Accordingly, part 748 of the EAR (15 CFR parts 730–774) is amended as follows:

PART 748—[AMENDED]

■ 1. The authority citation for part 748 continues to read as follows:

Authority: 50 U.S.C. 4601 *et seq.;* 50 U.S.C. 1701 *et seq.;* E.O. 13026, 61 FR 58767, 3 CFR, 1996 Comp., p. 228; E.O. 13222, 66 FR 44025, 3 CFR, 2001 Comp., p. 783; Notice of August 4, 2016, 81 FR 52587 (August 8, 2016).

■ 2. Amend supplement No. 7 to part 748 by revising the entry for ''Boeing Tianjin Composites Co. Ltd.'' in ''China (People's Republic of)'' to read as follows:

SUPPLEMENT NO. 7 TO PART 748—AUTHORIZATION VALIDATED END-USER (VEU): LIST OF VALIDATED END-USERS, RESPECTIVE ITEMS ELIGIBLE FOR EXPORT, REEXPORT AND TRANSFER, AND ELIGIBLE DESTINATIONS

Country	Validated end-user	Eligible items (by ECCN)	Eligible destination	**Federal Register** citation
Nothing in this Supplement shall be deemed to supersede other provisions in the EAR, including but not limited to § 748.15(c).				
*	*	*	*	*
	Boeing Tianjin Composites Co. Ltd.	1B001.f, 1D001 (limited to ''software'' specially designed or modified for the ''use'' of equipment controlled by 1B001.f), 2B001.b.2 (limited to machine tools with accuracies no better than (*i.e.,* not less than) 13 microns), 2D001 (limited to ''software,'' other than that controlled by 2D002, specially designed or modified for the ''use'' of equipment controlled by 2B001.b.2), and 2D002 (limited to ''software'' for electronic devices, even when residing in an electronic device or system, enabling such devices or systems to function as a ''numerical control'' unit, capable of coordinating simultaneously more than 4 axes for ''contouring control'' controlled by 2B001.b.2).	Boeing Tianjin Composites Co. Ltd., 4566 Hebei Road, Marine Hi-Tech Development Area, Tanggu District, Tianjin, China 300451.	72 FR 59164, 10/19/07. 74 FR 19382, 4/29/09. 77 FR 10953, 2/24/12. 77 FR 40258, 7/9/12. 81 FR [INSERT PAGE NUMBER], September 6, 2016.
*	*	*	*	*

Dated: August 30, 2016.

Kevin J. Wolf,

Assistant Secretary for Export Administration.

[FR Doc. 2016–21333 Filed 9–2–16; 8:45 am]

BILLING CODE 3510–33–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. FDA–1975–N–0012; Formerly Part of Docket No. 1975N–0183H]

RIN 0910–AF69

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, we, or the Agency) is issuing this final rule establishing that certain active ingredients used in over-the-counter (OTC) consumer antiseptic products intended for use with water (referred to throughout this document as consumer antiseptic washes) are not generally recognized as safe and effective (GRAS/GRAE) and are misbranded. FDA is issuing this final rule 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 wash products that have come to the Agency's attention. This final rule amends the 1994 tentative final monograph (TFM) for OTC antiseptic drug products that published in the **Federal Register** of June 17, 1994 (the 1994 TFM). The final rule is part of the ongoing review of OTC drug products conducted by FDA.

DATES: This rule is effective September 6, 2017.

ADDRESSES: For access to the docket to read background documents or comments received, go to *http://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 Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Pranvera Ikonomi, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 5418, Silver Spring, MD 20993–0002, 240–402–0272.

SUPPLEMENTARY INFORMATION:

Table of Contents

Executive Summary

Purpose of the Final Rule

This final rule finalizes the consumer antiseptic wash proposed rule published in the **Federal Register** of December 17, 2013 (78 FR 76444) (2013 Consumer Wash Proposed Rule (PR)) and amends the 1994 TFM for OTC antiseptic drug products that published in the **Federal Register** of June 17, 1994 (59 FR 31402). The amendment is part of FDA's ongoing rulemaking to evaluate the safety and effectiveness of OTC drug products marketed in the United States on or before May 1972 (OTC Drug Review). This final rule applies to consumer antiseptic wash products that are intended for use with water and are rinsed off after use, including hand washes and body washes.

In response to several comments submitted to the 2013 Consumer Wash PR, FDA has deferred further rulemaking on three specific active ingredients used in OTC consumer antiseptic wash products to allow for the development and submission of new safety and effectiveness data to the record for these ingredients. The deferred active ingredients are benzalkonium chloride, benzethonium chloride, and chloroxylenol. Accordingly, FDA does not make a determination of general recognition of safety and effectiveness for these three active ingredients in this final rule. The monograph or new drug status of these three ingredients will be addressed either after completion and analysis of ongoing studies to address the safety and efficacy data gaps of these ingredients or at a later date if these studies are not completed.

With the exception of the three deferred consumer antiseptic wash active ingredients, this rulemaking finalizes the nonmonograph status of the remaining 19 active ingredients intended for use in consumer antiseptic washes identified in the 2013 Consumer Wash PR. As explained, either no additional data were submitted or the data and information that were submitted were not sufficient to support monograph conditions for these 19 consumer antiseptic wash ingredients. Therefore, with the exception of the three deferred consumer antiseptic wash active ingredients, this rule finalizes the 2013 Consumer Wash PR, which proposed amending the 1994 TFM, with the remaining 19 consumer antiseptic wash active ingredients found to be not GRAS/GRAE. Accordingly, these 19 consumer antiseptic wash drug products are misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 352) and are new drugs under section 201(p) of the 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.

In separate rulemakings, we are proposing conditions under which OTC consumer antiseptic rubs (products that are not rinsed off after use, including hand rubs and antibacterial wipes) (81 FR 42912, June 30, 2016) and OTC antiseptics intended for use by health care professionals in a hospital setting or other health care situation outside the hospital (80 FR 25166, May 1, 2015) are GRAS/GRAE. Accordingly, this final rule covers only OTC consumer antiseptic washes that are intended for use as either a hand wash or a body wash, and does not cover health care antiseptics (80 FR 25166), consumer antiseptic rubs (81 FR 42912), antiseptics identified as ''first aid antiseptics'' in the 1991 First Aid TFM (56 FR 33644), or antiseptics used by the food industry. Those antiseptic products are not addressed in this final rule.

Summary of the Major Provisions of the Final Rule

A. Effectiveness

As explained in the 2013 Consumer Wash PR, a determination that an active ingredient is GRAS/GRAE for a particular intended use requires a benefit-to-risk assessment for that particular use of the ingredient. If the active ingredient in a drug product carries the potential risk associated with the drug (*e.g.,* reproductive toxicity or carcinogenicity), but does not provide a clinical benefit, then the benefit-to-risk calculation shifts towards a not GRAS/GRAE status for that drug. New information on potential risks posed by the use of certain consumer antiseptic washes prompted us to reevaluate the data needed for classifying consumer antiseptic wash active ingredients as generally recognized as effective (GRAE). As a result, we proposed that the risk from the use of a consumer antiseptic wash drug product must be balanced by a demonstration—through studies that demonstrate a direct clinical benefit (*i.e.,* a reduction of infection)—that the product is superior to washing with nonantibacterial soap and water in reducing infection (78 FR 76444 at 76450).

We have considered the recommendations from the public meetings held by the Agency on antiseptics (see section II.B, table 2) and evaluated the available literature, as well as the data, the comments, and other information that were submitted to the rulemaking on the effectiveness of the consumer antiseptic wash active ingredients addressed in this final rule. The data and information submitted for these active ingredients are insufficient to demonstrate that there is any additional benefit from the use of these active ingredients in consumer antiseptic wash products compared to nonantibacterial soap and water. Consequently, the available data do not support a GRAE determination for these consumer antiseptic wash active ingredients.

B. Safety

As explained in the 2013 Consumer Wash PR, several important scientific developments that affect the safety evaluation of consumer antiseptic wash active ingredients have occurred since FDA's 1994 evaluation of the safety of consumer antiseptic active ingredients under the OTC Drug Review. New data suggests that the systemic exposure to these active ingredients is higher than previously thought, and new information about the potential risks from systemic absorption and long-term exposure is now available. New safety information also suggests that widespread antiseptic use could have an impact on the development of bacterial resistance. To support a classification of generally recognized as safe (GRAS) for consumer antiseptic wash active ingredients, we proposed that additional data was needed to demonstrate that those ingredients meet current safety standards (78 FR 76444 at 76453 to 76458).

The minimum data needed to demonstrate safety for all consumer antiseptic wash active ingredients falls into three broad categories: (1) Safety data studies described in current FDA guidance (*e.g.,* nonclinical and human pharmacokinetic studies, developmental and reproductive toxicity studies, and carcinogenicity studies); (2) data to characterize potential hormonal effects; and (3) data to evaluate the development of bacterial resistance.

We have considered the recommendations from the public meetings held by the Agency on antiseptics (see section II.B, table 2) and evaluated the available literature, as well as the data, the comments, and other information that were submitted to the rulemaking on the safety of consumer antiseptic wash active ingredients addressed in this final rule. The available information and published data for the 19 active

ingredients considered in this final rule are insufficient to establish the safety of long-term, daily repeated exposure to these active ingredients used in consumer wash products. Consequently, the available data do not support a GRAS determination for the consumer antiseptic wash active ingredients included in this rule.

C. Costs and Benefits

This final rule establishes that 19 active ingredients, including triclosan and triclocarban, are not GRAS/GRAE and consumer antiseptic wash products containing these ingredients are misbranded for use in consumer antiseptic washes. Regulatory action is being deferred on three active ingredients that were included in the proposed rule: Benzalkonium chloride, benzethonium chloride, and chloroxylenol. The primary estimated benefits come from reduced exposure to antiseptic active ingredients by 2.2 million pounds per year. Limitations in the available data characterizing the health effects resulting from widespread long-term exposure to these ingredients prevent us from translating the estimated reduced exposure into monetary equivalents of health effects. The primary estimate of costs annualized over 10 years is approximately $23.6 million at a 3 percent discount rate and $27.6 million at a 7 percent discount rate. These costs consist of total one-time costs of relabeling and reformulation ranging from $106.3 to $402.8 million. Under the final rule, we estimate that each pound of reduced exposure to antiseptic active ingredients will cost $12.97 to $14.28 at a 3 percent discount rate and $16.36 to $18.02 at a 7 percent discount rate.

Summary of the costs and benefits of the final rule	Total benefits	Total costs annualized over 10 years (in millions)	Total one-time costs (in millions)
Total	Reduced exposure to antiseptic ingredients by 2.2 million pounds annually.	$23.6 (at 3%) $27.6 (at 7%)	$106.3 to $402.8.

I. 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 wash active ingredients that are the subject of this final rule.

A. Terminology Used in the OTC Drug Review Regulations

1. Proposed, Tentative Final, and Final Monographs

To conform to terminology used in the OTC Drug Review regulations (§ 330.10 (21 CFR 330.10)), the advance notice of proposed rulemaking 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), and the **Federal Register** of December 17, 2013 (78 FR 76444) (2013 Consumer Wash PR) were each designated as a TFM (see table 1 in section II.A).

2. Category I, II, and III Classifications

The OTC drug procedural regulations in § 330.10 use the terms ''Category I'' (generally recognized as safe and effective and not misbranded), ''Category II'' (not generally recognized as safe and effective or misbranded), and ''Category III'' (available data are insufficient to classify as safe and effective, and further testing is required). Section 330.10 provides that any testing necessary to resolve the safety or effectiveness issues that 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 this final monograph stage, FDA does not use the terms ''Category I,'' ''Category II,'' and ''Category III.'' In place of Category I, the term ''monograph conditions'' is used; in place of Categories II and III, the term ''nonmonograph conditions'' is used.

B. Topical Antiseptics

The OTC topical antimicrobial rulemaking has had a broad scope, encompassing drug products that may contain the same active ingredients, but that are labeled and marketed for different intended uses. The 1974 ANPR for topical antimicrobial products encompassed products for both health care and consumer use (39 FR 33103). The 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 antiseptics.'' We published a separate TFM covering first aid antiseptics in the **Federal Register** of July 22, 1991 (56 FR 33644). In section III.E, we address comments filed in this rulemaking related to first aid antiseptics, but we do not otherwise discuss first aid antiseptics further in this document. This final rule does not have an impact on the monograph 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) health care personnel hand wash; (3) patient preoperative skin preparation; and (4) surgical hand scrub (59 FR 31402 at 31442). This final rule does not have an impact on the monograph status of health care personnel hand washes, patient preoperative skin preparations, or surgical hand scrubs. 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). In section III.B.4, we address comments filed in this rulemaking on antiseptics for use by the food industry, but we do not otherwise further discuss these antiseptics in this document. This final rule does not have an impact on the monograph status of antiseptics for food industry use.

In the 2013 Consumer Wash PR, we proposed that our evaluation of OTC antiseptic drug products be further subdivided into health care 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 risk for

infection. In the 2013 Consumer Wash PR (78 FR 76444 at 76446 to 76447) and the consumer antiseptic rub proposed rule published in the **Federal Register** of June 30, 2016 (81 FR 42912) (2016 Consumer Rub PR), 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) (78 FR 764444 at 76447). Consumer antiseptic wash products are intended to be used when soap and water are available, whereas, consumer antiseptic rub products are intended to be used when soap and water are unavailable, and thus, are left on and not rinsed off. To account for the differences between consumer washes and consumer rubs, the safety and effectiveness of the active ingredients are being evaluated for each intended use separately. This final rule does not have an impact on the monograph status of consumer antiseptic rub products.

C. This Final Rule Only Covers Consumer Antiseptic Washes

We refer to the group of products covered by this final rule as ''consumer antiseptic washes.'' Consumer antiseptic washes include a variety of personal care products intended to be used with water, such as antibacterial soaps, hand washes, and antibacterial body washes. As discussed further in section III.B.3, these products may be used by consumers for personal use in the home and public settings on a frequent, daily basis. In the United States consumer setting, where the target population is composed of generally healthy individuals, the risk of infection and the scope of the spread of infection is relatively low compared to the health care setting, where patients are generally more susceptible to infection and the potential for spread of infection is high.

This final rule covers only OTC consumer antiseptic washes that are intended for use as either a hand wash or a body wash, but that are not identified as ''first aid antiseptics'' in the 1991 First Aid TFM (56 FR 33644), health care antiseptics (80 FR 25166), consumer antiseptic rubs (81 FR 42912), or antiseptics used by the food industry. The distinctions between consumer washes and rubs, and between consumer hand washes and body washes are discussed in detail in the 2013 Consumer Wash PR (78 FR at 76446 to 76447) and the 2016 Consumer Rub PR (81 FR 42912). Completion of the monograph for Consumer Antiseptic Wash Products and certain other monographs for the active ingredient triclosan is 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.).

II. Background

In this section, we describe the significant rulemakings and public meetings relevant to this rulemaking and discuss our response to comments received on the 2013 Consumer Wash PR.

A. Significant Rulemakings Relevant to This Final Rule

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

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

FEDERAL REGISTER notice	Information in notice
1974 ANPR (September 13, 1974, 39 FR 33103).	We published an advance notice of proposed rulemaking 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 Healthcare 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 health care antiseptic drug products. These antiseptics are generally intended for use by health care 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 15, 2015, 80 FR 25166).	We issued a proposed rule to amend the 1994 TFM and establish data standards for determining whether OTC health care 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 health care 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.

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

B. Public Meetings Relevant to This Final Rule

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

TABLE 2—PUBLIC MEETINGS RELEVANT TO CONSUMER ANTISEPTICS

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 health care 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 health care antiseptics (Ref. 3).
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 health care antiseptic active ingredients (Ref. 6).

C. Scope of This Final Rule

This rulemaking finalizes the nonmonograph status for the 19 listed consumer antiseptic wash active ingredients (see section II.D). Requests were made that benzalkonium chloride, benzethonium chloride, and chloroxylenol be deferred from inclusion in this consumer antiseptic wash final rulemaking to allow more time for interested parties to complete the studies necessary to fill the safety and efficacy data gaps identified in the 2013 Consumer Wash PR for these ingredients. In March 2016, we agreed to defer rulemaking on these three ingredients (see Docket No. 1975–N–0012 at *http://www.regulations.gov*). Accordingly, in this final rulemaking we do not discuss whether benzalkonium chloride, benzethonium chloride, and chloroxylenol are GRAS/GRAE for use as active ingredients in consumer antiseptic washes. The monograph or new drug status of these three ingredients will be finalized either after completion and analysis of ongoing studies to address the safety and efficacy data gaps of these ingredients or at a later date if these studies are not completed.

