from the market.

(Response 5) In section VII, we explain that we recognize that manufacturers will need time to comply with this document. Thus, as proposed in the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912 at 42930 to 42931), this document will be effective 1 year after the date of the document’s publication in the **Federal Register**. On or after that date, any OTC consumer antiseptic rub drug product containing an active ingredient that we have found in this document to be ineligible for consideration under the OTC Drug Review for the OTC consumer antiseptic rub monograph cannot be introduced or delivered for introduction into interstate commerce unless it is the subject of an approved NDA or ANDA. FDA strives to minimize risk to consumers by monitoring the market and, where appropriate, undertaking efforts to remove violative OTC drug products from the market.

6. Public Education

(Comment 6) A number of comments included questions or concerns about the ways in which FDA communicates with consumers about the antiseptic rulemakings. One comment asked how the general public is notified of the Agency’s findings. Another comment argued that educating the public on antiseptic products is necessary because the products’ labeling lacks specificity and because consumers may not take the time to read the labeling. Another comment asked FDA to be cautious in its communications with consumers about the Agency’s work on the antiseptic monographs. This comment pointed to a September 12, 2016, posting on FDA’s website entitled “Antibacterial Soap? You Can Skip It—Use Plain Soap and Water.” The comment argued that the headline misleadingly implies that antibacterial soaps in any setting (and also, by implication, potentially any topical antimicrobial product) do not work. This comment also criticized FDA’s claim that antibacterial soaps “may do more harm than good over the long term.” The comment asked that FDA be clear in its communications that alcohol

(when used as an active ingredient in topical antiseptic products) has no known safety signals and there is no reason to believe that alcohol-based hand sanitizers are associated with creating “supergerms” or antibacterial resistant organisms.

(Response 6) FDA communicates about its various activities, including the findings it has made as part of the antiseptic rulemaking, in several ways. Each of the various antiseptic rulemakings has an official docket, which is publicly available and can be accessed at <https://www.regulations.gov>. These dockets contain the proposed and final rules in which FDA sets forth its findings, along with various supporting documents. FDA also communicates with the public through our website. The entire rulemaking history for OTC antiseptic products can be found at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm070821.htm>. In addition, FDA communicates with Congress, consumers, industry, and other stakeholders, such as patient advocacy groups and professional associations, through press releases and our accounts on social media sites, including Facebook, Twitter, and LinkedIn. We appreciate and will take under consideration the commenters’ suggestions regarding our communications with consumers about the antiseptic rulemakings.

7. Overlapping Data Requirements and Collections

(Comment 7) We received comments asking that data that are collected to fill in a data gap for one antiseptic indication or in response to one proposed or final rule also be applied to fill in data gaps for other antiseptic indications or rules. The comments stated that studies conducted and data submitted to support a finding that an active ingredient is GRAS/GRAE for a healthcare antiseptic indication or for use as a consumer antiseptic wash should also provide sufficient support for a finding that the ingredient is GRAS/GRAE for use as a consumer antiseptic rub. One comment argued that safety and efficacy data submitted for the healthcare personnel hand rub use will be particularly relevant to the consumer antiseptic hand rub use. The comments specifically anticipated that MUSt studies performed to support healthcare indications would also support consumer indications, because maximal usage in a healthcare setting would exceed maximal usage in the various consumer settings. Because of

this, the comments asked FDA to consolidate MUSt requirements and testing between the different indications and the different monographs to minimize the number of trials needed.

(Response 7) Whenever it is scientifically appropriate to do so, publicly available efficacy and safety data developed to support one use of an antiseptic active ingredient may be cross referenced to support other uses. Generation of duplicative data is not necessary. We agree that the PK data generated from a MUSt study that is sufficient to support a healthcare antiseptic indication will also be sufficient to support a consumer antiseptic indication, because the maximal usage across consumer settings is lower than the maximal usage in a healthcare setting.

C. Comments on Effectiveness and FDA Response

1. In Vitro Testing

(Comment 8) One comment requested that FDA clarify the in vitro testing requirements that the Agency proposed in the 2016 Consumer Antiseptic Rub proposed rule for evaluating active ingredients for use in consumer antiseptic rubs (81 FR 42912 at 42921). The comment asked whether FDA is requiring minimum bactericidal concentration (MBC), minimum inhibitory concentration (MIC), and time-kill testing using the bacteria specified in the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912 at 42921). The comment then asked whether time-kill testing alone would suffice to meet the in vitro testing requirements. Finally, the comment asked why FDA did not provide an American Type Culture Collection (ATCC) number for the three strains of gram-negative bacteria specified in the 2016 Consumer Antiseptic Rub proposed rule—*Haemophilus influenzae*, *Bacteroides fragilis*, and *Enterobacter* species.

(Response 8) The in vitro testing requirements for consumer antiseptic rubs are specified in the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912 at 42921). We require MBC or MIC testing of 25 representative clinical isolates and 25 reference (e.g., ATCC) strains of each of the microorganisms listed in section VII.B.1 of the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912 at 42921). We also require time-kill testing of each microorganism and ATCC strain listed in section VII.B.1 of the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912 at 42921). Alternative approaches to filling

the relevant data gaps are unlikely to be sufficient.

