



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 333

[Docket No. FDA-1975-N-0012] (formerly Docket No. 1975N-0183H)

RIN 0910-AF69

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing this proposed rule to amend the 1994 tentative final monograph or proposed rule (the 1994 TFM) for over-the-counter (OTC) antiseptic drug products. In this proposed rule, we are proposing to establish conditions under which OTC consumer antiseptic products intended for use with water (referred to throughout as consumer antiseptic washes) are generally recognized as safe and effective. In the 1994 TFM, certain antiseptic active ingredients were proposed as being safe for antiseptic handwash use by consumers based on safety data evaluated by FDA as part of our ongoing review of OTC antiseptic drug products. However, in light of more recent scientific developments and changes in the use patterns of these products we are now proposing that additional safety data are necessary to support the safety of antiseptic active ingredients for this use. We also are proposing that all consumer antiseptic wash active ingredients have data that demonstrate a

clinical benefit from the use of these consumer antiseptic wash products compared to nonantibacterial soap and water.

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

ADDRESSES: You may submit comments, identified by Docket No. FDA-1975-N-0012 and Regulatory Information Number (RIN) number 0910-AF69, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-1975-N-0012 and RIN 0910-AF69 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided.

Docket: 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 document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Colleen Rogers, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5411, Silver Spring, MD 20993, 301-796-2090.

SUPPLEMENTARY INFORMATION:

Executive Summary

Purpose of the Regulatory Action

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

FDA is proposing to establish new conditions under which OTC consumer antiseptic products intended for use with water are generally recognized as safe and effective (GRAS/GRAE) based on FDA’s reevaluation of the safety and effectiveness data requirements proposed in the 1994 TFM in light of comments received, input from subsequent public meetings, and our independent evaluation of other relevant scientific information it has identified and placed in the docket. We are not, at this time, proposing conditions under which OTC consumer antiseptic hand rubs (commonly called hand sanitizers) or antiseptics intended for use by health care professionals are GRAS/GRAE.

Summary of the Major Provisions of the Regulatory Action in Question

We are proposing that additional safety and effectiveness data are necessary to support a GRAS/GRAE determination for OTC antiseptic active ingredients intended for repeated daily

use by consumers. The safety data, the effectiveness data, and the effect on the previously proposed classification of active ingredients are described briefly in this summary.

Effectiveness

A determination that an active ingredient is GRAS/GRAE for a particular intended use requires consideration of the benefit-to-risk ratio for the drug for that use. 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-risk calculation shifts, and the drug is not GRAS/GRAE. New information on potential risks posed by the use of certain consumer antiseptic washes has prompted us to reevaluate the data needed for classifying consumer antiseptic wash active ingredients as generally recognized as effective (GRAE). As a result, the risk from the use of a consumer antiseptic wash drug product must be balanced by a demonstration that it is superior to washing with nonantibacterial soap and water in reducing infection.

We have evaluated the available literature, and the data and other information that were submitted to the rulemaking on the effectiveness of consumer antiseptic wash active ingredients, as well as the recommendations from the public meetings held by the Agency on antiseptics. The record does not currently contain sufficient data to show that there is any additional benefit from the use of consumer antiseptic hand or body washes compared to nonantibacterial soap and water. Adequate and well-controlled clinical outcome studies capable of identifying the conditions of use that reduce the numbers of infections would demonstrate whether there is a benefit from the use of consumer antiseptic washes. Consequently, we are proposing that data from clinical outcome studies (demonstrating a reduction in infections) are necessary to support a GRAE determination for consumer antiseptic wash active ingredients.

Safety

Several important scientific developments that affect the safety evaluation of these ingredients have occurred since FDA's 1994 evaluation of the safety of consumer antiseptic active ingredients under the OTC Drug Review. New data suggest 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 have become available. New safety information also suggests that widespread antiseptic use can have an impact on the development of bacterial resistance.

The previous GRAS determinations were based on safety principles that have since evolved significantly due to advances in technology, development of new test methods, and experience with performing test methods. The standard battery of tests that were used to determine the safety of drugs has changed over time to incorporate improvements in safety testing. In order to ensure that consumer antiseptic wash active ingredients are GRAS, data that meet current safety standards are needed.