For the 19 active ingredients included in this final rule, either no additional data were submitted since the 2013 Consumer Antiseptic Wash PR, or the data and information that were submitted were insufficient to support GRAS/GRAE findings. Therefore, these ingredients are not included in a monograph at this time. These active ingredients are not GRAS/GRAE for use in consumer antiseptic wash drug products and products containing these ingredients are new drugs for which approved new drug applications are required. Accordingly, FDA is amending part 310 (21 CFR part 310) to add the active ingredients covered by this final rule to the list in § 310.545 (21 CFR 310.545) of OTC drug products that are not GRAS/GRAE and are misbranded in the absence of an approved new drug application.

D. Eligibility for the OTC Drug Review

An OTC drug is covered by the OTC Drug Review if its conditions of use existed in the OTC drug marketplace on or before May 11, 1972 (37 FR 9464) (Ref. 7).[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 § 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 will require FDA approval through the new drug application (NDA) process. Ineligibility for use as a consumer antiseptic rub does not affect eligibility under any other OTC drug monograph.

1. Eligible Active Ingredients

There are 19 of the antiseptic active ingredients eligible for the OTC Drug Review for use as a consumer antiseptic wash that are addressed in this final rule. These ingredients are:

- Cloflucarban
- Fluorosalan
- Hexachlorophene
- Hexylresorcinol
- Iodophors (Iodine-containing ingredients)
  - Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
  - Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
  - Nonylphenoxypoly (ethyleneoxy) ethanoliodine
  - Poloxamer—iodine complex
  - Povidone-iodine 5 to 10 percent
  - Undecoylium chloride iodine complex
- Methylbenzethonium chloride
- Phenol (greater than 1.5 percent)
- Phenol (less than 1.5 percent)
- Secondary amyltricresols
- Sodium oxychlorosene
- Tribromsalan
- Triclocarban
- Triclosan
- Triple dye

In the 2013 Consumer Wash PR, we describe the lack of adequate data needed for a GRAS/GRAE determination for consumer antiseptic wash active ingredients (78 FR 76444). As discussed in section II.C, rulemaking has been deferred for three of the consumer antiseptic wash active ingredients—benzalkonium chloride, benzethonium chloride, and chloroxylenol. Accordingly, any references to consumer antiseptic wash active ingredients refer only to the 19 consumer antiseptic wash active ingredients listed in this section, unless otherwise stated.

2. Ineligible Active Ingredients

In the 2013 Consumer Wash PR, we also identified certain active ingredients

[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 in the OTC monograph system based on submission of a time and extent application. (See § 330.14).

that were considered ineligible for evaluation under the OTC Drug Review as a consumer antiseptic wash; but, we noted that if the requested documentation for eligibility was submitted, these active ingredients could be determined to be eligible for evaluation (78 FR 76444 at 76448). The active ingredients proposed to be ineligible in the 2013 Consumer Wash PR were:

- Alcohol (ethyl alcohol)
- Benzalkonium cetyl phosphate
- Cetylpyridinium chloride
- Chlorhexidine gluconate
- Isopropyl alcohol
- Polyhexamethylene biguanide
- Salicylic acid
- Sodium hypochlorite
- Tea tree oil
- Combination of potassium vegetable oil solution, phosphate sequestering agent, and triethanolamine

We have not received any new information since the 2013 Consumer Wash PR demonstrating that these active ingredients are eligible for evaluation under the OTC Drug Review for use as a consumer antiseptic wash. Consequently, drug products containing these active ingredients are new drugs that will require FDA approval.

III. Comments on the Proposed Rule and FDA Response

A. Introduction

In the 2013 Consumer Wash PR, interested parties were invited to submit comments on the proposed rule by June 16, 2014. In addition, interested parties had until December 16, 2014, to submit new data or information to the docket, with 2 additional months provided to submit comments on any new data or information submitted (78 FR 76444 at 76447).

In response to the 2013 Consumer Wash PR, FDA received approximately 40 comments from drug manufacturers, trade associations, academia, testing laboratories, consumer groups, and health professionals, as well as over 1,800 comments filed by individuals. FDA also received additional data and information for certain consumer antiseptic wash active ingredients.

We describe and respond to the comments in section III.B through III.F. We have numbered each comment to help distinguish between 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 or importance or the order in which comments were received.

B. Description of General Comments and FDA Response

1. Advance Notice of Proposed Rulemaking

(Comment 1) Several comments asserted that the new efficacy testing requirements proposed in the 2013 Consumer Wash PR were unprecedented. They stated that given the significance of the proposed change to the efficacy testing requirements for consumer antiseptics and the lack of precedent for this action, FDA should withdraw the proposed rule and reissue it as an ANPR to give industry and other stakeholders an opportunity to engage with FDA on the GRAE testing requirements for the active ingredients and surrogate endpoint testing of final formulations.

(Response 1) The purpose of an ANPR is to allow the public a period of time to comment on regulations that the FDA may pursue as part of a future rulemaking. As explained in section II.A, we issued an ANPR for a monograph for OTC topical antimicrobial drug products in 1974, and a proposed rulemaking in the form of a TFM in 1978. We have amended the TFM for OTC topical antimicrobial drug products to address, for example, different categories of topical antimicrobial drug products and indications of use, as well as the need for new safety and effectiveness data based on evolving scientific developments and new information on risks associated with use of these drug products (59 FR 31402; 56 FR 33644; 78 FR 764444; 80 FR 25166; 81 FR 42912). For each amendment, we have allowed interested parties to submit comments on the proposals.

In the 2013 Consumer Wash PR, we proposed that data from clinical outcome studies (demonstrating a reduction in infections) are necessary to support a GRAE determination for consumer antiseptic wash active ingredients (78 FR 76444). We explained that, if the active ingredient in a drug product does not provide clinical benefit but potentially increases the risk associated with the drug (*e.g.,* from reproductive toxicity or carcinogenicity), then the benefit-to-risk calculation shifts, and the drug is not GRAS/GRAE. For the consumer antiseptic wash ingredients at issue here, because of new concerns about the potential risks (*e.g.,* resistance and hormonal effects), the log reduction standard (a clinical simulation standard) proposed in the 1994 TFM, which was based on an invalidated surrogate endpoint (*i.e.,* number of bacteria removed from the skin), is insufficient for establishing effectiveness of consumer antiseptic washes. Therefore, we proposed that clinical outcome studies were needed to demonstrate a direct clinical benefit.

This proposed effectiveness requirement is consistent with the NDAC's recommendations from the October 2005 NDAC meeting regarding consumer antiseptics (Ref. 4). The October 2005 NDAC concluded that the existing test methods are based on the premise that bacterial reductions translate to a reduced potential for infection, and, although bacterial reduction can be demonstrated using tests that simulate conditions of actual use, there are no corresponding clinical data to demonstrate that bacterial reductions of the required magnitude produce a corresponding reduction in infection. Accordingly, the October 2005 NDAC recommended clinical outcome studies to demonstrate the clinical benefit of consumer antiseptic wash active ingredients and their superiority compared to a nonantibacterial wash, such as soap and water. In October 2008, we also held a public feedback meeting to discuss the demonstration of effectiveness of consumer antiseptic active ingredients.

At each stage of this process, interested parties have had an opportunity to participate in these proceedings. It is not necessary now to withdraw the 2013 Consumer Wash PR and reissue it as an ANPR.

(Comment 2) Several comments argued that the 2013 Consumer Wash PR should be reissued as an ANPR because the proposed rule only requests testing on the active ingredients to demonstrate effectiveness and fails to confirm whether the Agency will impose additional surrogate efficacy requirements for a final formulation. The comments contended that the Agency's approach is inconsistent with the approach taken in the 1994 TFM and other OTC monographs.

(Response 2) The issue of whether the 2013 Consumer Wash PR should be reissued as an ANPR to include final product formulation testing does not need to be addressed in this final rule because we have determined that none of the active ingredients subject to this final rule are GRAE for use as a consumer antiseptic wash. Final formulation testing would be required for testing formulations containing active ingredients that have been determined as GRAS/GRAE.

2. Effective Date

(Comment 3) Several comments stated that FDA's timeline under the 2013 Consumer Wash PR for new data submission is unreasonable and that completing clinical outcome studies within the timeframe proposed by the Agency is unrealistic.

(Response 3) We understand that, in certain circumstances, planning, implementing, and analyzing the data generated from a clinical outcome study can be a time-consuming process that may not be completed within the period granted for submission of additional data in response to the 2013 Consumer Wash PR. Accordingly, in the 2013 Consumer Wash PR, we provided a process for seeking an extension of time to submit the required safety and/or effectiveness data if needed (78 FR 76444 at 76447). As explained in the proposed rule, we stated that we would consider all the data and information submitted to the record in conjunction with all timely and completed requests to extend the timeline to finalize the monograph status for a given ingredient (78 FR 76444 at 76447). Consideration for deferral for an ingredient was given to requests with clear statements of intent to conduct the necessary studies required to fill all the data gaps identified in the proposed rule for that ingredient. After analyzing the data and information submitted related to the requests for extensions, we determined that deferral is warranted for three consumer antiseptic wash active ingredients—benzalkonium chloride, benzethonium chloride, and chloroxylenol—to allow more time for interested parties to complete the studies necessary to fill the safety and efficacy data gaps identified for these ingredients as indicated in the 2013 Consumer Wash PR. These three ingredients are not included in this final rule and will be addressed either after completion and analysis of ongoing studies to address the safety and efficacy data gaps of these ingredients or at a later date if these studies are not completed. We decline to defer final action on the proposed rule for the 19 remaining consumer antiseptic wash active ingredients.

(Comment 4) One comment requested that the Agency finalize the monograph finding that triclosan and other antimicrobial chemicals are not GRAS/GRAE, and, in so finding, require that all consumer antiseptic wash active ingredients that are not GRAS/GRAE be removed from the market either immediately or within 6 months of the publication of the final rule.

(Response 4) As discussed in section IV of this document, the data submitted to the Agency for the non-deferred consumer antiseptic wash active ingredients is insufficient to fill all the safety and effectiveness data gaps identified in the 2013 Consumer Wash PR. Thus, we find that these consumer antiseptic wash active ingredients, including tricoslan, are not GRAS/GRAE for use in OTC consumer antiseptic wash drug products. Products containing those ingredients are therefore not eligible for inclusion in a monograph and must be removed from the market or must be approved through an NDA or an abbreviated new drug application (ANDA).

This final rule involves over 700 consumer antiseptic wash drug products, which are formulated with one or more of the 19 active ingredients discussed in this final rule. In the 2013 Consumer Wash PR, we recognized, based on the scope of products subject to this final rule, that manufacturers would need time to comply with the rule (78 FR 76444 at 76470). We therefore proposed that the final rule be effective 1 year after the publication in the **Federal Register**, finding that a period later than 1 year after publication of the final rule would neither be appropriate nor necessary (78 FR 76444 at 76470). We also believe that making the final rule effective immediately upon publication or effective 6 months after publication does not afford manufacturers the time necessary to remove from the market, or reformulate their products containing these active ingredients, given the broad scope of products that are the subject of this final rule. Thus, we decline to adopt an immediate or 6-month effective date for this rule and, instead, as discussed in section V, adopt our proposal that this final rule be effective 1 year after publication in the **Federal Register**.

3. Definition of Consumer Antiseptic Washes

(Comment 5) Several comments requested that the Agency clarify the definition of consumer antiseptic washes, stating that the definition of consumer antiseptics in the 2013 Consumer Wash PR does not include antiseptic products used in institutional settings. The commenters stated that by not including such products in the definition of consumer antiseptic washes, we put the general population at risk for increased levels of bacteria on skin, which may lead to increased infection and diseases for the general population.

(Response 5) In the 2013 Consumer Wash PR, we explained that consumer antiseptic wash drug products addressed by this rulemaking include a variety of personal care products intended to be used with water, such as antibacterial soaps, hand washes, and body washes, which may be used by consumers for personal use in the home and in certain public settings on a frequent, even daily, basis (78 FR 76444 at 76446). We also indicate that ''consumer antiseptic'' is a broad term and meant to include all the types of antiseptic products used on a frequent or daily basis by consumers. This is consistent with the October 2005 NDAC meeting, at which consumer antiseptics were categorized as products used by the general public, including the use of those products in institutional and public settings (Ref. 4). Therefore, we clarify that consumer antiseptic wash products are products intended for use with water by the general population in the home or public settings on a frequent or daily basis. As such, antiseptic wash products used by health care professionals or commercial food handlers or as first aid antiseptic products are not considered consumer antiseptic wash products.

4. Food Handler Antiseptics

(Comment 6) Several comments requested that FDA make a distinction between hand wash products for use by consumers and hand wash products for use by commercial food handlers. The comments explained that the food industry includes commercial enterprises involved in food processing, preparation, or handling, but does not include home preparation. In addition, they explained that the food industry provides a different environment for hand washing compared to consumer use, and as a result, a separate monograph category should be created to define standards for food handlers. An opposing comment, however, objected to FDA creating another category of antiseptics for the food industry, arguing that these antiseptics raise the same safety concerns as consumer antiseptic wash products.

The comments that advocated for a separate category for antiseptics used by the food industry stated that FDA recognized the distinction between consumer hand washes and hand washes in the food industry in the 2013 Consumer Wash PR by stating that ''antiseptics for use by the food industry are not discussed further in this document'' (78 FR at 76446). The comments said that, despite this statement, the absence of further language specifically addressing hand wash products for use in the food industry creates the potential that

antiseptic hand wash products used in the food industry may, by default, be subject to the requirements of the 2013 Consumer Wash PR. They also requested that FDA clarify that hand wash products for use by the food industry can continue to be marketed under the current regulatory framework.

(Response 6) As stated in the 2013 Consumer Wash PR and the 2015 Health Care Antiseptic PR, we continue to classify the food handler antiseptic washes as a separate and distinct monograph category, and we clarify that such products are not part of these rulemakings on the consumer antiseptic monograph (78 FR 76444 at 76446; 80 FR 25166 at 25168). A separate category is warranted because of additional issues raised by the public health consequences of foodborne illness, differences in frequency and type of use, and contamination of the hands by grease and other oils. We plan to address OTC antiseptic products for use by the food handler industry in a separate rulemaking.[2] We plan to do a thorough evaluation of the safety and effectiveness of antiseptic active ingredients intended for this category of use. We also confirm that this final rule is not intended to affect antiseptic products indicated for use by the food industry.

C. Comments on Effectiveness and FDA Response

1. Clinical Outcome Studies

(Comment 7) Several comments challenged FDA's proposal that clinical outcome studies be conducted to demonstrate the effectiveness of the active ingredients for consumer antiseptic wash products, for the following reasons: (1) Clinical outcome studies are unjustified and not feasible; (2) the potential for antimicrobial resistance is unfounded because there has been no demonstration of a scientifically confirmed risk associated with the usage of consumer antiseptic products; (3) FDA has not properly considered the potential risks caused by lack of access to antibacterial products in consumers where specific populations of consumers may be at increased risk of infection; (4) the requirement for clinical outcome studies is far more extensive than antiseptic requirements for consumer, food, or health care antiseptics in other countries; and (5) simulation studies are a valid and feasible way to determine efficacy because they have been used since the publication of 1978 TFM, can be modified to include additional controls and surrogate endpoints that would satisfy the Agency's standards, and have been used to support approval of several NDAs.

(Response 7) In the 2013 Consumer Wash PR, we proposed that data from clinical outcome studies (demonstrating a reduction in infections) are necessary to support a GRAE determination for consumer antiseptic wash active ingredients (78 FR 76444 at 76450). We explained that new concerns about the potential risks (*e.g.,* resistance and hormonal effects) shifted the benefit-risk calculation. Therefore, the log reduction standard (a clinical simulation standard) proposed in the 1994 TFM, which was based on an invalidated surrogate endpoint (*i.e.,* number of bacteria removed from the skin), was insufficient for establishing effectiveness of consumer antiseptic washes. The requirement for clinical outcome studies is based on the fact that sufficient data to clearly demonstrate the benefit from the use of consumer antiseptic washes compared to nonantibacterial soap and water are not available. Additionally, existing data cannot demonstrate a correlation between log reductions of bacteria achieved by antiseptic hand washing in surrogate testing and reduction of infection and, as the October 2005 NDAC also concluded, the ability of consumer antiseptic wash products to decrease bacteria on the skin is insufficient for a GRAE finding if it is not supported by a direct clinical benefit (Ref. 4). Hence, in general consumer settings where soap and water are readily available the benefit of using an antiseptic wash product must be supported by clinical outcome studies. The efficacy requirements for consumer antiseptic washes differ from the efficacy requirements proposed for consumer antiseptic rub products because the wash products are intended to be used when soap and water are not available (81 FR 42912) (2016 Consumer Rub PR). In addition, the consumer antiseptic wash efficacy requirements differ from the efficacy requirements for health care antiseptics used in a hospital setting, where study design limitations and ethical concerns prevent the use of clinical outcome studies (80 FR 25166 at 25175 to 25176).