The Agency has not specified ATCC strain numbers for *H. influenzae*, *B. fragilis*, and *Enterobacter* species in order to provide manufacturers with options for conducting the necessary studies. Manufacturers may select any available strain of these bacteria. For MBC or MIC testing, 25 representative clinical isolates and 25 reference (ATCC) strains of each one of these organisms (*H. influenzae*, *B. fragilis*, and *Enterobacter* species) are necessary. For time-kill testing, any one ATCC strain for these three organisms is sufficient.

2. In Vivo Testing

(Comment 9) We received comments on the in vivo efficacy testing requirements that the Agency proposed in the 2016 Consumer Antiseptic Rub proposed rule for evaluating active ingredients for use in consumer antiseptic rubs (81 FR 42912 at 42921). One comment asked that we confirm that the following test conditions are suitable:

- Two pivotal studies would be conducted.
- A single use wash would be applied.
- A physiological saline solution would be used as the control.
- Avagard, the only healthcare personnel hand rub approved under an NDA would be used as the active control, if pilot studies confirm its appropriateness.

(Response 9) Based on the updated statistical analysis for efficacy that we outline in section IV.D., we confirm that two adequate and well-controlled clinical simulation pivotal studies should be conducted for the consumer antiseptic rub indication at two separate independent laboratory facilities by independent principal investigators. These studies should include a minimum sample size of 100 subjects per treatment arm for each of the deferred ingredients (alcohol, benzalkonium chloride, and isopropyl alcohol). This sample size will ensure that the ATE will be estimated precisely for the deferred ingredients and can be used for future reference in final product monographs. To determine the minimum sample size, FDA analyzed several studies that included a wide range of sample sizes and concluded that a minimum of 100 subjects is appropriate to support the external validity of the results. We note that establishing a minimum sample size of 100 subjects per study arm was not solely based on statistical considerations; multiple factors, including robustness and sensitivity of

log reduction to experimental conditions, were taken into account. The study could have a larger sample size to meet the criteria for non-inferiority and superiority after an assessment of variability.

We also confirm that it is appropriate to study a single rub application of the active ingredient being tested for use as a consumer antiseptic rub. In the 2016 Consumer Antiseptic Rub proposed rule, we proposed revisions to the log reduction criteria for consumer antiseptic rubs based on the recommendations of the March 2005 NDAC meeting and comments to the 1994 TFM, which argued that the demonstration of a cumulative antiseptic effect for these products is unnecessary (81 FR 42912 at 42922). We agreed that the critical element of effectiveness is that a product must be effective after the first application because that represents the way in which consumer antiseptic hand rubs are used. Given that we are no longer requiring a cumulative antiseptic effect, the efficacy criteria were revised to reflect a single product application.

Finally, as noted in section IV.D., with regard to the negative control used in the studies, saline solution is appropriate, but only if the test vehicle cannot be used. With regard to the active control used in the studies, an FDA-approved antiseptic rub product should be selected. We have discussed and will continue to discuss the selection of an appropriate active control with the manufacturers and trade organizations that requested the deferrals for alcohol, benzalkonium chloride, and isopropyl alcohol (see Docket Nos. FDA-2015-N-0101 and FDA-2016-N-0124 at <https://www.regulations.gov>).

(Comment 10) Comments proposed that the Agency recognize specific ASTM (American Society for Testing and Materials International) protocols as standardized test methods for demonstrating that an active ingredient is GRAE for use in consumer antiseptics. These ASTM protocols include ASTM E2755-15 "Standard Test Method for Determining the Bacteria-Eliminating Effectiveness of Healthcare Personnel Hand Rub Formulations Using Hands of Adults," ASTM E1054-08 "Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents", and ASTM E2783-11 "Standard Test Method for Assessment of Antimicrobial Activity for Water Miscible Compounds Using a Time-Kill Procedure."

(Response 10) We have reviewed these test methods and believe they may be useful to help establish GRAE status

for the three deferred antiseptic active ingredients for use in consumer antiseptic rub products. We are currently discussing with manufacturers and trade organizations that requested the deferrals how these test methods may be used to meet the current effectiveness criteria (see Docket Nos. FDA-2015-N-0101 and FDA-2016-N-0124 at <https://www.regulations.gov>).

(Comment 11) Comments were submitted that addressed the testing requirements for the final formulations of specific consumer antiseptic rub products. Comments argued that neither MIC nor MBC testing should be necessary for final formulations. The comments contended that an in vitro time-kill study against an appropriate list of relevant microorganisms would suffice; one comment set forth specific recommendations for the conduct of such a study.

With regard to in vivo efficacy testing requirements, comments argued that full-scale pivotal studies of final formulations should not be necessary, because less burdensome testing can confirm that a product's formulation has not inhibited the activity of the active ingredient. Comments suggested confirmatory in vivo testing comparing a finally formulated product to an active control after a single use. One comment argued that an active ingredient that was found to be GRAS/GRAE should be the active control, not an approved product. The comment noted that the only approved alcohol-based hand sanitizer has two active ingredients. Another comment proposed a specific study design with recommended success criteria.

Finally, one comment recommended that a dermatological evaluation be conducted on finally formulated consumer antiseptic rub products to ensure skin safety.