Based on these developments, we are now proposing that additional safety data will need to be submitted to the administrative record for each consumer antiseptic wash active ingredient to support a GRAS classification. The data requirements proposed in this proposed rule are the minimum data necessary to establish the safety of long-term, daily, repeated exposure to antiseptic active ingredients used in consumer wash products in light of the new safety information. The data we propose is 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., preclinical 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 resistance.

Active Ingredients

In the 1994 TFM, 22 antiseptic active ingredients were classified for OTC antiseptic handwash use (59 FR 31402 at 31435) (for a list of all active ingredients covered by this proposed rule, see tables 3 and 4). Among these 22 active ingredients are triclosan and triclocarban, two of the most commonly used active ingredients in consumer antiseptic washes and the subject of much scientific debate. Our detailed evaluation of the effectiveness and safety of triclosan and triclocarban, as well as other active ingredients for which data were submitted, can be found in sections VI.A and VII.D of this proposed rule. In the 1994 TFM, only one active ingredient that is being evaluated for use as a consumer antiseptic wash, povidone-iodine (5 to 10 percent), was proposed to be classified as GRAS/GRAE (59 FR 31402 at 31436). However, we now propose that none of the consumer antiseptic wash active ingredients classified in the 1994 TFM (including povidone-iodine) has the safety and effectiveness data needed to support a classification of GRAS/GRAE for consumer antiseptic hand or body washes. The data available and the data that are missing are discussed separately in this proposed rule for each active ingredient.

Several consumer antiseptic wash active ingredients evaluated in the 1994 TFM were proposed as GRAS, but not GRAE, because they lack sufficient evidence of effectiveness for consumer use. We are now proposing that these ingredients need additional safety data, as well as effectiveness data, to be classified as GRAS/GRAE.

Costs and Benefits

We estimate the benefits of the proposed rule in terms of the 2.2 millions pounds reduction in annual aggregate exposure to antiseptic active ingredients, including triclosan, chloroxylenol, and benzalkonium chloride. The inadequacy of the available dermal exposure data prevents us from characterizing the health effects resulting from widespread long-term exposure to such ingredients and prevents us from translating the estimated reduced exposure into monetary equivalents of health effects. We estimate the costs of the proposed rule, consisting of one-time costs of relabeling and reformulation, ranging from \$112.2 to \$368.8 million.. Annualized over 10 years, the primary cost estimate is approximately \$23.6 million at a 3 percent discount rate and \$28.6 million at a 7 percent discount rate. Under the proposed rule, we estimate that each pound of reduced exposure to antiseptic active ingredients would cost \$3.86 to \$43.67 at a 3 percent discount rate and \$4.69 to \$53.04 at a 7 percent discount rate.

Summary of Costs and Benefits of the Proposed Rule	Total Benefits	Total Costs Annualized Over 10 Years (in millions)	Total One-Time Costs (in millions)
Total	Reduced exposure to antiseptic active ingredients by 2.2 million pounds annually	\$23.6 (at 3%) \$28.6 (at 7%)	\$112.2 to \$368.8

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I. Introduction

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

A. Terminology Used in the OTC Drug Review Regulations

1. Proposed, Tentative Final, and Final Monographs

To conform to terminology used in the OTC Drug Review regulations (§ 330.10 (21 CFR 330.10)), the September 1974 advance notice of proposed rulemaking (ANPR) was designated as a "proposed monograph." Similarly, the notices of proposed rulemaking, which were published in the Federal Register of January 6, 1978 (43 FR 1210) (the 1978 TFM), and in the Federal Register of June 17, 1994 (59 FR 31402) (the 1994 TFM), were each designated as a "tentative final monograph." The present proposed rule, which is a reproposal regarding consumer antiseptic wash drug products, is also designated as a "tentative final monograph."

2. Category I, II, and III Classifications

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

(i.e., a final rule or regulation). Therefore, this proposed rule (at the tentative final monograph stage) retains the concepts of Categories I, II, and III.