Moreover, as explained in the 2013 Consumer Wash PR, FDA's OTC regulations (§ 330.10(a)(4)(ii)) define the standards for establishing an OTC active ingredient as GRAE. These regulations require the efficacy of active ingredients for OTC drug products be demonstrated by controlled clinical trials (§§ 330.10(a)(4)(ii) and 314.126(b) (21 CFR 314.126(b)), unless this requirement is waived as provided in § 330.10(a)(4)(ii). These studies must be well controlled and able to distinguish the effect of a drug from other influences, such as a spontaneous change in the course of the disease, placebo effect, or biased observation (§ 314.126(a)).

The requirement for controlled clinical trials also is consistent with the recommendations of the October 2005 NDAC that clinical outcome studies be used to demonstrate the clinical benefit of consumer antiseptic wash products and their superiority compared to a nonantibacterial wash, such as soap and water (Ref. 4). Although two clinical outcome studies we identified in the 2013 Consumer Wash PR did not demonstrate a benefit from the use of the tested antiseptic active ingredient, these studies were randomized, blinded, and placebo-controlled, and demonstrate that such clinical outcome studies are feasible. For these reasons, FDA's requirement that clinical outcome studies be conducted to demonstrate the effectiveness of the active ingredients for consumer antiseptic wash products is warranted and reasonable.

(Comment 8) One comment also argued that FDA's requirement for clinical outcome studies based on its concern about the potential for increased antimicrobial resistance and endocrine disruption because of use of consumer antiseptic wash active ingredients is unfounded. The comment asserted that the requirement of clinical outcome studies is not supported by any demonstration of a confirmed risk associated with the use of consumer antiseptic products.

(Response 8) We agree that the development of resistant mechanisms in natural settings is not sufficiently studied. However, as discussed in more detail in section III.D.2, the concerns regarding the extended use of antiseptics, its potential consequences on the systemic exposure, and its potential consequences on the development of bacterial resistance, must be assessed. A GRAS/GRAE determination for an active ingredient for a particular intended use requires a benefit-to-risk assessment—in this case, the risk posed by use of a consumer antiseptic wash drug product must be balanced by a demonstration that the product is statistically significant (p-value <0.05) in reducing infections compared to washing with nonantibacterial soap and water, which refers to a soap formulation, solid or

[2] The Personal Care Products Council and American Cleaning Institute submitted a citizen petition in this rulemaking requesting FDA action on issues related to food handler antiseptic wash products. This citizen petition and other issues related to food handler products will be addressed in future documents.

liquid, that does not contain any antimicrobial ingredient.

(Comment 9) Commenters also contend the Agency has not considered the potential risks of an increase in infections among consumers by their not having access to antibacterial product formulations and commenters included publications in support of their position.

(Response 9) Although the submitted publications demonstrate some increase of infection in consumer settings, they do not address the effectiveness of consumer antiseptic wash products in the prevention or reduction of infections. The cited studies underscore the urgency of scientifically demonstrating the contribution of consumer antiseptics in lowering the infection rates in consumer settings. Although we acknowledge that there may be populations with increased vulnerability to bacterial infection, such as the elderly and persons with suppressed immune systems, the data to support the benefit of the use of consumer antiseptic wash products over that of nonantibacterial soap and water in these populations is still lacking.

(Comment 10) Several comments stated that the clinical outcome requirements proposed in the 2013 Consumer Wash PR are more extensive and demanding than requirements for establishing GRAE for active ingredients in other OTC monographs, and more demanding than what is required for antiseptics that are approved for use in other countries.

(Response 10) Although the requirement for clinical outcome studies for consumer antiseptic wash active ingredients may be a more stringent requirement than is used by some other countries, FDA's proposed effectiveness requirement is supported by FDA's regulations, the recommendations of the October 2005 NDAC, as well as by available data and publications studying the clinical outcome of antiseptics, all of which support the requirement of clinical outcome studies (Refs. 8 and 9). Moreover, the existence of published studies demonstrates that clinical outcome studies are feasible. For the reasons explained in this section, clinical outcome studies are necessary to assure that the potential risk from use of consumer antiseptic wash products is balanced by a demonstrated clinical benefit.

(Comment 11) Several comments argued that clinical simulation studies are a valid way to demonstrate efficacy and that the log reduction of bacteria on skin proposed to demonstrate efficacy since the 1978 TFM, has been used to support the approval of several NDAs. The comments also proposed that clinical simulation studies can be modified to include additional controls and neutralizers to satisfy the Agency's requirements. The comments stated that neutralization solutions are already included in the American Society for Testing and Materials (ASTM) [3] E1174 ''Standard Test method for Evaluation of the Effectiveness of Health Care Personnel Hand Wash Formulations,'' and a vehicle control and an active control such as Hibiclens 4 percent could also be included in clinical simulation studies.

(Response 11) We agree that clinical simulation studies and surrogate endpoints have been used since the publication of the 1978 TFM (43 FR 1210) and continued to be a requirement for demonstrating effectiveness in the 1994 TFM (59 FR 31402). As addressed in the 2015 Health Care Antiseptic PR (80 FR 25166), we will continue to evaluate the effectiveness of health care antiseptic products based on both in vitro testing and clinical simulation studies. However, the ethical concerns and challenges of designing clinical trials in the hospital setting do not apply to the consumer antiseptic wash setting, where washing with soap and water is a readily available alternative for consumers, and clinical trials to demonstrate clinical superiority are ethical and feasible.

With respect to approved marketing applications, we note that the Agency has not approved any applications for consumer antiseptic wash products since the publication of the 1994 TFM. The approved NDA products for which evaluation of efficacy is based on in vitro testing results and clinical simulation studies have been for antiseptic products used in the health care setting.

Moreover, although the addition of vehicle and active controls, as well as the inclusion of neutralization solutions in the test method, may increase the accuracy of the testing itself, it does not meet the requirement of establishing a direct connection between the use of consumer antiseptic wash active ingredients and infection reduction in a general consumer setting. A surrogate study, with or without additional controls, is founded on the premise that reduction of bacteria on skin because of use of a consumer antiseptic active ingredient (or product) will result in reduction of infections, but it is not a direct proof of reduced infections. While we continue to propose the use of surrogate endpoints as a demonstration of effectiveness for health care antiseptics and consumer antiseptic rubs, the reasons for those different requirements, such as the challenges of conducting such studies in the health care setting, and the fact that consumer rubs, which are intended for use when soap and water is unavailable, do not apply to consumer antiseptic wash products used in general consumer settings. In addition, the infection risk in healthcare settings is greater than in consumer settings, and as such, a clinical outcome study for healthcare antiseptics raises ethical questions regarding the use of non-antimicrobial vehicle in patients. Studying the effectiveness of consumer wash antiseptics via clinical outcome studies in consumer settings is not unethical and, as previously shown, it is feasible (Refs. 8 and 9).

As stated in the 2013 Consumer Wash PR, we have evaluated all clinical simulation studies that were submitted to the OTC Drug Review for evidence of antiseptic consumer wash active ingredient effectiveness demonstrated under the log reduction criteria (78 FR 76444 at 76451). We also evaluated the publications referenced in the comments submitted in response to the 2013 Consumer Wash PR. The studies described in the referenced publications lack the appropriate controls of a clinical outcome study, so we cannot, without additional evidence, attribute the reduction of infection rates to the use of antiseptic consumer wash active ingredients (Refs. 10 and 11). In sum, the studies we have evaluated are not adequately controlled to support an accurate assessment of the effectiveness of consumer antiseptic wash active ingredients.

A demonstration of the effectiveness of the active ingredients used in consumer antiseptic wash products should result from robust, properly designed, randomized studies with adequate numbers of subjects and clearly defined endpoints and analysis, using reduction in infection rates rather than reduction in pathogen counts. For the reasons discussed in this section and in the 2013 Consumer Wash PR, adequate clinical outcome studies that identify the conditions of use on which an antiseptic active ingredient can demonstrate a reduction in the number of infections, are required to demonstrate the GRAE status of consumer antiseptic wash active ingredients.

2. Testing of the Active Ingredient

(Comment 12) Several comments argued that the testing of the active ingredients rather than testing of final

[3] General information about ASTM can be found at *https://www.astm.org/*.

formulation products is unnecessary and not feasible because the delivery of the active ingredient is heavily dependent on its vehicle and testing of the active ingredient alone is not possible. One comment stated that although several consumer antiseptic wash products may contain the same active ingredient, they can also contain different product formulations that account for the effective delivery of the active ingredient, and, thus, test results of one specific wash product may not represent the effectiveness of a variety of consumer antiseptic wash products formulated with the same active ingredient.

(Response 12) The controlled clinical trials required by FDA's regulations are intended to demonstrate that the pharmacological effect of the drug when used under adequate directions for use will provide clinically significant relief of the type claimed (§§ 330.10(a)(4)(ii) and 314.126(b); 78 FR 76444 at 76450)), *i.e.* efficacy for the stated indication. GRAE determinations are made based on the active ingredient, not the product. We understand that testing the effectiveness of only the active ingredient using clinical outcome studies may not be feasible because the consumer uses the product in its final formulation form and not necessarily in the form of the isolated active ingredient. We agree that a variety of aspects of a final product formulation such as its pH, surfactancy, solubility, as well as the product's stability, depend on the formulation of the vehicle and can have an impact on the delivery of the active ingredient, as well as its antibacterial activity. We agree that test results of one specific wash product may not represent the effectiveness of a variety of consumer antiseptic wash products formulated with the same active ingredient. However, the proposal for conducting adequate and well-controlled clinical outcome studies to demonstrate that the active ingredient of a consumer antiseptic wash product is GRAE was not intended to be a study conducted only on the active ingredient, but rather a study designed to determine the contribution of the active ingredient to the effectiveness of the product. To determine that the active ingredient is GRAE, the clinical outcome studies should include at least two arms: The final formulation of the product and the vehicle. The effectiveness of the active ingredient, and hence its contribution in the reduction of infections, will be determined by comparing the infection rate of the active ingredient plus its vehicle to the infection rate of the vehicle in a consumer population. In the 2013 Consumer Wash PR, the referenced clinical outcome studies (Refs. 8 and 9) are two-arm studies where the effect of the antiseptic product in reduction of infections in a population is compared to a non-antibacterial product. It is in the presence of these controls (*i.e.,* the vehicle or a non-antibacterial product) that the contribution of the active ingredient contained in a consumer wash antiseptic product can be determined. We note that if an ingredient is so highly formulation dependent that the results of the efficacy testing cannot be extrapolated to demonstrate the active ingredient's effectiveness, products containing such an ingredient may require an NDA.

3. In Vitro Testing/Time-Kill Assays

(Comment 13) Several comments urged FDA to revise its proposed in vitro test methods for consumer wash antiseptic active ingredients. They stated that for demonstrating antibacterial activity of active ingredients, it is more relevant to perform a minimal inhibitory concentration and minimal lethal concentration (MIC/MLC) test to determine the potency and spectrum of the antibacterial activity of the proposed active ingredient before it is included in an antibacterial product formulation. Several comments also recommended that FDA not establish specific performance criteria for MIC/MLC testing of the active ingredients because the ingredients have not yet been formulated.

(Response 13) In addition to the clinical outcome studies FDA proposed in the 2013 Consumer Wash PR, FDA proposed an in vitro study consisting of a modified time-kill assay conducted on selected reference organisms and their respective clinical isolates, which are representative of bacterial strains most commonly encountered in general consumer settings (78 FR 76444 at 76452 to 76453). The purpose of the in vitro study is to characterize the antimicrobial activity of the active ingredients used in consumer antiseptic wash products.

As explained in the 2013 Consumer Wash PR, the requirement for clinical outcome studies lessens the need for extensive in vitro studies, given that the primary support for a GRAE determination is the clinical outcome study. MIC/MLC tests assess the minimal concentration of the active ingredient needed to cause inhibition of growth and/or lethality to bacteria after a 24-hour exposure to the active ingredient. However, the exposure time of consumer wash active ingredients, based on the indications of use for antiseptic wash products, is much shorter—several minutes maximum. Thus, information on the ability of the antiseptic wash active ingredient to inhibit or eliminate bacterial growth after the prolonged exposure times used in the MIC/MLC testing is not relevant to the actual use of the consumer antiseptic wash product.

The time-kill assay, on the other hand, is designed to test shorter exposure times against the microorganisms selected for testing with the test material, and as such, it provides more relevant information on how quickly the tested active ingredient eliminates the tested microorganisms. The time-kill assay also includes strains and clinical isolates of organisms most commonly found in consumer settings and provides relevant information on the kinetics of the antimicrobial activity of active ingredients with regard to the bactericidal activity of active ingredients used in consumer antiseptic wash products.

Given that we are not requiring MIC/MLC tests to be performed, we do not address whether specific performance criteria should or should not be established for MIC/MLC testing of the active ingredients.

(Comment 14) Several comments also contended that the time-kill assay should be used for characterization of final product formulation, rather than for evaluation of the effectiveness of the active ingredient, given that many characteristics of the formulation, such as its stability, solubility, and pH, have a significant influence on the performance outcome of the antiseptic product. They urged FDA to adopt ASTM E2783, ''Standard Test Method for Assessment of Antimicrobial Activity for Water Miscible Compounds Using a Time-Kill Procedure,'' as the standard for conducting the time-kill assay. They also argued that the performance criteria for the time-kill assay proposed in the 2013 Consumer Wash PR are more demanding than the performance abilities of approved health care antiseptic products.

(Response 14) Testing requirements for the final product formulations are not addressed in this final rule because none of the active ingredients that are the subject of this final rule are considered GRAE for use in consumer antiseptic wash products, given the lack of sufficient effectiveness data for these ingredients. The testing requirements for final formulations of products containing the three deferred active ingredients will be addressed after a decision is made regarding the monograph status of those ingredients.

In addition, for purposes of the three deferred active ingredients, we have reviewed the ASTM E2783–11 and do not disagree with the use of this method for the deferred active ingredients to help establish GRAE status for a consumer antiseptic wash product with a bacterial indication, as long as all the bacterial strains and the respective clinical isolates proposed in the 2013 Consumer Wash PR are included in the test.

With regard to the comment that the performance criteria of the time-kill assay are more demanding than the performance abilities of approved health care antiseptic products, the proposed 99.9 percent elimination of bacteria describes the concentration and the time of contact at which the active ingredient would be considered bactericidal. This criterion is based on the performance of alcohol formulations (61 percent to 85 percent) and on the expectation that an effective consumer antiseptic product will demonstrate a comparable bactericidal activity. The 2013 Consumer Wash PR did not propose that a 99.9 percent performance criterion would have to be achieved on all the proposed reference strains and clinical isolates to make a GRAE determination for the active ingredient.

In summary, the clinical results necessary to support a GRAE finding for any of the consumer antiseptic wash active ingredients addressed in this final rule have not been demonstrated. The effectiveness of each of the three consumer wash active ingredients deferred from this rulemaking will be evaluated on a case-by-case basis in the future.

4. Melon Ball Model To Support a GRAE Determination

In the 2013 Consumer Wash PR, we evaluated a study submitted to the OTC Drug Review involving a testing protocol referred to as the Melon Ball Disease Transmission (MBDT) model (78 FR 76444 at 76451 to 76452). The MBDT model attempts to link the efficacy of washing with antibacterial consumer wash to infection reduction by correlating the reduction of bacterial transfer to a food item following the use of a consumer antiseptic hand wash to a reduction of infection. In the 2013 Consumer Wash PR, FDA raised several concerns regarding the validity of the MBDT model. We found the MBDT model deficient and inadequate to link reduction of bacteria to a reduction in infection incidences (78 FR 76444 at 76451). Therefore, we concluded, the results of the MBDT study did not demonstrate the effectiveness of the consumer antiseptic hand wash used in the study.