(Response 11) In this document, we do not find any active ingredients GRAS/GRAE for use as a consumer antiseptic rub. As a result, this document does not specifically address requirements for anticipated final formulation testing. The testing requirements for finally formulated products containing one of the three deferred active ingredients will be addressed after one or more of the active ingredients are found to be GRAS/GRAE for use in consumer antiseptic rub products.

D. Comments on Safety and FDA Response

1. Need for Additional Safety Data

(Comment 12) One comment objected to the fact that FDA based its decision

to require additional safety data on the fact that systemic exposure is higher than previously thought, and new information is available about the potential risks from systemic absorption and long-term exposure (80 FR 42912 at 42923). The comment argued that before FDA could require additional safety data, it would need to present "definitive evidence" that systemic exposure is higher than previously thought. The comment also argued that the evidence should consist of either in vitro or dose-dependent data, and not risk, because, the comment explained, the commenter was unaware of FDA's current thinking regarding risk assessment.

(Response 12) We do not agree that FDA can only require additional safety data if there is "definitive evidence" in the form of in vitro or dose-dependent data that systemic exposure is higher than we believed it to be when the 1994 TFM was published. In the 2016 Consumer Antiseptic Rub proposed rule, we explained that, 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. 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. 8 to 10). Given the frequent repeated use of consumer antiseptic rubs, systemic exposure may occur. Although some systemic exposure data exist for all three deferred consumer antiseptic rub active ingredients, data on systemic absorption after maximal use are lacking. We believe that the degree of systemic exposure should be determined, and its consequences assessed, to support our risk-benefit analysis for consumer antiseptic rub use.

(Comment 13) Some comments argued that FDA should do a more robust analysis of existing safety data about human exposure and risk and that this analysis should precede any proposal requiring additional testing. Comments also argued that, in declining to find ingredients GRAS based on existing information, FDA is inappropriately discounting the significant human marketing experience and global acceptance of consumer antiseptic hand rub products and the low incidence of adverse events. The comments assert that the low incidence of adverse events is evidenced by the fact that FDA's Safety Information and

Adverse Event Reporting Program, MedWatch, contains no safety-related complaints related to topical antiseptic products, and by the fact that FDA has not issued any safety alerts regarding such products. A comment also stated that the Nurses' Health Studies, which are a series of long-term studies of health outcomes in several large cohorts of nurses, provide evidence of the safety of topical antiseptics. The comment asserted that these studies did not show any evidence that the use of topical antiseptic products leads to adverse health outcomes in nurses.

(Response 13) FDA summarized the existing data and information on the three deferred active ingredients alcohol, benzalkonium chloride, and isopropyl alcohol in the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912 at 42927 to 42930). As explained in the 2016 Consumer Antiseptic Rub proposed rule, the existing data and information support the conclusion that there is the potential for systemic exposure to antiseptic active ingredients through repeated dermal applications. At the same time, we lack the PK data that would tell us precisely the degree of systemic exposure under maximal use conditions. In addition, in vivo animal safety and toxicokinetic data are lacking for some ingredients. Both human and animal data are needed to determine the safety margin for OTC human use. If there is publicly available data or information regarding the three deferred active ingredients that FDA has not found or has overlooked, that information can be submitted to the docket and considered by the Agency.

(Comment 14) One comment argued that FDA should consider the level of human exposure to each of the antimicrobial active ingredients and assess the potential for harm from those exposures prior to determining the need for additional safety data. The comment states that in assessing exposure to active ingredients in consumer antiseptic rub products, FDA should allow alternative methods to MUsT studies, including physiologically based pharmacokinetic (PBPK) models and potentially other animal or human studies. The comment also states that FDA should provide additional guidance on how a MUsT study may be conducted in a reasonable manner.

(Response 14) In the 2017 Health Care Antiseptic final rule, we explained that the MUsT paradigm has been used in the evaluation of topical dermatological agents approved in the United States since the early 1990s (82 FR 60474 at 60492 to 60493). It represents over 20 years of interactions with multinational drug companies, during which time the

study design has been refined into its current state. Moreover, the MUsT is a published methodology that has been presented at both national and international meetings. We also explained that we understand and recognize the potential of PK and PBPK modeling. FDA has considered these options and others and has concluded that currently, they are not validated adequately to substitute for the MUsT described in the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912 at 42923 to 42924) and the 2015 Health Care Antiseptic proposed rule (80 FR 25166 at 25182). FDA has been reviewing the MUsT protocol designs submitted by the manufacturers and trade organizations that requested deferrals of the three consumer antiseptic rub active ingredients and is currently discussing protocol design issues with these manufacturers and trade organizations.

With regard to the recommendation that FDA provide guidance on MUsT studies, in May 2018 the Agency issued a draft guidance for industry entitled "Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations" (Ref. 11). The guidance, when finalized, will outline FDA's recommendations for designing and conducting a MUsT, which, based on input from the NDAC, FDA has determined is generally important to support a GRAS/GRAE determination for a topical active ingredient. The guidance, when finalized, will address critical study elements, data analysis, and considerations for special topic areas (e.g., pediatrics, geriatrics). The guidance, when finalized, will also encourage study sponsors to seek feedback from FDA on their overall approach and the design of a particular study.