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

B. Topical Antiseptics

The OTC topical antimicrobial rulemaking has had a broad scope, encompassing drug products that may contain the same active ingredients, but that are labeled and marketed for different intended uses. In 1974, the Agency published an ANPR for topical antimicrobial products that encompassed products for both health care and consumer use (39 FR 33103, September 13, 1974). The ANPR covered seven different intended uses for these products: (1) Antimicrobial soap; (2) health care personnel handwash; (3) patient preoperative skin preparation; (4) skin antiseptic; (5) skin wound cleanser; (6) skin wound protectant; and (7) surgical hand scrub (39 FR 33103 at 33140). FDA subsequently identified skin antiseptics, skin wound cleansers, and skin wound protectants as antiseptics used primarily by consumers for first aid use and referred to them collectively as "first aid antiseptics". We published a separate TFM covering the first aid antiseptics in the Federal Register of July 22, 1991 (56 FR 33644) (First Aid TNM). Thus, first aid antiseptics are not discussed further in this document.

The four remaining categories of topical antimicrobials were addressed in an amended TFM, published on June 17, 1994 (59 FR 31402). This TFM covered: (1) Antiseptic handwash (i.e., consumer handwash); (2) health care personnel handwash; (3) patient preoperative skin preparation; and (4) surgical hand scrub (59 FR 31402 at 31442). In the 1994 TFM, FDA also identified a new category of antiseptics for use by the food industry and requested relevant data

and information (59 FR 31402 at 31440). Antiseptics for use by the food industry are not discussed further in this document.

With regard to the health care and consumer antiseptic products, we are now proposing that our evaluation of OTC antiseptic drug products be further subdivided into health care antiseptics and consumer antiseptics. We believe that these categories are distinct based on the proposed use setting, target population, and the fact that each setting presents a different risk for infection. Therefore, the safety and effectiveness should be evaluated for each intended use separately.

Health care antiseptics are drug products intended for use by health care professionals in a hospital setting or other health care situations outside the hospital, and include health care personnel hand antiseptics, surgical hand scrubs, and patient preoperative skin preparations. In 1974, when the ANPR (39 FR 33103) to establish an OTC topical antimicrobial monograph was published in the Federal Register, antimicrobial soaps used by consumers were distinct from professional use antiseptics, such as health care personnel handwashes. (See section I.C of this proposed rule about the term "antimicrobial soaps".) In contrast, in the 1994 TFM, we proposed that both consumer antiseptic handwashes and health care personnel handwashes should have the same effectiveness testing and performance criteria. In response to the TFM we received submissions from the public arguing that consumer products serve a different purpose and should continue to be distinct from health care antiseptics. We agree, and in this proposed rule we make a distinction between consumer antiseptics for use by the general population and health care antiseptics for use in hospitals or in other specific health care situations.

We refer to the group of products covered by this proposed rule as "consumer antiseptics." Consumer antiseptic drug products addressed by this proposal include a variety of

personal care products intended to be used with water, such as antibacterial soaps, handwashes, and antibacterial body washes. These products do not include consumer antiseptic hand rubs (commonly called hand sanitizers). These products may be used by consumers for personal use in the home on a frequent, even daily, basis. In the U.S. 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.

C. This Proposed Rule Covers Only Consumer Antiseptic Washes

In this proposed rule, FDA proposes the establishment of a monograph for OTC consumer antiseptics that are intended for use as either a handwash or a body wash, but that are not identified as "first aid antiseptics" in the 1991 First Aid TFM. When the 1994 TFM was published, the term for daily consumer use antiseptics was changed to "antiseptic handwash." In response to this change, we received comments that the term "antiseptic handwash" did not include all of the consumer products on the market, such as hand rubs and body washes. Therefore, in this proposed rule, we use the term "consumer antiseptic," which is a broad term and meant to include all of the types of antiseptic products used on a frequent or daily basis by consumers. The proposed rule does not include consumer antiseptic hand rubs (commonly called hand sanitizers).

The distinctions between washes and rubs, and between handwashes and body washes are discussed in this section.

1. Consumer Washes and Consumer Rubs

Consumer antiseptics (other than first aid antiseptics) fall into two categories: (1) Products that are rinsed off, including handwashes and body washes, and (2) products that are

not rinsed off after use, including hand rubs and antibacterial wipes. The 1994 TFM did not distinguish between products that we are now calling antiseptic washes and products we are now calling antiseptic rubs. Nor did the 1994 TFM distinguish between consumer antiseptic handwashes and rubs and health care antiseptic handwashes and rubs. This proposed rule covers consumer antiseptic washes only and does not cover consumer antiseptic rubs. 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 United States 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.).