(Comment 15) Several comments disagreed with the Agency's concerns and supported the use of the MBDT model for establishing a GRAE classification for relevant active ingredients, as well as supported optional final formulation testing that is intended to correlate clinical simulation study results with clinical outcome. Published data and recent studies were included in the comments submitted in response to the 2013 Consumer Wash PR to address the validity of the MBDT model and two other models used along with the MBDT model: (1) The Palmar hand-contamination method—the model of bacterial hand contamination and (2) a computational simulation model known as the Quantitative Microbial Risk Assessment (QMRA) model.

(Response 15) We reviewed and evaluated the submitted materials, including the studies previously addressed in the 2013 Consumer Wash PR. The studies show a reduction of bacteria on skin, as well as reduced bacterial transfer from hands to objects or food items because of use of consumer antiseptic wash products. In the Schaffner et al. study, statistical analysis and the QMRA model were used, in addition to the previously reported MBDT model, in an effort to establish a quantitative link between the effectiveness of antiseptic products and the reduced potential for disease such as *Shigellosis* and other low-dose enteric pathogens (Ref. 12).

After evaluation, however, we find that the submitted data, which include the Palmar method and QMRA model, do not address the deficiencies of the MBDT model previously analyzed in the 2013 Consumer Wash PR for the following reasons:

- The Palmar method is not reflective of the intended use of consumer antiseptic wash products and does not take into consideration the bacteria residing under the fingernails, which is an important reservoir for bacteria. Sufficient data to compare the Palmar method to the full-hand contamination method currently used are not provided.
- The limitations of the dose-response model generated from *S. flexneri* dose-response studies, including the small number of subjects, variability in the dose-response data, and lack of uniformity on criteria used for the definition of illness, remains the same as previously addressed in the 2013 Consumer Wash PR (78 FR 76444 at 76451).
- Although melon is a readily found food item, it cannot be used as a standardized tool for bacterial transfer. There are other factors besides the size of the melon balls, such as the melon's ripeness and surface texture, which may introduce variability to bacterial transfer. Also, bacterial transfer may be affected by the amount of fat/grease contained in a food item. These issues cannot be addressed by using the melon ball as a standardized object to study bacterial transfer (Ref. 13). The comments provided no useful data to assess the effects of these variables on the absolute counts of bacteria transferred from hands to food items and the overall study outcome.

Overall, the MBDT model, including the QMRA analysis, cannot be used as a standardized method to validate the effectiveness of consumer antiseptic wash active ingredients. Such a model assesses bacterial transfer as a surrogate for disease and is not capable of showing the direct clinical benefit of an antiseptic active ingredient or an antiseptic product for the general consumer population. Instead, it measures the transfer of bacteria from contaminated hands to melon balls, a measurement that is then used in a risk assessment model to provide a hypothetical infection reduction estimate based on infection data generated from *S. flexneri* dose-response studies with limited data. The proposed MBDT model reflects only one facet of the multiple uses of consumer antiseptic wash products. Consumers can be exposed to pathogenic organisms not only through food preparation activities, but also through contact with a variety of fomites in the domestic setting. Furthermore, the MBDT model does not address the scenario where a consumer would transfer the disease from their contaminated hands to other parts of their bodies (self-inoculate).

Although the QMRA analysis may be useful for exploratory analysis for risk assessment and management, it is not used for demonstrating the efficacy of drugs for approval. The comment provided references to show that QMRA analyses have been adopted by many agencies, including FDA. Our literature search confirms that QMRA analyses are used to estimate the impact of food safety policies (Ref. 14), or to predict the probability of adverse effects in vaccination (Ref. 15). However, we did not find any evidence of QMRA analysis employed as direct proof in determining the efficacy of a drug product or an active ingredient.

The MBDT model fails to prove that reduction of the pathogen counts on hands will translate into a clinically meaningful benefit, and as such, the MBDT model cannot be a substitute for

adequate clinical outcome studies that identify conditions of use under which an antiseptic wash active ingredient is capable of reducing the number of infections. The data demonstrating the effectiveness of the active ingredients used in consumer antiseptic wash products should result from robust, properly designed, randomized studies with adequate numbers of subjects and clearly defined endpoints and analysis, assessing reduction in infection rates rather than reduction in pathogen counts.

5. American Society for Testing and Materials Standard Methods

(Comment 16) Several comments addressed the test methods for demonstration of effectiveness for final product formulations and proposed that the Agency recognize several ASTM test methods for determination of effectiveness for final product formulations, including the ASTM E1174 ''Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel Hand Wash Formulations,'' the ASTM E2784 ''Standard Test Method for Evaluation of the Effectiveness of Hand Wash Formulations Using the Paper Towel (Palmar) Method of Hand Contamination,'' the ASTM E1874 ''Standard Test Methods for Recovery of Microorganisms From Skin Using the Cup Scrub Technique,'' and the ASTM E2783 method ''Standard Test Method for Assessment of Antimicrobial Activity for Water Miscible Compounds Using a Time-Kill Procedure.''

(Response 16) As discussed in section IV, none of the active ingredients subject to this final rule have been found to be GRAE for use in a consumer antiseptic wash product. We will evaluate the GRAS/GRAE status of the three deferred active ingredients either upon completion and analysis of all safety and effectiveness studies required for these ingredients or at a later date if these studies are not completed (78 FR 76444 at 76458). For these reasons, it is premature to discuss final product formulation testing requirements before a decision is made on the adequacy of data to provide to support monograph status of the three deferred active ingredients.

We note, however, that the suggestion to accept the ASTM test methods used in clinical simulation studies for final product formulation testing is based on the assumption that for the consumer antiseptic wash active ingredients for which clinical outcome studies will demonstrate effectiveness, only antibacterial claims would be supported. The guidelines for clinical outcome study design provided by the Agency with regard to the three deferred consumer antiseptic wash active ingredients allow for demonstration of reduction of infections of either bacterial or viral origin. If the clinical outcome studies demonstrate that these active ingredients can reduce infections of origin other than bacterial (*i.e.* viruses), additional testing to further characterize the activity of these ingredients must be determined. Therefore, testing requirements for final product formulation cannot be finalized before we have made a determination that a deferred active ingredient is GRAE. Depending on the indication(s) supported by clinical outcome studies for an active ingredient, additional final product formulation testing, other than the ASTM methods suggested, may be required.

D. Comments on Safety and FDA Response

1. Additional Safety Testing Requirements

(Comment 17) One comment stated that before proposing new safety testing, FDA must consider the actual risks. The comment argued that if current product exposures do not present risk based on the existing data, new data should not be required. The comment further recommended that existing data should be reviewed in relation to increased risk rather than increased analytic sensitivity and that if FDA finds that there is no demonstration of risk, FDA should conclude that the active ingredients and formulations are safe.

(Response 17) We decline to withdraw our requirement in the 2013 Consumer Wash PR for the additional safety data that we determined is necessary to support a GRAS classification for the consumer antiseptic wash active ingredients. As explained in the 2013 Consumer Wash PR, several important scientific developments that affect the safety evaluation of the consumer antiseptic wash active ingredients have occurred since FDA's 1994 evaluation. New data and information on the antiseptic wash active ingredients raise concerns regarding potential risks from systemic absorption and long-term exposure, as well as development of bacterial resistance related to use of consumer antiseptic washes (78 FR 76444 at 76445). The data required by the 2013 Consumer Wash PR is necessary for FDA to conduct an adequate safety evaluation. The comments do not provide sufficient data to support a determination that these consumers antiseptic wash active ingredients can be classified as GRAS.

2. Resistance

(Comment 18) Numerous comments relating to the issue of bacterial resistance were submitted in response to the 2013 Consumer Wash PR. Some comments argued that the pervasive use of consumer antiseptics poses an unacceptable risk for the development of resistance and that these products should be removed from the market. Other comments disagreed and criticized the data on which they believe FDA has based its concerns.

Specifically, several comments dismissed the in vitro data cited by FDA in the 2013 Consumer Wash PR as not reflecting real-life conditions. The comments recommended 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 this type have reinforced the evidence that resistance and cross-resistance associated with antiseptics is a laboratory phenomenon observed only when tests are conducted under unrealistic conditions. Another comment 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 (Ref. 16).

(Response 18) Laboratory studies have identified and characterized bacterial resistance mechanisms that confer a reduced susceptibility to antiseptics and, in some cases, clinically relevant antibiotics (Refs. 17 through 27). Bacteria expressing these resistance mechanisms with a decreased susceptibility to antiseptics have been isolated from a variety of natural settings (Refs. 28 through 30). These studies found that the prevalence of antiseptic tolerant subpopulations in the natural microbial populations studied is currently low. Morrissey et al. concluded, however, that their study findings could not rule out the existence of other resistant isolates that could be found if more isolates were analyzed.

In general, studies have not clearly demonstrated an impact of antiseptic bacterial resistance mechanisms in the natural setting. However, the available studies have limitations. As FDA noted in the 2013 Consumer Wash PR, studies in a natural setting that it evaluated were limited by the small numbers and types of organisms, the brief time

periods, and the locations examined; and more importantly, none of these studies address the level of exposure to the antiseptic active ingredient (Refs. 30 through 33) (78 FR 76444 at 76454). These limitations were also found in the studies cited by the comments (Refs. 35 through 37). There was, however, one study that found a difference in the antiseptic and antibiotic susceptibilities of some of the bacteria evaluated (Ref. 38).

Carson et al. assessed the effect of antibacterial product use (cleaning products containing quaternary ammonium compounds including benzalkonium chloride and hand soap containing 0.2 percent triclosan) in the home environment on susceptibility to benzalkonium chloride, triclosan, and antibiotics. Data were collected as part of a longitudinal double-blind, randomized clinical trial that compared the susceptibilities of bacteria isolated from antibacterial user and nonuser households at baseline and after 1 year. The MICs of 645 isolates were evaluated. The study found that after 1 year of assigned product usage, bacterial isolates with high benzalkonium chloride MICs were more likely to have high triclosan MICs and be resistant to one or more antibiotics.

Other data on a possible correlation between antiseptic and antibiotic resistance are conflicting. Copitch et al. found that the majority of isolates with decreased resistance to triclosan were also resistant to multiple antibiotics in their series of 428 isolates screened for decreased susceptibility to triclosan and a panel of antibiotics (Ref. 29). Conversely, Skovgaard et al. found no significant association between antibiotic resistance and triclosan tolerance when they compared the susceptibilities of current isolates of *Staphylococcus epidermidis* with isolates collected in the 1960s before introduction of triclosan to the market in Denmark (Ref. 30). An analysis of 1,600 isolates of *Staphlococcus aureus* has shown a moderate correlation between susceptibility to benzalkonium chloride and some classes of antibiotics (*e.g.,* quinolones, beta-lactams, and macrolides), but not for triclosan (Ref. 39).

In conclusion, bacteria expressing resistance mechanisms with a decreased susceptibility to antiseptics and some antibiotics have been isolated from a variety of natural settings (Refs. 28 and 29). Although the prevalence of antiseptic tolerant subpopulations in natural microbial populations is currently low, continued overuse of antiseptic active ingredients has the potential to select for resistant microorganisms.

Adequate data do not currently exist 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) Other comments disagreed that the development of resistance to a particular ingredient has been demonstrated. The comments also disagreed on the type of data needed to assess the risk of the development of resistance. One comment disagreed with the proposed testing described in the 2013 Consumer Wash PR, arguing that there are no standard laboratory methods for evaluating the development of antimicrobial resistance. With regard to the recommendation for mechanism studies, some comments asserted 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/formulation effects may be highly relevant. The comments also believed that data characterizing the potential for transferring a resistance determinant to other bacteria is an unrealistic requirement for a GRAS determination.

Conversely, one comment recommended that antimicrobial resistance be addressed first through in vitro MIC determinations. If an organism is shown to develop resistance rapidly, then the comment recommended that FDA should consider this negative information in its evaluation. The comment believed that this test of the potential for the development of resistance is important because consumer compliance with recommended use of consumer antiseptic wash products is variable and products that result in rapid antimicrobial resistance would pose a public health risk.

(Response 19) In the 2013 Consumer Wash PR, we proposed a tiered approach as an efficient means of developing data to address this issue. Laboratory studies were proposed as a feasible first step in evaluating the impact of exposure to nonlethal amounts of antiseptic active ingredients on antiseptic and antibiotic bacterial susceptibilities. We noted that only limited data exist on the effects of antiseptic exposure on the bacteria that are predominant in the oral cavity, gut, skin flora, and the environment, and that these organisms represent pools of resistance determinants that are potentially transferable to human pathogens (78 FR 76444 at 76457). Thus, we proposed broader laboratory testing of consumer antiseptic active ingredients that would more clearly define the scope of the impact of antiseptic active ingredients on the development of antibiotic resistance and may enable identification of those antiseptic active ingredients for which the development of resistance is not a concern. We are aware that there are no standard protocols for these studies. However, there are numerous publications in the literature of studies of this type that could provide guidance on the study design (Refs. 40 through 44).

For antiseptic active ingredients for which an effect on antiseptic and antibiotic susceptibilities is demonstrated, we proposed that additional data would be necessary to help assess the likelihood that changes in susceptibility observed in the preliminary studies would occur in the consumer setting. Several different types of data were recommended to assess whether or not ingredients with positive laboratory findings pose a public health risk, and the type of data needed would depend on what is already known about the antiseptic active ingredient's mechanism of action and persistence in the environment. We stated that we did not anticipate that it would be necessary to obtain data from multiple types of studies for each active ingredient to adequately assess its potential to affect resistance. Thus, the types of studies that would be acceptable to help address this issue are not limited to those described in the 2013 Consumer Wash PR (78 FR 76444 at 76457).

(Comment 20) One comment noted that the recommendations in the proposed rule pertaining to the type of data that could be used did not consider the safety of usage of antiseptics for another sensitive population: The immunocompromised. The comment stated that this growing population may be at greater risk of developing bacterial resistance from repeated usage of antiseptics, and the comment noted the dangers that result from associated infections that are unresponsive to traditional antibiotics. The comment

submitted no data to support its assertion, but asserted that there is a need for research to clarify whether the bacterial composition of immunocompromised individuals is adequately represented by the bacteria identified for testing in the proposed rule. The comment also suggested that there may be an additional need to perform surveillance of the effects seen in the immunocompromised after the use of consumer antiseptics for increased risk of bacterial resistance, because this has been demonstrated in clinical settings. Another comment recommended that FDA require that manufacturers establish and maintain active surveillance of this issue and require that this information be submitted to FDA every year.

(Response 20) We acknowledge that there are segments of the general population that may be more at risk from antiseptic/antibiotic cross-resistance and that further research is needed to address this facet of this issue. However, because no monograph is being established for the consumer antiseptic wash active ingredients in this final rule, the requests for an FDA requirement for active surveillance of this issue do not apply for purposes of this final rule.

3. Alternatives to Animal Studies

(Comment 21) One comment requested that FDA provide guidance on how to reduce the use of animals in testing done to assess the safety of consumer antiseptic washes. The comment recommended that FDA require manufacturers to conduct efficacy testing in humans before safety testing in animals and to share the data resulting from any animal testing they conduct. The comment also recommended that FDA accept data from non-animal safety tests.

In addition, the comment recommended that FDA reduce the number of rodent cancer bioassays required, by allowing for the extrapolation of data from the dermal route of administration to the oral route, and from the oral route to the dermal route. The comment requested that FDA consider whether physiologically based toxicokinetic modeling (PBTK), along with certain non-animal in vivo and in vitro absorption, distribution, metabolism, and excretion (ADME) data, could support route-to-route extrapolation. The comment further recommended that FDA adopt in vitro testing strategies to replace testing using animal models. Lastly, the comment stated that FDA should require manufacturers to share the data resulting from any animal testing they conduct.

(Response 21) The required number of rodent cancer bioassay studies have in some cases been reduced for drug products; for instance, a waiver of dermal carcinogenicity may be considered for a substance used previously by another route if a chronic dermal study in an appropriate non-rodent species shows no potential neoplastic effects and there are no other causes for concern, such as absence of a positive genotoxicity signal and absence of association of exposure to the drug with a positive tumor signal in systemic carcinogenicity data (Refs. 45 and 46). However, at this point, the Agency has not adopted a policy regarding the use of route to route extrapolation method using alternatives to animal testing such as in vitro data, ADME and PBTK tools.