(Comment 15) One comment argued that FDA should not require additional carcinogenicity studies for benzalkonium chloride. This comment stated that a good quality systemic carcinogenicity data set exists for benzalkonium chloride, along with data from in vitro genetic toxicology studies. The comment contended that, given that no tumors developed in an oral study of the product, and provided that good quality in vitro genetic toxicity data are available, a dermal study should not be necessary. The comment also contended that it is highly unlikely that the dermal route of administration would result in a higher systemic exposure than the oral route of administration.

(Response 15) As we stated in the 2016 Consumer Antiseptic Rub

proposed rule, no dermal carcinogenicity studies of benzalkonium chloride have been submitted to FDA (81 FR 42912 at 42929). Although, as the comment states, we have data generated by two oral carcinogenicity studies, the potential for topically applied benzalkonium chloride to cause skin cancer remains unstudied. There are no validated methods currently known to the Agency for predicting dermal carcinogenicity risk from data generated in studies that employed a non-dermal route of administration. As we explained in the 2016 Consumer Antiseptic Rub proposed rule, the magnitude of exposure to the skin from a topical product can be much higher than would be covered by systemic studies (81 FR 42912 at 42926). 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 (81 FR 42912 at 42926). Data on the potential for benzalkonium chloride to induce a neoplastic response in the skin with repeated dermal application are necessary in order to assess the safety of benzalkonium chloride for use in consumer antiseptic rub products.

(Comment 16) One comment stated that there are data suggesting that some antiseptic active ingredients have hormonal effects. The comment asked why products containing active ingredients with hormonal effects are still on the market.

(Response 16) As we explained in the 2016 Consumer Antiseptic Rub proposed rule, with the exception of human pharmacokinetic data under maximal use conditions, there are adequate safety data to determine that alcohol is GRAS (81 FR 42912 at 42928). This includes adequate data on the hormonal effects of alcohol in animals and humans. Similarly, although there are other gaps in the safety data for benzalkonium chloride, there are adequate data to make a determination that benzalkonium chloride does not have hormonal effects (81 FR 42912 at 42928 to 42930). With regard to isopropyl alcohol, the existing data are not adequate to characterize its potential for hormonal effects (81 FR 42912 at 42930). As we explained in section IV.C.1., FDA has deferred further rulemaking on alcohol, benzalkonium chloride, and isopropyl alcohol to allow for the development and submission to the record of new safety and effectiveness data for these ingredients. This includes the data necessary to

characterize isopropyl alcohol's potential for hormonal effects.

2. Animal Testing Issues

(Comment 17) Comments argued that numerous scientific and regulatory bodies have performed exposure-driven risk assessments of antiseptic products and have not requested the types of animal and human study data that FDA is requiring before making a finding that such products are safe. Comments asserted that under standard international practice, safety evaluations for antiseptic ingredients are based on conservative assumptions of exposure and potential differences between species, rather than correlation of findings from animal toxicity studies to humans based on kinetic information from both animals and humans.

One comment requested that FDA expand its discussion of ways in which animal use may be minimized and feature this discussion more prominently in rulemaking. These include that efficacy testing take precedence over safety testing, that sharing of data be required, that route-to-route extrapolation be accepted for carcinogenicity studies, and that data from human-relevant, non-animal methods be accepted. This comment stated that if FDA does not have a policy regarding the use of alternatives to animal testing, the Agency should thoroughly evaluate their applicability in each individual case.

With regard to benzalkonium chloride in particular, one comment argued that additional animal testing should not be necessary unless the following conditions are met:

- Use of conservative approaches to calculate the margin of exposure is inadequate.
- The margin of exposure justifies the need for more data, but it is not possible to generate the data by non-animal approaches, such as using PBPK modeling, or through animal alternative test methods.
- There is a perceived need for all ingredients to have the same type of information.

Another comment pointed to proprietary data cited by the Environmental Protection Agency and the Cosmetic Ingredient Review to support their findings that benzalkonium chloride is safe for use in disinfectants and cosmetics. The Cosmetic Ingredient Review report summarizes data from a tumorigenicity study in mice and rabbits in which ulceration and inflammation, but no tumors, were observed. The comment urged FDA to try to obtain these data to avoid duplicative testing.

(Response 17) We understand that animal use in tests for the efficacy and safety of human and animal products has been and continues to be a concern. FDA is an active partner in efforts to reduce, refine, or replace (known as the 3Rs) the use of animals in drug development (Ref. 12). In general, however, there continues to be a need for data from studies conducted in living, intact mammalian systems, when there are currently no viable and validated alternatives in place to address the myriad questions inherent to the drug safety assessment process including determining the many interrelated local and systemic endpoints that are of concern in the overall safety assessment for an ingredient. The animal testing described in the deferral letters for each of the three deferred consumer antiseptic rub active ingredients was proposed in response to and in concurrence with NDAC guidance to generate the publicly available data needed to fill identified data gaps. The Agency remains open to considering data generated using non-animal methods.

We emphasize that FDA does not require that studies in animals be conducted before studies in humans. In fact, until human MUsT data have been generated and evaluated, we will not have the evidence of systemic bioavailability that would trigger the need for certain studies in animals. The need for studies could also be triggered by an adequately conducted toxicology program that reveals a safety signal for the ingredient or for any known structurally similar compound, and thereby, indicates the potential for adverse effects at exposure levels lower than those that result from maximal usage. If data generated from safety or efficacy testing in humans fail to meet the minimum criteria for a GRAS/GRAE determination, it may not be necessary to conduct animal studies including a dermal carcinogenicity study, an oral carcinogenicity study, embryofetal development studies in rodents and non-rodents, a fertility and early embryonic development study, and a pre- and post-natal development study.