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

However, there are still many areas where animal testing is considered necessary and non-animal testing is not yet a fully available option. FDA continues to support efforts to reduce animal testing, particularly whenever new alternative methods for safety evaluation have been validated and accepted by International Council on Harmonization (ICH) regulatory authorities, but these efforts have not yet resulted in the development of alternative testing that eliminate animal testing altogether. We will not be discussing further in this final rule the specific issues raised in the comments on animal testing because these issues are outside the scope of this rulemaking.

With respect to the recommendation that FDA require manufacturers to share the data resulting from any animal testing they conduct, FDA regulations require that data and information relevant to the monograph and a GRAS/GRAE determination be submitted to the docket for that monograph and made publicly available (§ 330.10(a)(2)). Accordingly, any such animal testing data should be publicly available and can be obtained from the docket for this rulemaking. We also note that although there is a process for submitting confidential information, the OTC drug monograph process is generally a public process. The Agency considers either non-confidential material that is submitted to the docket or information that is publicly available when making its evaluation of whether a given ingredient is GRAS/GRAE.

E. Comments on Active Ingredients and FDA Response

1. Ethanol

(Comment 22) A comment was submitted to this docket regarding the GRAS status of ethanol.

(Response 22) This active ingredient is not marketed as a consumer antiseptic wash product, and, therefore is not addressed. We will address this comment, and any other comments regarding the GRAS status of ethanol, to the extent that it applies to indications reviewed in the 2015 Health Care Antiseptic PR and the 2016 Consumer Rub PR.

2. Cetylpyridinium Chloride

(Comment 23) As noted in the 2013 Consumer Wash PR, subsequent to the 1994 TFM we received requests that certain active ingredients be added to the antibacterial monograph (78 FR 764444 at 76448). One of these submissions included a citizen petition that requested that we allow the use of cetylpyridinium chloride as an antibacterial active ingredient for household liquid soap (Ref. 47).

(Response 23) In the 2013 Consumer Wash PR, we identified certain active ingredients, including cetylpyridinium chloride that we considered ineligible for evaluation under the OTC Drug Review as a consumer antiseptic wash. We noted that if the requested documentation for eligibility was submitted, these active ingredients, including cetylpyridinium chloride, could be determined to be eligible for evaluation (78 FR 76444 at 76448). Neither the citizen petition, nor other submissions we have received in this rulemaking, include documentation demonstrating the eligibility of cetylpryridinium chloride for evaluation under the OTC Drug Review for use as a consumer antiseptic wash. Consequently, this citizen petition is denied and as indicated in section II.D, we consider consumer antiseptic wash products containing cetylpyridinium chloride to be new drugs that require FDA approval through the NDA process.

3. Hexylrescorinol

In the 2013 Consumer Wash PR, FDA proposed to classify hexylresorcinol as Category III for both safety and efficacy (78 FR 76444 at 76458). FDA determined that the administrative record for the safety of hexylresorcinol

was incomplete with respect to the following:

- Human pharmacokinetic studies under the maximal use conditions when applied topically, including documentation of validation of the methods used to measure hexylresorcinol and its metabolites
- Animal pharmacokinetic studies on ADME
- Data to help define the effect of formulation on dermal absorption
- Dermal carcinogenicity
- Developmental and reproductive toxicity (DART) data
- Potential hormonal effects
- Data from laboratory studies that assess the potential for the development of resistance to hexylresorcinol and cross-resistance to antibiotics in the types of organisms listed in section VII.C.3 of the 2013 Consumer Wash PR (78 FR 76444 at 76457)

(Comment 24) One comment referenced a 13-week oral toxicology study from the National Toxicology Program (NTP) conducted in rats, in which there were reports of reduction in the size of seminal vesicles and hypospermatogenesis (abnormally low sperm production). The comment asserted that FDA should evaluate these effects on the male rat reproductive organs to fill the DART data gap for hexylresorcinol.

(Response 24) Although this technical report was cited in the 2013 Consumer Wash PR (78 FR 76444 at 76475, Ref. 120) for hexylresorcinol, the data in this 13-week study is not sufficient to conduct an adequate DART assessment for hexylresorcinol (Ref. 48). Specifically, the NTP report described toxicity and carcinogenicity studies of hexylresorcinol. The report consisted of three sets of studies, 16-day studies, 13-week studies, and 2-year studies, all conducted in mice and rats of both sexes. Although the findings in the 13-week studies appear to show an effect of hexylresorcinol on the reproductive system in high-dose male rats, according to the NTP report, there was no difference in the reproductive findings between controls and high-dose-treated males. No adverse findings were noted for the reproductive organs examined in males and females treated with high doses of hexylresorcinol in the 2-year carcinogenicity studies in rats and mice. However, the findings from the general toxicity studies (13-week and 2-year carcinogenicity studies) do not address all relevant reproductive and developmental endpoints for hexylresorcinol. Accordingly, we find that the safety data gap for DART for hexylresorcinol has not been adequately addressed. No new data were submitted to the docket to fill other safety data gaps identified in the 2013 Consumer Wash PR. In addition, as discussed in section IV of this document, no new data were submitted to the docket to demonstrate the effectiveness of the active ingredients subject to this final rule, including hexylresorcinol, for use as a consumer antiseptic wash product. Therefore, hexylresorcinol is not GRAS/GRAE for use in consumer antiseptic wash products.

4. Iodophors/Povidone-Iodine

In the 2013 Consumer Wash PR, we proposed to classify iodophor complexes, including povidone-iodine, 5–10 percent, as Category III, determining that the available safety and effectiveness data were insufficient and further testing was required (78 FR 76444 at 76459). FDA determined that the administrative record for the safety of iodophors was incomplete with respect to the following:

- Human studies of the absorption of iodine following maximal dermal exposure to the complexes
- Human absorption studies of the carrier molecule for small molecular weight povidone molecules and the other carriers listed in the 2013 Consumer Wash PR
- Dermal carcinogenicity studies for each of the iodophor complexes
- Data from laboratory studies that assess the potential for the development of resistance to iodine and cross-resistance to antibiotics in the types of organisms listed in the 2013 Consumer Wash PR (78 FR 76444 at 76453)

(Comment 25) One comment requested that the Agency clarify that multiuse consumer antiseptic products containing the active ingredient povidone-iodine intended for first aid use and general purpose antiseptic cleansing and labeled for only short-term use over limited areas of the skin are outside the scope of the 2013 Consumer Antiseptic PR. The comment explained that the skin cleanser's primary use is as a first aid antiseptic and it is sold in the first aid aisle of retail stores. They also explained that although the labeling provides for uses as a wash, it recommends only short term use over limited areas of the skin, consistent with the 1991 First Aid TFM; and thus, the safety studies proposed in the 2013 Consumer Wash PR should not be required for such multiuse skin cleansing products. The comments also requested that if FDA determines that multiuse antiseptic products are within the scope of the 2013 Consumer Wash PR, that a category I classification be maintained for povidone-iodine, 5–10 percent, with a molecular weight at or above 35,000 Daltons.

(Response 25) The testing requirements for a GRAS/GRAE finding as proposed in the 2013 Consumer Wash PR, apply to all consumer antiseptic wash products containing the active ingredients that are the subject of this final rule and that are intended to be used with water, such as antibacterial soaps and antibacterial hand washes (76 FR 76444 at 76446). If the labeling for these products contains an indication for use as a consumer antiseptic wash, then the product is subject to the testing requirements of the 2013 Consumer Wash PR, even if the labeling also contains an indication for other uses, such as for a first aid antiseptic.

Moreover, because consumer antiseptic washes may be used on multiple occasions throughout a person's lifetime, this use pattern is considered to be chronic. According to the International Council for Harmonization guideline, a use is considered chronic if a certain drug is used for a period of at least 6 months over the user's lifetime, including repeated, intermittent use. Thus, chronic exposure testing is necessary for a GRAS/GRAE determination for the active ingredients used in these consumer antiseptic wash products even if a particular ingredient's labeling recommends that the product's use should be limited in duration.

In addition, we decline to classify povidone-iodine 5–10 percent with a molecular weight at or above 35,000 Daltons as Category I (GRAS/GRAE) for use in consumer washes. Although we stated in the 2013 Consumer Wash PR that the larger molecular weight-size povidone molecules pose no risk of absorption, and we only requested human absorption studies of the carrier molecule for small molecular weight povidone molecules, there are still remaining safety data gaps for the iodophors, including large molecule povidone-iodine (76 FR 76444 at 76459 to 76461). For example, we determined that the administrative record for the safety of iodophors was incomplete for dermal carcinogenicity studies. Accordingly, because the safety data gaps have not been addressed, we cannot make a GRAS determination on the iodophors, including the large molecule povidone-iodine.

(Comment 26) Another comment stated that human absorption data required for the iodophors should take precedence over the requirement for dermal carcinogenicity studies to fill the

safety data gaps for the iodophors. The comment argued that data from the human absorption studies may reduce the number of carcinogenicity studies needed to fill the safety data gaps for iodophors.

(Response 26) Antiseptic products, such as povidone-iodine, are applied topically and require toxicological evaluation in dermal studies to assess the potential safety signals following the exposure. The reason for requiring dermal assessment is because the skin dose resulting from a topically applied drug product can be much higher than the dose detected in the skin as a result of systemic exposure. In addition, systemic exposure to the parent drug and metabolites can differ significantly in topically applied products compared to orally administered products because the skin has its own metabolic capability, and the first-pass metabolism, which is available following oral exposure, is bypassed in the topical route of administration. In some cases, a waiver of dermal carcinogenicity may be considered for a substance used previously by another route if a chronic dermal study in an appropriate non-rodent species shows no potential neoplastic effects and there are no other causes for concern, such as absence of a positive genotoxicity signal and absence of association of exposure to the drug with a positive tumor signal in systemic carcinogenicity data (Refs. 45 and 46). Furthermore, the absence of significant systemic absorption is not a qualifying reason to waive the requirement for the dermal carcinogenicity study.

(Comment 27) A comment submitted on behalf of a marketer of an OTC antiseptic product containing povidone-iodine asserted that povidone-iodine does not pose a risk for the development of resistance (see section III.D.2 for a more general discussion on resistance). The comment noted that none of the studies cited in the 2013 Consumer Wash PR concerning the development of antiseptic/antibiotic resistance involve povidone-iodine. The comment stated that historically, povidone-iodine has not been associated with the development of resistance, and that it has been found to be a useful tool against several multidrug resistant bacteria. In support of its position, the comment submitted data on the chemistry and antimicrobial effects of povidone-iodine and studies of povidone-iodine's in vitro and in vivo effectiveness (Refs. 49 through 54).

(Response 27) Elemental iodine, which is the active antimicrobial component of iodine containing antiseptics like povidone-iodine, is generally believed to be nonspecific in its antimicrobial action (Ref. 55). The antimicrobial activity of iodine is caused by its oxidizing effects on amino (NH-), thiol (SH-), phenolic hydroxyl (OH-) groups of amino acids and nucleotides. These reactions lead to a loss in protein structure and function and an inhibition of protein synthesis. Iodine also reacts with the double bonds of unsaturated fatty acid components of cell wall and organelle membranes, compromising the integrity of these structures. The effects of povidone-iodine on cell ultrastructure have been observed at concentrations as low as 0.025 percent povidone-iodine in *Staphylococcus aureus, Esherichia coli,* and *Candida albicans* (Ref. 49). A decrease in enzyme (β-galactosidase) activity and nucleotide efflux was also apparent at 0.42 and 0.83 percent povidone-iodine (Ref. 49). These concentrations are well below the concentrations of povidone-iodine found in currently marketed products.

A search of the published literature revealed two studies that attempted to select for resistant bacterial strains after repeated exposure to sublethal concentrations of povidone-iodine (Refs. 56 and 57). Houang et al. studied the potential for the development of resistance to povidone-iodine by serial passage of two strains of each of the following organisms: *Escherichia coli, Klebsiella aerogenes,* and one strain of *Serratia marcescens* in sub-inhibitory concentrations (Ref. 56). The authors reported no significant differences in MIC, minimum bactericidal concentration, or killing time after 20 passages. Similarly, Prince et al. reported that they had failed to detect any changes in the MIC of six Gram-negative bacteria (*Proteus mirabilis, Serratia marcescens, Serratia rubidaea, Pseudomonas cepacia (now known as Burkholderia cepacia), Pseudomonas aeruginosa,* and *Salmonella enteritidis*) after 20 serial passages in povidone-iodine (Ref. 57).

The search also revealed some reports of *Burkholderia cepacia* contamination of povidone-iodine products (Refs. 58 through 62). However, the antiseptic susceptibilities of the organisms isolated were never established, making it hard to determine whether the contamination was the result of an existing intrinsic antiseptic resistance that has been associated with *Burkholderia cepacia* or the development of an increased tolerance. In addition, the literature search revealed no reports of the development of resistance to povidone-iodine. Consequently, given iodine's multiple nonspecific toxic effects on bacteria at low concentrations and the lack of reports of the development of resistance to iodine, there currently are insufficient data on which to base a concern about the development of resistance to povidone-iodine. Consequently, additional data on the development of antimicrobial resistance to povidone-iodine are not needed to make a GRAS determination.

5. Triclocarban

In the 2013 Consumer Wash PR, FDA proposed to classify triclocarban as Category III for safety and efficacy (78 FR 76444 at 76449). FDA determined that the administrative record for the safety of triclocarban was incomplete with respect to the following:

- Human pharmacokinetic studies under the maximal use conditions when applied topically, including documentation of validation of the methods used to measure triclocarban and its metabolites
- Animal pharmacokinetic studies on ADME
- Data to help define the effect of formulation on dermal absorption
- Dermal carcinogenicity
- Developmental and reproductive toxicity data
- Potential hormonal effects
- Data from laboratory studies that assess the potential for the development of resistance to triclocarban and cross-resistance to antibiotics in the types of organisms listed in section VII.C.3 of the 2013 Consumer Wash PR (78 FR 76444 at 76456 to 76462)

(Comment 28) One comment referenced a DART study conducted by Monsanto in 1979. The study was summarized in a triclocarban data set compiled in 2002 by the Triclocarban (TCC) Consortium and the Soap and Detergent Association. The comment requested that FDA evaluate the results of the study to fill the DART safety gap for triclocarban.

(Response 28) The TCC Consortium Report was retrieved from the Environmental Protection Agency (EPA) High Production Volume Information System Web site. We were unable to locate the 1979 Monsanto study in the docket and it does not appear to be available in the public domain. Thus, we cannot review this study for purposes of this final rule. The data cited in the TCC Consortium data set are proprietary and are publicly available only in the form of a summary (Ref. 63). In addition, the submitted safety assessments with the study summaries do not constitute an adequate record on which to base a GRAS classification (§ 330.10(a)(4)(i)). For FDA to evaluate

the safety of triclocarban for this rulemaking, there must be published studies or publicly available data with sufficient details that enable an independent review of such data.

(Comment 29) One comment also stated that triclocarban was nominated to the NTP for toxicological evaluation in 2014, and based on this nomination, a Research Concept has been adopted by NTP (Ref. 64). The comment asserted that the author of the Triclocarban Research Concept only discussed FDA's proposal in regard to human absorption studies even though it identified several data gaps that were identified by FDA, including ADME and DART studies. The comment concluded that FDA should coordinate its efforts with those of the NTP to ensure that experiments on the toxicological testing of triclocarban are not being duplicated.

(Response 29) We concur with the comment that FDA should coordinate efforts with NTP. NTP through collaboration with FDA regularly meets with FDA scientists to coordinate research efforts and eliminate duplicative work whenever possible. Although this ongoing study may provide important information on triclocarban, there are still other missing data gaps for triclocarban for which information has not been submitted and no interested parties have committed to filling these data gaps. Accordingly, deferring consideration of this active ingredient until the study is completed is unwarranted.

In conclusion, we find that the safety data gap for DART for triclocarban has not been adequately addressed. No new data for triclocarban were submitted to the docket to fill other safety data gaps identified in the 2013 Consumer Wash PR. In addition, as discussed in section IV, no new data were submitted to the docket to demonstrate the effectiveness of the active ingredients subject to this final rule, including triclocarban, for use as a consumer antiseptic wash product. Therefore, triclocarban is not considered GRAS/GRAE for use in consumer antiseptic wash products.

6. Triclosan

In the 2013 Consumer Wash PR, the Agency found that the administrative record for triclosan was incomplete with respect to several safety data and requested that additional information be submitted for the following safety gaps (76 FR 76444 at 76467 to 76470):

- Animal ADME
- Dermal carcinogenicity
- Data regarding the potential for formation of photodegradation products on human skin and their effects on the skin
- Potential hormonal effects
- Data to clarify the relevance of antimicrobial resistance laboratory findings to the consumer setting

(Comment 30) In response to the 2013 Consumer Wash PR, several comments were submitted regarding the safety data gaps for triclosan. One comment argued that recent and existing studies on triclosan in each of the safety categories prove that the existing studies, including additional studies that were not cited in the 2013 Consumer Wash PR, are adequate to classify triclosan as GRAS.

(Response 30) FDA has conducted a thorough review of all existing and new data that have been submitted to the docket for this rulemaking, including recent studies, as well as opinion papers published by other regulatory agencies regarding the safety of triclosan. In some cases, we identified new data that have been published since the 2013 Consumer Wash PR—for example, the new animal ADME dermal data discussed in the following section. In other cases, no new data having an impact on the safety profile of triclosan were identified—for example, we found that certain references submitted in one of the comments did not provide additional information that would have an impact on the safety assessment of triclosan (Refs. 65 through 67). In sum, the total available data regarding the safety profile of triclosan does not contain sufficient information to determine that triclosan is GRAS for use in consumer antiseptic wash products.

In the following sections, we discuss comments addressing the specific safety data gaps for triclosan.

a. Absorption, Distribution, Metabolism, and Excretion (ADME) Data

The 2013 Consumer Wash PR discussed in detail the animal ADME data available for triclosan (78 FR 76444 at 76467) and the data that were still lacking. FDA requested that additional ADME data be submitted to allow bridging of animal data to human exposure.

(Comment 31) Several comments were submitted regarding animal ADME data for triclosan. Some of the comments asserted that oral absorption, metabolism, and excretion are comparable between hamsters and humans, justifying data extrapolation. They also asserted that oral absorption data are complete in all species tested and that metabolism is similar for both dermal and oral exposure. In addition, some of the comments urged FDA to evaluate key toxicokinetic studies in hamsters, mice, and rats that have been submitted as part of the European Union's Registration, Evaluation, Authorisation, and Restriction of Chemicals registration, as well as evaluate other referenced publications of regulatory agencies.

(Response 31) We agree that there are a number of similarities in pharmacokinetic parameters between humans and hamsters; however, the hamster data available do not include dermal ADME data that can be compared to the metabolic profile in humans following dermal exposure to triclosan.

We have reviewed data that were submitted to the docket for this rulemaking, including recent studies that were published after the 2013 Consumer Wash PR, as well as opinion papers published by other regulatory agencies regarding the safety of triclosan (Ref. 68). With the exception of one study that we have identified that provided new animal dermal ADME data, there were no additional ADME data for triclosan that were submitted to the docket. The ADME study that was identified has been recently published by National Center for Toxicology Research (NCTR) scientists (Ref. 68) where a 13-week dermal-dose range-finding toxicity study was conducted to determine the ADME profile of triclosan after dermal exposure in mice. Based on a previous dermal toxicity study in the mouse where a no observed adverse effect level of 12.5 milligram (mg)/kilogram (kg) of body weight (bw)/day was shown, doses of 10 and 100 mg/kg bw triclosan were used. In this study, mice of both sexes were exposed to topical application of [^{14}C(U)]triclosan (10 or 100 mg triclosan/kg body weight) in 95 percent ethanol up to 72 hours post exposure. Treated mice were covered with Elizabethan collars to prevent inadvertent oral ingestion of triclosan. As a comparator group, mice of both sexes were dosed with 100 mg/kg bw where Elizabethan collars were not placed on their necks to determine the extent of oral ingestion because of the normal grooming behavior in mice. The study reported a dose-dependent increase in absorption was noted when comparing the 10 mg/kg bw to the 100 mg/kg bw. The study also reported that distribution of radiolabeled [^{14}C(U)]triclosan was evaluated to determine distribution up to 72 hours after dosing in the plasma and liver. The earliest radioactivity measureable was seen as early as 30 minutes post dosing, while maximum distribution was reached at approximately 8 to 12 hours after dosing for both plasma and liver. The major metabolite detected in the plasma and liver was triclosan sulfate, whereas the minor metabolite was

triclosan glucuronide. Maximum levels occurred 12 to 24 hours after dosing, and the excretion half-life ($t_{1/2E}$) ranged from 9.3 to 23.1 hours. The study also reported that the majority of the excretion monitored over 72 hours occurred via the feces in both sexes and that fecal excretion of the absorbed triclosan was ~2.5 to 6-fold greater than urinary excretion.

The data obtained from this study can be used to extrapolate a safety margin for humans following chronic dermal exposure once the dermal carcinogenicity study in the mouse, which is currently ongoing at the NCTR, is completed. No further data is needed for the animal ADME for triclosan.

b. Photodegradation and Phototoxicity

(Comment 32) Several comments were submitted regarding the phototoxicity of triclosan. One comment explained that a study is currently ongoing at the NTP in response to the data gap on dermal photocarcinogenicity from dioxins formed by light-induced degradation of triclosan. The comments urged FDA to await the results of this study before any further studies are conducted. Two other comments argued that concern about triclosan dermal photolysis to ''dioxins'' is unfounded, and that the most likely photolysis product, 2, 8-dichlorbenzodioxin is toxicologically inert based on the toxicology equivalency factor (TEF) concept (which compares the toxicity of known members for a given chemical family and attributes a specific TEF for each compound compared to the most toxic chemical of that family).

(Response 32) We note that the comments did not provide any further justification or calculation of the TEF for the photolysis product, 2, 8-dichlorbenzodioxin, to support the claim that FDA's concern about triclosan dermal photolysis to ''dioxins'' is unfounded. Instead, an assumption was made that 2, 8-dichlorbenzodioxin is toxicologically inert based on the TEF concept. The TEF concept refers only to adverse effects (*e.g.,* cancer) following interactions with their targets (*e.g.,* cellular aryl hydrocarbon receptors). Other toxic effects of dioxins and dioxin-like compounds are not quantified by this method. In addition, TEF values vary for different animal species. Therefore, the ability of triclosan degradants, which belong to the dioxin family, to form photodegradation products on human skin cannot be assessed using the TEF concept. Furthermore, it is currently unknown whether the photoactivity of triclosan is caused by one of the photoproducts or caused by the interaction of triclosan itself with ultraviolet (UV) light.

(Comment 33) Another comment stated that triclosan has been found to degrade into four different byproducts under certain conditions: 2, 7-dibenzodichloro-p-dioxin; 2, 8-dibenzodichloro-p-dioxin; 2, 4-dichlorophenol (DCP); and 2, 4, 6-trichlorophenol (TCP). In the presence of UV light (sunlight), triclosan has been shown to degrade into two dioxins: 2, 7-dibenzodichloro-p-dioxin; and 2, 8-dibenzodichloro-p-dioxin. The comment suggested that although the concentrations of the degradants are low, dioxin byproducts raise some concern because of their potential to accumulate in the human body because of their lipophilicity. Both 2, 4-DCP and 2, 4, 6-TCP are more stable than triclosan, suggesting that the degradants may have longer half-lives than the parent drug, triclosan.

(Response 33) Regardless of the causative chemical, it is unknown at this time whether exposure to triclosan under UV light will lead to phototoxicity or photocarcinogenicity events. In conclusion, the comments provided insufficient data and information for assessing the photodegradation of triclosan on human skin. Accordingly, the safety data gap for triclosan regarding the potential for formation of photodegradation products on human skin and their effects on the skin has not been filled.

c. Dermal Carcinogenicity

(Comment 34) Several comments were received regarding the dermal carcinogenicity of triclosan. One comment argued that, based on FDA and EPA assessments, oral carcinogenicity studies in hamsters, rats, and mice, supported by negative in vitro and in vivo mutagenicity studies show that triclosan is not a carcinogen. Therefore, the comments argued that the ongoing dermal carcinogenicity study is unnecessary. Another comment stated that dermal carcinogenicity is not supported by existing data, and no chemical having negative mutagenicity and oral carcinogenicity data should be expected to demonstrate dermal carcinogenicity potential.

(Response 34) We disagree that no dermal carcinogenicity study is needed for triclosan based only on the negative mutagenicity and oral carcinogenicity studies. The requirement for dermal assessment is based on several factors: First, the dose available to the skin tissue resulting from a topically applied drug product can be much higher than that from a dose resulting from systemic exposure. In addition, systemic exposure to the parent drug and metabolites can differ significantly in topically applied products compared to orally administered products because the skin has its own metabolic capability, and the first-pass metabolism, which is available following oral exposure, is bypassed in the topical route of administration. As was explained in the 2013 Consumer Wash PR, we reiterate here that short-term dermal toxicity studies do not meet the chronic duration requirement for a given drug to cause an increase in the carcinogenic potential resulting from a lifelong exposure to a drug, such as triclosan, which is used by consumers from various products over a lifetime. In addition, we note that the 13-week dermal toxicity study showed dose-related dermal adverse effects, which further amplifies the need to evaluate longer term toxicity studies, such as the 2-year dermal carcinogenicity bioassay. A dermal carcinogenicity study is currently ongoing at NCTR but has not been completed at this time. Although this ongoing study may provide important information on triclosan, there are still other missing data gaps for triclosan for which information has not been submitted and no interested parties have committed to filling these data gaps. In sum, no new data or information were submitted to the docket to fill the dermal carcinogenicity safety data gap for triclosan.

d. Hormonal Effects

In the 2013 Consumer Wash PR, we stated that recent studies have demonstrated that triclosan showed effects on the thyroid, estrogen, and testosterone systems in several animal species, including mammals, the implications of which on human health, especially for children, are still not well understood (78 FR 76444 at 76468).

(Comment 35) One comment stated that the Organisation for Economic Co-operation and Development (OECD) TG 443 extended one-generation reproductive toxicity assay provides an alternative to animal studies and includes endocrine-sensitive endpoints. The comment asserted that the OECD TG 443 study design allows for investigation of developmental toxicity, developmental immunotoxicity, or developmental neurotoxicity in the same study, and that non-animal methods, when used in an integrated system, can provide embryotoxicity and teratogenicity information. The comment also referenced several other non-animal assays that were conducted to assess the reproductive toxicity potential for triclosan.

(Response 35) We reviewed all available data on the hormonal effects of triclosan, including those generated from the extended one-generation reproductive toxicity assay mentioned previously in this document. We also reviewed the previously conducted studies for triclosan (general toxicity and reproductive toxicity) where reproductive toxicity endpoints were evaluated; however, we note that the previously conducted studies were not designed to investigate specific endpoints for evaluating the hormonal effects of triclosan, especially with respect to the thyroid findings. In terms of the alternative animal model argument, it is possible that in some instances that non-animal assays, such as those referenced in comment 35, can be used to explore potential DART findings for a new chemical entity. However, in the case of triclosan, there are many in vivo studies that have assessed DART endpoints, thus making the reliance on findings from the referenced non-animal assays unnecessary.

(Comment 36) Several other comments asserted that the existing database of in vitro and in vivo animal and human studies does not support a conclusion that triclosan causes hormonal effects in humans at actual relevant exposure concentrations. The comments asserted that the reports of high throughput screening and animal studies showing thyroid or other hormonal activity demonstrated conflicting results for the effects of triclosan on various hormonal endpoints (androgen-, estrogen-, and thyroid-related toxicity). One comment also argued that additional testing for potential hormonal effects is not justified because of the existence of adequate reproductive toxicity data that, given the doses used, endpoints measured and study duration, should have detected a potential for the indication of biologically significant androgen-, estrogen-, or thyroid-related toxicity if such toxicity occurred. The comment maintained that available in vitro high throughput screen information on these endpoints fails to indicate a justifiable level of concern.

(Response 36) We agree that some data for hormonal effects for triclosan can be gleaned from previously conducted studies (chronic toxicity, DART, and multigenerational studies). Although we concur that the previously conducted toxicology and reproductive studies can be useful, we note that the previously conducted studies were not designed to investigate specific endpoints for evaluating the hormonal effects of triclosan. In particular, the effects of triclosan on the thyroid gland during critical windows of growth and development when subtle functional and/or histopathologic changes are taking place could result in disturbing the normal homeostasis of the organism; for example, whether long-term exposure to triclosan is associated with an adverse impact on the growth or neurobehavioral aspects of animals treated during critical windows of development is currently unknown.

We have evaluated the recently published articles in the literature reporting on the endocrine effects of triclosan in mammalian species. Data available to date do not provide conclusive evidence regarding the effects of triclosan on the levels of estrogen, androgen, and thyroid hormones and whether a link between the hormonal effects and the biologically relevant outcomes on the tested animal model can be drawn. Although no significant findings were noted for reproductive endpoints, the thyroid gland may be a potential target for triclosan in animals exposed to high doses of triclosan. The reported findings in the thyroid included a dose dependent decrease in the levels of some thyroid hormones in the rat model (T_3 & T_4) (Ref. 69). This observation was seen in pubertal males and females, in pregnant dams and their pre-weaned exposed pups, as well as in young male and female rats (up to day 53 postpartum age). It is also important to note that the available rat studies for which the thyroid effects were investigated in detail only covered a short duration (up to 30 days of exposure). These changes seen in thyroid hormone levels in the rat do not necessarily predict a similar scenario in humans because of differences in the physiology and metabolic characteristics that triclosan imparts on the hormonal homeostasis in the two species. Based on the available data, a conclusion regarding the significance of the thyroid findings in the rat to that in humans cannot be made. Using a weight-of-evidence approach for the thyroid findings, we find that no further nonclinical data are recommended for the characterization of potential hormonal effects of triclosan in humans. Available in vitro and in vivo animal studies cannot be used to predict a potential human hormonal signal. Clinical studies may be better able to evaluate the effects of triclosan on the endocrine system in humans.

e. Resistance

(Comment 37) Comments from a manufacturer of consumer antiseptic products containing triclosan asserted that there is no proof of triclosan resistance or confirmation that triclosan/antibiotic cross-resistance is becoming a problem in the real world. The comment also noted that although bacteria can develop reduced susceptibilities to triclosan in the laboratory, the level of sensitivity is still well below the at-use concentration. However, other comments disagreed and argued that recent studies provide evidence of the development of resistance to triclosan (Refs. 29 and 30).

(Response 37) We agree that currently there is no evidence of bacterial resistance to actual-use concentrations of triclosan. However, bacterial exposure to triclosan is not limited to actual-use concentrations. In a natural setting, bacteria are exposed to sublethal concentrations of the antiseptic active ingredient that can trigger the expression of bacterial resistance mechanisms. The European Commission's Subcommittee on Consumer Safety noted that there are environmental concentrations of triclosan in a number of geographically distinct areas that were high enough to suggest that this triggering of bacterial resistance could occur (Ref.70). Furthermore, as previously discussed, there are data that document the existence of numerous bacterial resistance mechanisms to triclosan, and there is some expression of these mechanisms in the natural microbial populations. Although the available studies do not prove definitively that triclosan/antibiotic resistance currently poses a public health risk, they do suggest that susceptibility to triclosan may be decreasing. Data are not currently available to assess the magnitude of this risk that triclosan poses for the development of resistance. As we stated in the in the 2013 Consumer Wash PR, data to clarify the relevance of antimicrobial resistance laboratory findings to the consumer setting would be necessary to determine the GRAS status of triclosan.

f. Other Issues

(Comment 38) Several comments expressed concern that antiseptic chemicals, including triclosan, are contaminating waterways and aquatic wildlife, and are having a negative impact on the wastewater treatment process and the environment. The comments supported restrictions on the use of triclosan in consumer antiseptic washes and urged FDA and EPA to coordinate their evaluation of chemicals like triclosan to better protect human health and the environment, as well as protect the wastewater treatment process.

(Response 38) We do not address these comments in this final rule because they are outside the scope of this rulemaking. We note, however, that we have conferred with EPA, wherever there were issues in common between the two Agencies (*e.g.,* some of the animal toxicology studies were independently reviewed by both EPA and FDA), at various stages of the antiseptic proceedings on matters applicable to these rulemakings.

In sum, the total available data regarding the safety profile of triclosan do not contain sufficient information to find that triclosan is GRAS for use in consumer antiseptic wash products. Moreover, we reviewed studies submitted in the comments to support efficacy for triclosan. These studies are not designed as adequate and well-controlled clinical outcome studies and are not sufficient to determine the GRAE status of triclosan as a topical antiseptic. Moreover, these studies lack an adequate vehicle or placebo controls, which makes it difficult to determine the contribution of antiseptic hand wash implementation to reduction of methicillin-resistance *Staphylococcus aureus* infections. Thus, we find that insufficient data were submitted to the docket to demonstrate the effectiveness of triclosan for use as a consumer antiseptic wash product. Therefore, triclosan is not GRAS/GRAE for use in consumer antiseptic wash products.