With regard to the proposal to incorporate route-to-route extrapolation in assessing potential carcinogenicity risk, for drug products whose primary route of administration is via topical dermal application, a target tissue of concern is the skin and associated substructures. As we explained earlier, there are no validated methods currently known to the Agency for predicting dermal carcinogenicity risk from data generated in studies that employed a non-dermal route of

administration. Data on the potential for the active ingredient under study to induce a neoplastic response in the skin with repeated dermal application are necessary in order to assess the safety of alcohol, benzalkonium chloride, and isopropyl alcohol for use in consumer antiseptic rub products. If these data adequately confirm a lack of carcinogenicity potential in the skin and, further, raise no concerns of any systemic targets of toxicity, and if an adequately conducted MUsT demonstrates low systemic bioavailability of the active ingredient, then an oral carcinogenicity study, a fertility and early embryonic development study, and a pre- and post-natal development study are unlikely to be necessary to support a GRAS/GRAE determination, again unless an adequately conducted toxicology program reveals safety signals for a particular active ingredient or for any known structurally similar compound. Total animal usage would thereby be reduced significantly.

3. Bacterial Resistance Testing

(Comment 18) Comments relating to the issue of bacterial resistance were submitted in response to the 2016 Consumer Antiseptic Rub proposed rule. In general, the comments were split with regard to whether antiseptics pose a public health risk from bacterial resistance. Some comments agreed that the pervasive use of consumer antiseptic rubs poses a risk for the development of bacterial resistance. Other comments disagreed and criticized the data on which they believe FDA based its concerns.

Specifically, comments dismissed the in vitro data cited by FDA in the proposed rule as not reflecting real-life conditions. The comments argued that the most useful assessment of the risk of biocide resistance and cross-resistance to antibiotics are in-situ studies, studies of clinical and environmental strains, or biomonitoring studies. Some comments asserted that studies of these types have reinforced the idea that resistance and cross-resistance associated with antiseptics is a laboratory phenomenon observed only when tests are conducted under unrealistic conditions. One comment stated that there is little credible evidence that antiseptic products play any role in antibiotic resistance in human disease. The comment stated that, while some in vitro lab studies have been successful in forcing expression of resistance to antiseptic active ingredients in some bacteria, real world data from community studies using actual product formulations show no correlation

between the use of such products and antibiotic resistance. The comment stated that further evidence of real-world data showing no antimicrobial resistance development after the continued use of consumer products containing antimicrobial active compounds can be extracted from oral care clinical studies, which provide *in vivo* data, under well-controlled conditions, on exposure to antimicrobial-containing formulations over prolonged periods of time (e.g., 6 months to 5 years). The comment also cited the conclusions of an International Conference on Antimicrobial Research held in 2012 on a possible connection between biocide (antiseptic or disinfectant) resistance and antibiotic resistance to support the point that there is no correlation between antiseptic use and antibiotic resistance.

(Response 18) As explained in the 2016 Consumer Antiseptic Rub proposed rule, we continue to believe that the development of bacteria that are resistant to antibiotics is an important public health issue, and that 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 (81 FR 42912 at 42926). Thus, we have conducted ingredient-specific reviews of the literature pertaining to antiseptic resistance and antibiotic cross-resistance, and determined that additional studies to assess the development of cross-resistance to antibiotics are needed for only one of the deferred active ingredients, benzalkonium chloride. In the case of ethyl alcohol and isopropyl alcohol, sufficient data have been provided to assess the risk of antiseptic resistance and antibiotic cross-resistance.

Laboratory studies have identified and characterized bacterial resistance mechanisms that confer a reduced susceptibility to antiseptics and, in some cases, antibiotics. Specifically, these data suggest that resistance development in the laboratory is very common for some active ingredients, such as benzethonium and benzalkonium chloride (Refs. 13 to 17), and chloroxylenol, used in topical antiseptic products (Refs. 18 to 23). In contrast, resistance to other active ingredients, such as povidone-iodine (Refs. 24 to 26) occurs infrequently in the laboratory setting. We acknowledge that observations made in the laboratory setting are not necessarily replicated in the real-world setting. Therefore, we assessed additional studies performed in the clinical setting.

Studies performed using clinical isolates found strong evidence of antiseptic resistance to benzethonium and benzalkonium chloride (Refs. 27 to 35). Antiseptic resistance genes *qacA/B* and *qacE* (Ref. 32) were identified and, in 83 percent and 73 percent of the isolates tested, respectively, correlated with reduced susceptibility to benzalkonium and benzethonium chloride. In contrast, two studies published by Kawamura-Sato et al. (Refs. 36 and 37) found the MIC of benzalkonium chloride for 283 clinical isolates to be well within in-use concentration.