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

(Comment 39) Several comments raised issues concerning the preliminary regulatory impact analysis and the Agency's assessment of the net benefit of the rulemaking.

(Response 39) Our response is provided in the full discussion of economic impacts, available in the docket for this rulemaking (Docket No. 1975–N–0012, *http://www.regulations.gov*) and at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.*

IV. Ingredients Not Generally Recognized as Safe and Effective

In addition to the individual active ingredients discussed in section III.E, no additional safety or effectiveness data have been submitted to support a GRAS/GRAE determination for the remaining consumer antiseptic wash active ingredients. Thus, the following active ingredients are not GRAS/GRAE for use as a consumer antiseptic wash:

- Cloflucarban
- Fluorosalan
- Hexachlorophene
- Hexylresorcinol
- Iodophors (Iodine-containing ingredients)
  - Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
  - Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
  - Nonylphenoxypoly (ethyleneoxy) ethanoliodine
  - Poloxamer—iodine complex
  - Povidone-iodine 5 to 10 percent
  - Undecoylium chloride iodine complex
- Methylbenzethonium chloride
- Phenol (greater than 1.5 percent)
- Phenol (less than 1.5 percent)
- Secondary amyltricresols
- Sodium oxychlorosene
- Tribromsalan
- Triclocarban
- Triclosan
- Triple dye

Accordingly, OTC consumer antiseptic wash drug products containing these active ingredients are misbranded, and are new drugs for which approved new drug applications are required for marketing.

V. Effective Date

In the 2013 Consumer Wash PR, 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 2013 Consumer Wash PR (78 FR 76444 at 76470), this final rule will be effective 1 year after the date of the final rule's publication in the **Federal Register**. On or after that date, any OTC consumer antiseptic wash drug product containing an ingredient that we have found in this final rule to be not GRAS/GRAE or to be misbranded, cannot be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application.

VI. Economic Analysis of Impacts

The summary analysis of benefits and costs included in this final rule is drawn from the detailed Regulatory Impact Analysis that is available at *http://www.regulations.gov,* Docket No. FDA–1975–N–0012 (formerly Docket No. 1975N–0183H).

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct 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). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. The Office of Management and Budget (OMB) has determined that 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. Because a majority of firms that will be affected by this rule are defined as small businesses, we find that the final rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before 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 $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule would result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

As discussed in the preamble of this final rule, this rule establishes that 19 active ingredients, including triclosan and triclocarban, are not generally recognized as safe and effective and are misbranded for use in OTC consumer antiseptic washes. Regulatory action is being deferred on three active ingredients that were included in the 2013 Consumer Wash PR: Benzalkonium chloride, benzethonium chloride, and chloroxylenol. The costs and benefits of the final rule are summarized in table 3, entitled *Economic Data: Costs and Benefits Statement.* As table 3 shows, the primary estimated benefits come from reduced exposure to antiseptic active ingredients by 2.2 million pounds per year. We note that triclosan and triclocarban, are the most widely used OTC consumer antiseptic wash active ingredients on the market, based on available data, thus, our analysis focuses

on these two products. Using the primary estimates, the combined total consists of a reduction in triclosan exposure by 799,426 pounds per year, and triclocarban exposure by 1.4 million pounds per year. Limitations in the available data characterizing the health effects resulting from widespread long-term exposure to these ingredients prevent us from translating the estimated reduced exposure into monetary equivalents of health effects.

The primary estimate of costs annualized over 10 years is approximately $23.6 million at a 3 percent discount rate and $27.6 million at a 7 percent discount rate. These costs consist of total one-time costs of relabeling and reformulation ranging from $106.3 to $402.8 million. Under the final rule, we estimate that each pound of reduced exposure to antiseptic active ingredients will cost $12.97 to $14.28 at a 3 percent discount rate and $16.36 to $18.02 at a 7 percent discount rate.

TABLE 3—ECONOMIC DATA: COSTS AND BENEFITS STATEMENT

Economic Data: Costs and Benefits Statement							
				Units			
Category	Primary estimate	Low estimate	High estimate	Year dollars	Discount rate (%)	Period covered	Notes
Benefits							
Annualized Monetized $millions/year.					7 3	Annual. Annual.	
Annualized Quantified	2,197,737 2,197,737	989,856 989,856	3,405,619 3,405,619		7 3	Annual .. Annual.	Reduced antiseptic active ingredient exposure (in pounds).
Qualitative							
Costs							
Annualized Monetized $millions/year.	27.6 23.6	14.1 12.1	53.6 45.8	2014 2014	7 3	Annual .. Annual.	Annualized costs of relabeling and reformulation. Range of estimates captures uncertainty.
Annualized Quantified					7 3		
Qualitative							
Transfers							
Federal Annualized Monetized $millions/year.					7 3		None.
From/To	From:			To:			
Other Annualized Monetized $millions/year.					7 3		
From/To	From:			To:			
Effects							
State, Local, or Tribal Government: Not applicable.							
Small Business							
Annual cost per affected small entity estimated as $0.11–$0.41 million, which will represent 0.28–1.10 percent of annual shipments.							
Wages: No estimated effect.							
Growth: No estimated effect.							

The full analysis of economic impacts is available in the docket for this final rule (Docket No. FDA–1975–N–0012) and at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.*

VII. Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by OMB under the Paperwork Reduction Act of 1995 is not required.

VIII. 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.

IX. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to ''construe . . . a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.'' The sole statutory provision giving preemptive effect to the final rule is section 751 of the FD&C Act (21 U.S.C. 379r). We have complied with all of the applicable requirements under the Executive order and have determined that the preemptive effects of this rule are consistent with Executive Order 13132.

X. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *http://www.regulations.gov.* FDA has verified all Web site addresses as of the date of this document, but Web sites 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. Available at *http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4098T1.htm.*
2. Comment submitted in Docket No. FDA–1975–N–0012, available at *http://www.regulations.gov* with Comment No. FDA–1975–N–0012–0081.
3. Transcript of the March 23, 2005, Nonprescription Drugs Advisory Committee. Available at *http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4184T1.pdf.*
4. Transcript of the October 20, 2005, Meeting of the Nonprescription Drugs Advisory Committee 2005. Available at *http://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 *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://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM421121.pdf.*
7. Part 130-New Drugs, Procedures for Classification of Over-the-Counter Drugs, 37 FR 9464 (1972). Available at *https://www.federalregister.gov/agencies/library-of-congress.*
8. Luby, S. P., et al., ''Effect of Handwashing on Child Health: A Randomised Controlled Trial,'' *Lancet,* 366(9481): p. 321–329, 2005. Available at *http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(05)66912-7.pdf.*
9. Larson, E. L., et al., ''Effect of Antibacterial Home Cleaning and Handwashing Products on Infectious Disease Symptoms: A Randomized, Double-Blind Trial,'' *Annals of Internal Medicine,* 140(5): p. 321–9, 2004. Available at *http://annals.org/article.aspx?articleid=717252.*
10. Webster, J., J. L. Faoagali, and D. Cartwright, ''Elimination of Methicillin-Resistant *Staphylococcus aureus* from a Neonatal Intensive Care Unit After Hand Washing with Triclosan,'' *Journal of Paediatrics and Child Health,* 30(1): p. 59–64, 1994. Available at *http://www.ncbi.nlm.nih.gov/pubmed/8148192.*
11. Zafar, A. B., et al., ''Use of 0.3% Triclosan (Bacti-Stat) to Eradicate an Outbreak of Methicillin-Resistant *Staphylococcus aureus* in a Neonatal Nursery,'' *American Journal of Infection Control,* 23(3): p. 200–8, 1995. Available at *http://www.ajicjournal.org/article/0196-6553(95)90042-X/pdf.*
12. Schaffner, D. W., et al., ''Quantitative Microbial Risk Assessment of Antibacterial Hand Hygiene Products on Risk of Shigellosis,'' *Journal of Food Protection,* 77(4): p. 574–82, 2014. Available at *http://www.ncbi.nlm.nih.gov/pubmed/?term=Quantitative+microbial+risk+assessment+of+antibacterial+hand+hygiene+products+on+risk+of+shigellosis.*
13. Chen, Y., et al., ''Quantification and Variability Analysis of Bacterial Cross-Contamination Rates in Common Food Service Tasks,'' *Journal of Food Protection,* 64(1): p. 72–80, 2001. Available at *http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.492.3167&rep=rep1&type=pdf.*
14. Chen, Y., et al., ''FDA-iRISK—A Comparative Risk Assessment System for Evaluating and Ranking Food-Hazard Pairs: Case Studies on Microbial Hazards,'' *Journal of Food Protection,* 76(3): p. 376–85, 2013. Available at *http://www.ncbi.nlm.nih.gov/pubmed/?term=FDA-iRISK-a+comparative+risk+assessment+system+for+evaluating+and+ranking+food-hazard+pairs%3A+case+studies+on+microbial+hazards.*
15. Ball, R., et al., ''Statistical, Epidemiological, and Risk-Assessment Approaches to Evaluating Safety of Vaccines Throughout The Life Cycle at the Food and Drug Administration,'' *Pediatrics,* 127 Suppl 1: p. S31–8, 2011. Available at *http://pediatrics.aappublications.org/content/pediatrics/127/Supplement_1/S31.full.pdf.*
16. Oggioni, M. R., et al., ''Recent Advances in the Potential Interconnection Between Antimicrobial Resistance to Biocides and Antibiotics,'' *Expert Review of Anti-Infective Therapy,* 11(4): p. 363–6, 2013. Available at *http://www.ncbi.nlm.nih.gov/pubmed/23566146.*
17. Hansen, L. H., et al., ''Substrate Specificity of the OqxAB Multidrug Resistance Pump in *Escherichia coli* and Selected Enteric Bacteria,'' *Journal of Antimicrobial Chemotherapy,* 60(1): p. 145–7, 2007. Available at *http://pediatrics.aappublications.org/content/127/Supplement_1/S31.*
18. Mavri, A. and S. S. Mozina, ''Involvement of Efflux Mechanisms in Biocide Resistance of *Campylobacter jejuni* and *Campylobacter coli*,'' *Journal of Medical Microbiology*, 61(Pt. 6): p. 800–8, 2012. Available at *http://www.ncbi.nlm.nih.gov/pubmed/?term=Involvement+of+efflux+mechanisms+in+biocide+resistance+of+Campylobacter+jejuni+and+Campylobacter+coli8.*
19. Mavri, A. and S. S. Mozina, ''Development of Antimicrobial Resistance in *Campylobacter jejuni* and *Campylobacter coli* Adapted to Biocides,'' International Journal of Food Microbiology, 160(3): p. 304–12, 2013. Available at *http://www.ncbi.nlm.nih.gov/pubmed/23290239.*
20. Curiao, T., et al., ''Polymorphic Variation in Susceptibility and Metabolism of Triclosan-Resistant Mutants of *Escherichia coli* and *Klebsiella pneumoniae* clinical Strains Obtained After Exposure to Biocides and Antibiotics,'' *Antimicrobial Agents and Chemotherapy,* 59(6): p. 3413–23, 2015. Available at *http://aac.asm.org/content/59/6/3413.full.*
21. Rensch, U., et al., ''*Salmonella enterica* Serovar *Typhimurium* Multidrug Efflux Pumps EmrAB and AcrEF Support the Major Efflux System AcrAB in Decreased Susceptibility to Triclosan,'' *International Journal of Antimicrobial Agents,* 44(2): p. 179–80, 2014. Available at *http://www.ncbi.nlm.nih.gov/pubmed/25059442.*
22. Rensch, U., G. Klein, and C. Kehrenberg, ''Analysis of Triclosan-Selected *Salmonella enterica* Mutants of Eight Serovars Revealed Increased Aminoglycoside Susceptibility and Reduced Growth Rates,'' *PLOS One,* 8(10): p. e78310, 2013. Available at *http://journals.plos.org/plosone/article/authors?id=10.1371%2Fjournal.pone.0078310.*
23. Fernando, D. M., et al., ''Triclosan Can Select for an AdeIJK-Overexpressing Mutant of *Acinetobacter baumannii* ATCC 17978 that Displays Reduced Susceptibility to Multiple Antibiotics,'' *Antimicrobial Agents and Chemotherapy,* 58(11): p. 6424–31, 2014. Available at *http://aac.asm.org/content/58/11/6424.full.pdf+html.*
24. Grandgirard, D., et al., ''Mutations Upstream of fabI in Triclosan Resistant *Staphylococcus aureus* Strains are

Associated with Elevated fabI Gene Expression,'' *BMC Medical Genomics,* 16: p. 345, 2015. Available at *http://bmcgenomics.biomedcentral.com/articles/10.1186/s12864-015-1544-y.*

25. Buffet-Bataillon, S., et al., ''Molecular Mechanisms of Higher MICs of Antibiotics and Quaternary Ammonium Compounds for *Escherichia coli* Isolated From Bacteraemia,'' *Journal of Antimicrobial Chemotherapy,* 67(12): p. 2837–42, 2012. Available at *http://jac.oxfordjournals.org/content/67/12/2837.full.pdf+html.*
26. Guo, W., et al., ''Resistant Mechanism Study of Benzalkonium Chloride Selected *Salmonella Typhimurium* Mutants,'' *Microbial Drug Resistance,* 20(1): p. 11–6, 2014. Available at *http://online.liebertpub.com/doi/abs/10.1089/mdr.2012.0225.*
27. Bore, E., et al., ''Adapted Tolerance to Benzalkonium Chloride in *Escherichia coli* K–12 Studied by Transcriptome and Proteome Analyses,'' *Microbiology,* 153(Pt. 4): p. 935–46, 2007. Available at *http://www.ncbi.nlm.nih.gov/pubmed/?term=Adapted+tolerance+to+benzalkonium+chloride+in+Escherichia+coli+K–12+studied+by+transcriptome+and+proteome+analyse.*
28. Morrissey, I., et al., ''Evaluation of Epidemiological Cut-Off Values Indicates that Biocide Resistant Subpopulations are Uncommon in Natural Isolates of Clinically-Relevant Microorganisms,'' *PLOS One,* 9(1): p. e86669, 2014. Available at *http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0086669.*
29. Copitch, J. L., R. N. Whitehead, and M. A. Webber, ''Prevalence of Decreased Susceptibility to Triclosan in *Salmonella enterica* Isolates from Animals and Humans and Association with Multiple Drug Resistance,'' *International Journal of Antimicrobial Agents,* 36(3): p. 247–51, 2010. Available at *http://www.ncbi.nlm.nih.gov/pubmed/20541914.*
30. Skovgaard, S., et al., ''*Staphylococcus epidermidis* Isolated in 1965 Are More Susceptible to Triclosan than Current Isolates,'' *PLOS One,* 8(4): p. e62197, 2013. Available at *http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0062197.*
31. Cole, E. C. et al., ''Investigation of Antibiotic and Antibacterial Susceptibility and Resistance in Staphylococcus from the Skin of Users and Non-users of Antibacterial Wash Products in Home Environments,'' International Journal of Microbiology Research 3 (2): p 90–96, 2003. Available at *http://www.bioinfopublication.org/files/articles/3_2_4_IJMR.pdf.*
32. Lear, J. C., ''Chloroxylenol- and Triclosan-Tolerant Bacteria from Industrial Sources—Susceptibility to Antibiotics and Other Biocides,'' *International Biodeterioration and Biodegradation,* 2006. Available at *http://www.sciencedirect.com/science/article/pii/S096483050500137X.*
33. Lear, J. C., et al., ''Chloroxylenol- and Triclosan-Tolerant Bacteria from Industrial Sources,'' *Journal of Industrial Microbiology and Biotechnology,* 29(5): p. 238–42, 2002. Available at *http://link.springer.com/article/10.1038/sj.jim.7000320#page-1.*
34. Aiello, A. E., et al., ''Relationship Between Triclosan and Susceptibilities of Bacteria Isolated from Hands in the Community,'' *Antimicrobial Agents and Chemotherapy,* 48(8): p. 2973–9, 2004. Available at *http://aac.asm.org/content/48/8/2973.full.pdf+html.*
35. Aiello, A. E., et al., ''Antibacterial Cleaning Products and Drug Resistance,'' *Emerging Infectious Diseases,* 11(10): p. 1565–70, 2005. Available at *http://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(03)00723-0.pdf.*
36. Cole, E. C., et al., ''Investigation of Antibiotic and Antibacterial Agent Cross-Resistance in Target Bacteria From Homes of Antibacterial Product Users and Nonusers,'' *Journal of Applied Microbiology,* 95(4): p. 664–676, 2003. Available at *http://www.ncbi.nlm.nih.gov/pubmed/12969278.*
37. Marshall, B. M., et al., ''The Frequency of Antibiotic-Resistant Bacteria in Homes Differing in Their Use of Surface Antibacterial Agents,'' *Current Microbiology,* 65(4): p. 407–15, 2012. Available at *http://www.ncbi.nlm.nih.gov/pubmed/22752336.*
38. Carson, R. T., et al., ''Use of Antibacterial Consumer Products Containing Quaternary Ammonium Compounds and Drug Resistance in the Community,'' *Journal of Antimicrobial Chemotherapy,* 62(5): p. 1160–2, 2008. Available at *http://www.ncbi.nlm.nih.gov/pubmed/?term=Carson+RT%2C+Larson+E%2C+Levy+SB%2C+Marshall+BM%2C+Aiello+AE.*
39. Coelho, J. R., et al., ''The Use of Machine Learning Methodologies to Analyse Antibiotic and Biocide Susceptibility in *Staphylococcus aureus,'' PLOS One,* 8(2): p. e55582, 2013. Available at *http://www.ncbi.nlm.nih.gov/pubmed/?term=Coelho+JR%2C+Carri%C3%A7o+JA%2C+Knight+D%2C+Mart%C3%ADnez+JL%2C+Morrissey+I%2C+Oggioni+MR%2C+Freitas+AT.*
40. Braoudaki, M. and A. C. Hilton, ''Adaptive Resistance to Biocides in *Salmonella enterica* and *Escherichia coli* O157 and Cross-Resistance to Antimicrobial Agents,'' *Journal of Clinical Microbiology,* 42(1): p. 73–8, 2004. Available at *http://www.ncbi.nlm.nih.gov/pubmed/14715734.*
41. Brenwald, N. P. and A. P. Fraise, ''Triclosan Resistance in Methicillin-Resistant *Staphylococcus aureus* (MRSA),'' *Journal of Hospital Infections,* 55(2): p. 141–4, 2003. Available at *http://www.ncbi.nlm.nih.gov/pubmed/14529640.*
42. Langsrud, S., G. Sundheim, and A. L. Holck, ''Cross-Resistance to Antibiotics of *Escherichia coli* Adapted to Benzalkonium Chloride or Exposed to Stress-Inducers,'' *Journal of Applied Microbiology,* 96(1): p. 201–8, 2004. Available at *http://www.ncbi.nlm.nih.gov/pubmed/14678175.*
43. Birosova, L. and M. Mikulasova, ''Development of Triclosan and Antibiotic Resistance in *Salmonella enterica* serovar *Typhimurium,'' Journal of Medical Microbiology,* 58(Pt. 4): p. 436–41, 2009. Available at *http://www.ncbi.nlm.nih.gov/pubmed/19273638.*
44. Joynson, J. A., B. Forbes, and R. J. Lambert, ''Adaptive Resistance to Benzalkonium Chloride, Amikacin and Tobramycin: The Effect on Susceptibility to Other Antimicrobials,'' Journal of Applied Microbiology, 93(1): p. 96–107, 2002. Available at *http://www.ncbi.nlm.nih.gov/pubmed/?term=Joynson+JA%2C+Forbes+B%2C+Lambert+RJ.*
45. International Conference on Harmonization S1B. Available at *http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1B/Step4/S1B_Guideline.pdf.*
46. Guidance for IndustryS1B Testing for Carcinogenicity of Pharmaceuticals. Available at *http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm074916.pdf.*
47. Citizen Petition submitted by Comprehensive Technology Center, FDA Docket No. 1996–P–0205–005, Aug. 9, 1996. Available at *https://www.regulations.gov/document?D=FDA-1996-P-0205-0001.*
48. ''NTP Toxicology and Carcinogenesis Studies of 4-Hexylresorcinol (CAS No. 136–77–6) in F344/N Rats and B6C3F1 Mice (Gavage Studies),'' National Toxicology Program Technical Rep Series, 330: p. 1–166, 1988. Available at *http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr300399/abstracts/tr330/index.html.*
49. Schreier, H., et al., ''Molecular Effects of Povidone-Iodine on Relevant Microorganisms: An Electron-Microscopic and Biochemical Study,'' *Dermatology,* 195 Suppl 2: p. 111–6, 1997. Available at *http://www.ncbi.nlm.nih.gov/pubmed/9403268.*
50. Reimer, K., et al., ''Antimicrobial effectiveness of povidone-iodine and consequences for new application areas,'' *Dermatology,* 204 Suppl 1: p. 114–20, 2002. Available at *http://www.ncbi.nlm.nih.gov/pubmed/12011534.*
51. Durani, P. and D. Leaper, ''Povidone-Iodine: Use in Hand Disinfection, Skin Preparation and Antiseptic Irrigation,'' *International Wound Journal,* 5(3): p. 376–87, 2008. Available at *http://www.ncbi.nlm.nih.gov/pubmed/18593388.*
52. Barabas, E. G. and H. G. Brittain., ''Povidone-Iodine in 25 Analytical Profiles and Excipients—Volume 25,'' *Academic Press, Inc.,* 25: p. 341–387, 1998. Available at *https://books.google.com/books?id=kia7bq8EM9IC&pg=PA341&lpg=PA341&dq=Barabas;+Povidone-Iodine+in+25+Analytical+Profiles+and+*

Excipients%E2%80%94Volume+25,%E2%80%9D+Academic+Press,+Inc&source=bl&ots=ba5Vqlsbem&sig=z87Vk2drikzKZ9cVuO4ZhAxoZYI&hl=en&sa=X&ved=0ahUKEwiz177BtYfOAhWCGT4KHTQ7BSoQ6AEIHjAA#v=onepage&q=Barabas%3B%20Povidone-Iodine%20in%2025%20Analytical%20Profiles%20and%20Excipients%E2%80%94Volume%2025%2C%E2%80%9D%20Academic%20Press%2C%20Inc&f=false.

53. Michel, D. and G. A. Zach, ''Antiseptic Efficacy of Disinfecting Solutions in Suspension Test in vitro Against Methicillin-Resistant *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli* in Pressure Sore Wounds After Spinal Cord Injury,'' *Dermatology,* 195 Suppl 2: p. 36–41, 1997. Available at *http://www.karger.com/Article/PDF/246028.*
54. Block, C., et al., ''Evaluation of Chlorhexidine and Povidone Iodine Activity Against Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant *Enterococcus faecalis* Using a Surface Test,'' *Journal of Hospital Infections,* 46(2): p. 147–52, 2000. Available at *http://www.ncbi.nlm.nih.gov/pubmed/?term=Evaluation+of+chlorhexidine+and+povidone+iodine+activity+against+methicillin-resistant+Staphylococcus+aureus+and+vancomycin-resistant+Enterococcus+faecalis+using+a+surface+test.*
55. Block, S. S., ''Disinfection, Sterilization, and Preservation,'' Philadelphia: Lippincott Williams & Wilkins, 2001. Available at. Available at *https://books.google.com/books?id=3f-kPJ17_TYC&printsec=frontcover&dq=Disinfection,+Sterilization,+and+Preservation&hl=en&sa=X&ved=0ahUKEwiNxurX6JHOAhWTix4KHVcKDKcQ6AEIHjAA#v=onepage&q=Disinfection%2C%20Sterilization%2C%20and%20Preservation&f=false.*
56. Houang, E. T., et al., ''Absence of Bacterial Resistance to Povidone Iodine,'' *Journal of Clinical Pathology,* 29(8): p. 752–5, 1976. Available at *http://jcp.bmj.com/content/29/8/752.long.*
57. Prince, H. N., et al., ''Drug resistance studies with topical antiseptics,'' *Journal of Pharmaceutical Sciences,* 67(11): p. 1629–31, 1978. Available at *http://www.ncbi.nlm.nih.gov/pubmed/712607.*
58. Panlilio, A. L., et al., ''Infections and pseudoinfections due to povidone-iodine solution contaminated with Pseudomonas cepacia,'' *Clinical Infectious Diseases,* 14(5): p. 1078–83, 1992. Available at *http://www.jstor.org/stable/4456469?seq=1#page_scan_tab_contents.*
59. Jarvis, W. R., ''Nosocomial Outbreaks: The Centers for Disease Control's Hospital Infections Program Experience, 1980–1990. Epidemiology Branch, Hospital Infections Program,'' *American Journal of Medicine,* 91(3B): p. 101S–106S, 1991. Available at *http://www.ncbi.nlm.nih.gov/pubmed/1656744.*
60. Prevention, CDC, ''Contaminated Povidone-Iodine Solution—Texas,'' in *Morbidity and Mortality Weekly Report,* p. 133–4, 1989. Available at *http://www.cdc.gov/mmwr/preview/mmwrhtml/00001358.htm.*
61. Berkelman, R. L., et al., ''Pseudobacteremia Attributed to Contamination of Povidone-Iodine with *Pseudomonas cepacia,'' Annals of Internal Medicine,* 95(1): p. 32–6, 1981. Available at *http://annals.org/article.aspx?articleid=694897.*
62. Craven, D. E., et al., ''Pseudobacteremia Caused by Povidone-Iodine Solution Contaminated with *Pseudomonas cepacia,'' New England Journal of Medicine,* 305(11): p. 621–3, 1981. Available at *http://www.nejm.org/doi/full/10.1056/NEJM198109103051106.*
63. Triclocarban (TCC) Consortium, Soap and Detergent Association. IUCLID Data Set: Triclocarban. December 12, 2002. Available at *http://www.aciscience.org/docs/Triclocarban_HPV_Robust_Study_Summaries.pdf.*
64. Sutherland, V., ''NTP Research Concept: Triclocarban.'' Available at *http://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2014/june/triclocarban_concept_508.pdf,* 2014.
65. Scientific Committee on Consumer Products (SCCP) opinion on Triclosan COLIPA n° P32. Available at *http://ec.europa.eu/health/archive/ph_risk/committees/04_sccp/docs/sccp_o_166.pdf.*
66. Addendum to the SCCP Opinion on Triclosan. Available at *http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_054.pdf.*
67. Registered substances. Available at *http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.*
68. Fang, J. L., et al., ''Absorption and Metabolism of Triclosan After Application to the Skin of B6C3F1 Mice,'' *Environmental Toxicology,* 2014. Avilable at *http://www.ncbi.nlm.nih.gov/pubmed/?term=Absorption+and+metabolism+of+triclosan+after+application+to+the+skin+of+B6C3F1+mice.*
69. Crofton, K. M., et al., ''Short-Term in vivo Exposure to the Water Contaminant Triclosan: Evidence for Disruption of Thyroxine, '' *Environmental Toxicology and Pharmacology,* 24(2): p. 194–7, 2007. Available at *http://www.ncbi.nlm.nih.gov/pubmed/?term=Short-term+in+vivo+exposure+to+the+water+contaminant+triclosan%3A+Evidence+for+disruption+of+thyroxine.*
70. European Commission Scientific Committee on Consumer Safety, Final Opinion on Triclosan (Antimicrobial Resistance), cited March 24, 2016, available at *http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm.*

List of Subjects in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

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

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

■ 2. In § 310.545, add paragraphs (a)(27)(iii) and (iv) and (d)(41), and remove from paragraph (d) introductory text the number ''(39)'' and add in its place the number ''(41)'' to read as follows:

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

(a) * * *

(27) * * *

(iii) *Consumer antiseptic hand wash drug products.* Approved as of September 6, 2017.

Cloflucarban
Fluorosalan
Hexachlorophene
Hexylresorcinol
Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
Methylbenzethonium chloride
Nonylphenoxypoly (ethyleneoxy) ethanoliodine
Phenol (greater than 1.5 percent)
Phenol (less than 1.5 percent)
Poloxamer iodine complex
Povidone-iodine (5 to 10 percent)
Secondary amyltricresols
Sodium oxychlorosene
Tribromsalan
Triclocarban
Triclosan
Triple Dye
Undecoylium chloride iodine complex

(iv) *Consumer antiseptic body wash drug products.* Approved as of September 6, 2017.

Cloflucarban
Fluorosalan
Hexachlorophene
Hexylresorcinol
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
Iodine tincture
Methylbenzethonium chloride
Nonylphenoxypoly (ethyleneoxy) ethanoliodine
Phenol (greater than 1.5 percent)

Phenol (less than 1.5 percent)
Poloxamer iodine complex
Povidone-iodine (5 to 10 percent)
Secondary amyltricresols
Sodium oxychlorosene
Tribromsalan
Triclocarban
Triclosan
Triple Dye
Undecoylium chloride iodine complex
* * * * *

(d) * * *

(41) September 6, 2017, for products subject to paragraph (a)(27)(iii) or (iv) of this section.

Dated: August 31, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016–21337 Filed 9–2–16; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–433]

Schedules of Controlled Substances: Placement of PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA into Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Drug Enforcement Administration places quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate (PB-22; QUPIC), quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate (5-fluoro-PB-22; 5F-PB-22), *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA) and *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (ADB-PINACA), including their salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, into schedule I of the Controlled Substances Act. This scheduling action is pursuant to the Controlled Substances Act which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis, or possess), or propose to handle PB-22, 5F-PB-22, AB-FUBINACA, or ADB-PINACA.

DATES: *Effective date:* September 6, 2016.

FOR FURTHER INFORMATION CONTACT: Michael J. Lewis, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598–6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

The Drug Enforcement Administration (DEA) implements and enforces titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. 21 U.S.C. 801–971. Titles II and III are referred to as the ''Controlled Substances Act'' and the ''Controlled Substances Import and Export Act,'' respectively, and are collectively referred to as the ''Controlled Substances Act'' or the ''CSA'' for the purposes of this action. 21 U.S.C. 801–971. The DEA publishes the implementing regulations for these statutes in title 21 of the Code of Federal Regulations (CFR), chapter II.

The CSA and its implementing regulations are designed to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while ensuring an adequate supply is available for the legitimate medical, scientific, research, and industrial needs of the United States. Controlled substances have the potential for abuse and dependence and are controlled to protect the public health and safety.

Under the CSA, each controlled substance is classified into one of five schedules based upon its potential for abuse, its currently accepted medical use in treatment in the United States, and the degree of dependence the substance may cause. 21 U.S.C. 812. The initial schedules of controlled substances established by Congress are found at 21 U.S.C. 812(c) and the current list of scheduled substances is published at 21 CFR part 1308. 21 U.S.C. 812(a).

Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, ''add to such a schedule or transfer between such schedules any drug or other substance if he * * * finds that such drug or other substance has a potential for abuse, and * * * makes with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of this title for the schedule in which such drug is to be placed * * *.'' The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the DEA, 28 CFR 0.100, who in turn has redelegated that authority to the Deputy Administrator of the DEA, 28 CFR part 0, appendix to subpart R.

The CSA provides that proceedings for the issuance, amendment, or repeal of the scheduling of any drug or other substance may be initiated by the Attorney General (1) on her own motion; (2) at the request of the Secretary of the Department of Health and Human Services (HHS);[1] or (3) on the petition of any interested party. 21 U.S.C. 811(a). This action was initiated by the former Deputy Administrator of the DEA on his own motion and is supported by a recommendation from the Assistant Secretary of the HHS and an evaluation of all other relevant data by the DEA. This action imposes the regulatory controls and administrative, civil, and criminal sanctions of schedule I controlled substances on any person who handles, or proposes to handle, PB-22, 5F-PB-22, AB-FUBINACA, or ADB-PINACA.

Background

On January 10, 2014, the DEA published a notice of intent to temporarily place quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate (PB-22; QUPIC), quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate (5-fluoro-PB-22; 5F-PB-22), *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA) and *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (ADB-PINACA) into schedule I pursuant to the temporary scheduling provisions of the CSA. 79 FR 1776. On February 10, 2014, the DEA published a final order amending 21 CFR 1308.11(h) to temporarily place these four synthetic cannabinoids into schedule I of the CSA. 79 FR 7577. That final order was effective on the date of publication, and was based on findings by the DEA that the temporary scheduling of these four synthetic cannabinoids was necessary to avoid an imminent hazard to the public safety pursuant to 21 U.S.C. 811(h)(1).

[1] As set forth in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993. Accordingly, all subsequent references to ''Secretary'' have been replaced with ''Assistant Secretary.''