Other studies examined a possible correlation between antiseptic and antibiotic resistance (Refs. 23 to 34 and 37 to 46). Comparisons suggest that alterations in the mean susceptibility of *Staphylococcus aureus* to antimicrobial biocides occurred between 1989 and 2000, but these changes were mirrored in both methicillin resistant and susceptible *S. aureus*, suggesting that methicillin resistance had little to do with these changes (Ref. 46). In *S. aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, several correlations (both positive and negative) between antibiotics and antimicrobial biocides were found (Refs. 37, 39, 41, 44, 46, and 47). From the analyses of these clinical isolates, it is very difficult to support a hypothesis that increased biocide resistance is a cause of increased antibiotic resistance in these species.

Bacteria expressing resistance mechanisms with a decreased susceptibility to antiseptics and some antibiotics have been isolated from a variety of natural settings (Refs. 48 and 49). Although the prevalence of antiseptic tolerant subpopulations in natural microbial populations is currently low, overuse of antiseptic active ingredients has the potential to select for resistant microorganisms.

In sum, adequate data do not exist currently to determine whether the development of bacterial antiseptic resistance could also select for antibiotic resistant bacteria or how significant this selective pressure would be relative to the overuse of antibiotics, an important driver for antibiotic resistance. Moreover, the possible correlation between antiseptic and antibiotic resistance is not the only concern. Reduced antiseptic susceptibility may allow the persistence of organisms in the presence of low-level residues and contribute to the survival of antibiotic resistant organisms. Data are not currently available to assess the magnitude of this risk.

(Comment 19) The comments also addressed the data needed to assess the risk of the development of resistance. One comment disagreed with the proposed testing described in the 2016 Consumer Antiseptic Rub proposed rule, arguing that there are no standard laboratory methods for evaluating the development of antimicrobial resistance. With regard to the recommendation for mechanism studies, they believed that it is unlikely that this kind of information can be developed for all active ingredients, particularly given that the mechanism(s) of action may be concentration dependent and combination and formulation effects may be highly relevant. The comments also argued that data characterizing the potential for transferring a resistance determinant to other bacteria is also an unrealistic requirement for a GRAS determination. Finally, a comment argued that the requirements for data and information should be able to be satisfied through an ingredient-specific review of the literature and without generation of new laboratory data.

(Response 19) In the 2016 Consumer Antiseptic Rub proposed rule, we described the data needed to help establish a better understanding of the interactions between antiseptic active ingredients used in consumer antiseptic rub products and bacterial resistance mechanisms and the data needed to provide the information necessary to perform an adequate risk assessment for these consumer antiseptic rub products. We suggested a tiered approach as an efficient means of developing data to address this resistance issue, beginning with laboratory studies in conjunction with a literature review aimed at evaluating the impact of exposure to nonlethal amounts of antiseptic active ingredients on antiseptic and antibiotic bacterial susceptibilities, along with additional data, if necessary, to help assess the likelihood that changes in susceptibility observed in the preliminary studies would occur in the consumer setting (81 FR 42912 at 42927 to 42927). As we explained in the 2016 Consumer Antiseptic Rub proposed rule, we recognize that the science of evaluating the potential of compounds to cause bacterial resistance is evolving and acknowledged the possibility that alternative data may be identified as an appropriate substitute for evaluating the development of resistance (81 FR 42912 at 42927).

For benzalkonium chloride, for which resistance testing is necessary as described in the applicable deferral letter, we have advised manufacturers, as an initial step, to conduct an active

ingredient-specific literature review related to antiseptic resistance and antibiotic cross-resistance to assess the active ingredient's effect on development of cross-resistance to antiseptics and antibiotics in the consumer setting, and to submit as much information and data as can be provided (Ref. 50). If the literature review results show evidence of antiseptic or antibiotic resistance, additional studies may be necessary, consistent with the recommendations outlined in the 2016 Consumer Antiseptic Rub proposed rule, to help assess the impact of the active ingredient on antiseptic and antibiotic susceptibilities. If, however, the literature review provides no evidence that the active ingredient affects antiseptic or antibiotic susceptibility, then it is likely that no further studies to address development of resistance will be needed to support a GRAS determination.

4. The Risk of Ingestion and Poisoning

(Comment 20) Comments raised concerns about the risks of poisoning from consumer antiseptic rubs containing alcohol and, in particular, about the risk of ingestion of these products by young children. A comment recommended that, if consumer antiseptic rubs are used in schools, that teachers store them in a safe place and that students only use them with adult supervision. The comment also recommended using hand sanitizing wipes or products that do not contain alcohol to reduce the risk of ingestion and poisoning.

(Response 20) We agree that hand sanitizers or antiseptic wipes should be stored out of the reach of children and should be used with adult supervision. We note that the labeling for all drugs marketed under an OTC monograph is required to contain the general warning "Keep out of reach of children" in bold type (21 CFR 330.1(g)). As we explained in the 2016 Consumer Antiseptic Rub proposed rule, however, the labeling for consumer antiseptic rub products containing a particular active ingredient will be addressed as part of the final rule if FDA makes a determination that the active ingredient is GRAS/GRAE (81 FR 42912 at 42913). Because all three of the ingredients that are eligible for consideration as a consumer antiseptic rub, including alcohol, have been granted deferrals, and FDA has not yet made a GRAS/GRAE determination for these active ingredients, we do not address their labeling in this document. If alcohol and/or isopropyl alcohol are subsequently found to be GRAS/GRAE, we will address its labeling in the final

monograph for that active ingredient. As the comment suggests, we may consider at that time whether the labeling for consumer antiseptic rub products containing alcohol should contain additional directions or warnings aimed at reducing the risk of ingestion by young children. We may also consider whether using hand sanitizing wipes or products that do not contain alcohol could reduce the risk of ingestion and poisoning and, if so, whether and how that information should be incorporated into labeling.

E. Comments on the Preliminary Regulatory Impact Analysis and FDA Response

(Comment 21) One comment raised issues concerning the preliminary regulatory impact analysis (RIA) and the Agency's assessment of the net benefit of the rulemaking. The comment stated that FDA's RIA did not account for all the costs and overestimated the benefits associated with the proposed regulation. The comment noted that if the active ingredients in consumer antiseptic rub products are safe, there is no benefit to avoiding exposure to them. In addition, there are costs associated with the loss of availability of hand rub antiseptics in consumer settings.

(Response 21) Our response is provided in the full discussion of economic impacts, available in the docket for this document (Docket No. FDA-2016-N-0124, (Ref. 51), <https://www.regulations.gov>) and at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

VI. Effective Date

In the 2016 Consumer Antiseptic Rub proposed rule, we recognized, based on the scope of products subject to this final rule, that manufacturers would need time to comply with this final rule. Thus, as proposed in the 2016 Consumer Antiseptic Rub proposed rule (81 FR 42912 at 42930 to 42931), this document will be effective 1 year after the date of the document's publication in the **Federal Register**. On or after that date, any OTC consumer antiseptic rub drug products containing an ingredient that we have found in this document to be ineligible for consideration under the OTC Drug Review for the OTC consumer antiseptic rub monograph cannot be introduced or delivered for introduction into interstate commerce unless it is the subject of an approved NDA or ANDA.

VII. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the document under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." This final rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Although the additional costs this document imposes on small entities are small, the consumer antiseptic rub product industry is mainly composed of establishments with 500 or fewer employees. Therefore, we find that the document will have a significant economic impact on a substantial number of small entities. We have analyzed various regulatory options to examine the impact on small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$154 million, using the most current (2018) Implicit Price Deflator for the Gross Domestic Product. This document would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

As discussed in the preamble, this document applies to active ingredients used in OTC consumer antiseptic rub products, including hand "sanitizers" and consumer antiseptic wipes. Here, we refer to consumer antiseptic rubs or consumer rubs as those products that

are intended to be used when soap and water are not available and are not intended to be rinsed off with water. 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). The only active ingredients eligible for evaluation under the OTC Drug Review for use in OTC consumer antiseptic rub products are ethyl alcohol (referred to subsequently as alcohol), isopropyl alcohol, and benzalkonium chloride. In response to requests submitted to the 2016 Consumer Antiseptic Rub PR, FDA has deferred regulatory action on these active ingredients. Accordingly, FDA does not make a GRAS/GRAE determination regarding these three active ingredients in this document. The monograph or non-monograph status of these three active ingredients will be addressed, either after completion and analysis of studies to address the safety and effectiveness data gaps of these active ingredients or at a later date, if these studies are not completed.

This document establishes that all other consumer antiseptic rub active ingredients are not eligible for consideration under the OTC Drug Review for use in consumer antiseptic rub products. Drug products containing the 28 ineligible active ingredients identified in the 2016 Consumer Antiseptic Rub PR will require approval under an NDA or ANDA prior to marketing. However, we expect that manufacturers of consumer antiseptic

rub products with ineligible active ingredients will either reformulate and relabel their products to include the three deferred active ingredients which are eligible for consideration under the OTC Drug Review, discontinue production of their consumer antiseptic rub products, or reformulate their products as antiseptic-free topical cleansers or wipes. In table 4, we provide a summary of the estimated costs of the document that involve product reformulation and relabeling of consumer rub products that contain active ingredients that are ineligible for consideration under the OTC Drug Review for use in consumer rubs. Manufacturers of consumer antiseptic rub products that contain the deferred active ingredients may also incur additional costs associated with the necessary safety and effectiveness testing required to demonstrate that the deferred active ingredient is GRAS/GRAE. However, these testing costs are not included in the regulatory impact analysis for this document because this document does not require any testing. Although the testing costs are not attributable to this document, we estimate and present these costs separately in the RIA analysis.

We estimate that the present value of the one-time costs associated with compliance range from \$1.07 million to \$2.50 million with a primary estimate of \$1.87 million. Annualizing upfront costs over a 10-year period at a discount rate of 3 percent, the costs of this

document are estimated to be between \$0.13 million and \$0.29 million per year; the corresponding estimated cost at a discount rate of 7 percent is between \$0.15 million and \$0.36 million per year.

A potential benefit of this document is that the removal of potentially harmful antiseptic active ingredients in consumer antiseptic rub products may prevent health consequences associated with exposure to such active 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. The document will lead to an estimated reduction in aggregate exposure to benzethonium chloride that ranges from 110 pounds to 254 pounds per year. This document may also result in reduced exposure to other ineligible active ingredients. However, FDA can only estimate the reduced exposure to benzethonium chloride at this time. Furthermore, we are unable to translate the aggregate exposure to benzethonium chloride into monetized benefits at this time because we lack information on the change in the short- and long-term health risks associated with a 1-pound increase in exposure to each antiseptic active ingredient in consumer antiseptic rub products.

TABLE 4—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF DOCUMENT

Category	Primary estimate	Low estimate	High estimate	Units			Notes (years)
				Year dollars	Discount rate (percent)	Period covered (years)	
Benefits:							
Annualized					7	10	Values represent pounds of reduced annual exposure to ineligible active ingredients.
Monetized \$millions/year					3	10	
Annualized	182	110	254		7	10	
Quantified	182	110	254		3	10	Values represent pounds of reduced annual exposure to ineligible active ingredients.
Qualitative							
Costs:							
Annualized	\$0.27	\$0.15	\$0.36	2017	7	10	
Monetized \$millions/year	0.22	0.13	0.29	2017	3	10	
Annualized					7		
Quantified					3		
Qualitative							
Transfers:							
Federal					7		
Annualized					3		
Monetized \$millions/year							

TABLE 4—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF DOCUMENT—Continued

Category	Primary estimate	Low estimate	High estimate	Units			Notes (years)
				Year dollars	Discount rate (percent)	Period covered (years)	
From/To	From:			To:			
Other	7	10	
Annualized	3	10	
Monetized \$millions/year	
From/To	From:			To:			
Effects:							
State, Local or Tribal Government: none.							
Small Business:							
Wages:							
Growth:							

In line with Executive Order 13771, in table 5 we estimate present and annualized values of costs and cost

savings over an infinite time horizon. Based on these costs this document

would be considered a regulatory action under Executive Order 13771.

TABLE 5—EXECUTIVE ORDER 13771 SUMMARY TABLE
[In \$ millions 2016 dollars, over an infinite time horizon]

Item	Primary estimate (7%)	Lower estimate (7%)	Upper estimate (7%)	Primary estimate (3%)	Lower estimate (3%)	Upper estimate (3%)
Present Value of Costs	\$1.77	\$1.02	\$2.37	\$1.77	\$1.02	\$2.37
Present Value of Cost Savings	0.00	0.00	0.00	0.00	0.00	0.00
Present Value of Net Costs	1.77	1.02	2.37	1.77	1.02	2.37
Annualized Costs	0.12	0.07	0.17	0.05	0.03	0.07
Annualized Cost Savings	0.00	0.00	0.00	0.00	0.00	.00
Annualized Net Costs	0.12	0.07	0.17	0.05	0.03	0.07

C. Summary of Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because many small entities produce consumer antiseptic rub products, we find that the document will have a significant economic impact on a substantial number of small entities. The Final Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act, can be found in the Regulatory Impact Analysis discussed below.

We have developed a comprehensive Regulatory Impact Analysis that assesses the impacts of the document. The full analysis of economic impacts is available in Docket No. FDA-2016-N-0124 (Ref. 51) and at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

VIII. Paperwork Reduction Act of 1995

This document contains no collection of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 is not required.

IX. 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.

X. Consultation and Coordination With Indian Tribal Governments

We have analyzed this document in accordance with the principles set forth in Executive Order 13175. We have determined that the document does not contain policies that have substantial direct effects on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and

responsibilities between the Federal Government and Indian Tribes. Accordingly, we conclude that the document does not contain policies that have tribal implications as defined in the Executive Order and, consequently, a tribal summary impact statement is not required.

XI. Federalism

We have analyzed this document 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 the document 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 effects of this document are consistent with Executive Order 13132.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Docket Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

- * 1. Transcript of the January 22, 1997, Meeting of the Joint Nonprescription Drugs and Anti-Infective Drugs Advisory Committees, OTC Vol. 230002. Available at <https://www.regulations.gov/document?D=FDA-2015-N-0101-0008>.
- * 2. Comment submitted in Docket No. FDA-1975-N-0012-0081. Available at <https://www.regulations.gov/document?D=FDA-1975-N-0012-0081>.
- * 3. Transcript of the March 23, 2005, Nonprescription Drugs Advisory Committee. Available at <http://wayback.archive-it.org/7993/20170404055944/https://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4098T1.htm>.
- * 4. Transcript of the October 20, 2005, Meeting of the Nonprescription Drugs Advisory Committee. Available at <http://wayback.archive-it.org/7993/20170404055923/https://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4184T1.pdf>.
- * 5. Summary Minutes of the November 14, 2008, Feedback Meeting with Personal Care Products Council and Soap and Detergent Association, OTC Vol. 230002. Available at Docket No. FDA-2015-N-0101 at <https://www.regulations.gov/document?D=FDA-1980-N-0006-0031>.
- * 6. Transcript of the September 3, 2014, Meeting of the Nonprescription Drugs Advisory Committee 2014. Available at <http://wayback.archive-it.org/7993/20161023222810/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM421121.pdf>.
- * 7. Deferral Letters submitted in Docket No. FDA-2016-N-0124. Available at <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm538131.htm>.
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- * 11. FDA, Draft Guidance for Industry, "Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Consideration," May 2018. Available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM608356.pdf>.
- * 12. ICH Guidance for Industry M3(R2) "Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," January 2010. Available at <https://www.fda.gov/downloads/drugs/guidances/ucm073246.pdf>.
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