2. Handwashes and Body Washes

Consumer antiseptic hand and body washes were not a category of topical antiseptic drug products specifically identified by the Advisory Review Panel on OTC Topical Antimicrobial I Drug Products (Antimicrobial I Panel or Panel). In the ANPR and the 1978 TFM, products for daily consumer use were called "antimicrobial soaps." This category encompassed deodorant soaps and hand soaps containing antimicrobial ingredients used for handwashing and personal hygiene.

In the 1994 TFM, we concluded that there was no reason to continue to include "antimicrobial soap" as a separate product category because soap was considered to be a dosage form and specific dosage forms were not being included in the monograph unless there was a particular safety or efficacy reason to do so (59 FR 31402 at 31407). At that time, we had not identified antiseptic body washes as a separate category of product.

Comments on the 1994 TFM noted that the elimination of the category of antimicrobial soaps in the 1994 TFM resulted in products that otherwise would have been considered antimicrobial soaps (such as antimicrobial bar soaps) being placed in the category of antiseptic handwashes. The comments stated that because the proposed labeling for antiseptic handwash products directs use on only the hands and forearms, this category is not appropriate for certain products that were originally proposed to be called "antimicrobial soaps" and that were to be used on the whole body (i.e., bar soaps). We agree with the comments to the extent that some products previously identified as antimicrobial soaps had, among other intended uses, the intended use of being used on the entire body. In this proposed rule, we are identifying products with the intended use of being used on the entire body as antiseptic body washes. Consequently, the active ingredients reviewed by the Panel for use in antimicrobial soaps have been reviewed for use in antiseptic body washes.

D. Comment Period

Because of the complexity of this proposed rule, we are providing a comment period of 180 days. Moreover, new data or information may be submitted to the docket within 12 months of publication, and comments on any new data or information may then be submitted for an additional 60 days (see § 330.10(a)(7)(iii) and (a)(7)(iv)). In addition, FDA will also consider requests for an extension of the time to submit new safety and/or effectiveness data to the record if such requests are submitted to the docket within the initial 180-day comment period. Upon the close of the comment period, FDA will review all data and information submitted to the record in conjunction with all timely and complete requests to extend. In assessing whether to extend the comment period to allow for additional time for studies to generate new data and information, FDA will consider the data already in the docket along with any information that is

provided in any requests to extend. FDA will determine whether the sum of the data, if timely submitted, is likely to be adequate to provide all the data that are necessary to make a determination of general recognition of safety and effectiveness.

II. Background

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

A. Significant Rulemakings Relevant to This Proposed Rule

A summary of the significant Federal Register publications relevant to this proposed rule is provided in table 1 of this proposed rule. Other Federal Register publications relevant to this proposed rule are available from the Division of Dockets Management (see ADDRESSES).

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

<u>Federal Register</u> 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 Panel, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class.
1978 Antimicrobial TFM (January 6, 1978, 43 FR 1210)	We published our tentative conclusions and proposed effectiveness testing for the drug product categories evaluated by the Panel. The 1978 TFM reflects our evaluation of the recommendations of the Panel and comments and data submitted in response to the Panel's recommendations.
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 that were referred to as OTC topical health care antiseptic drug products. These antiseptics are generally intended for use by health care professionals. In this proposed rule we also recognized the need for antibacterial personal cleansing products for consumers to help prevent cross contamination from one person to another and proposed a new

	antiseptic category for consumer use: Antiseptic handwash.
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B. Public Meetings Relevant to This Proposed Rule

In addition to the Federal Register publications listed in table 1 of this proposed rule, there have been three meetings of the Nonprescription Drugs Advisory Committee (NDAC) and one public feedback meeting that are relevant to the discussion of consumer antiseptic wash safety and effectiveness. These are summarized in table 2 of this proposed rule.

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)

C. Comments Received by FDA

In response to the 1994 TFM, FDA received approximately 160 comments from drug manufacturers, trade associations, academia, testing laboratories, consumers, health professionals, and law firms. Copies of the comments received are on public display at <http://www.regulations.gov> (see ADDRESSES).

Because only consumer antiseptic washes are discussed in this proposed rule, only those comments and data concerning the 1994 TFM that are related to consumer antiseptic wash active ingredients are addressed. If in the future we determine that there are monograph consumer antiseptic wash active ingredients that are safe and effective, we will address labeling and final formulation testing of consumer antiseptic washes, and the comments that were received on those subjects, in a future document. Comments that were received in response to the 1994 TFM regarding other intended uses of the active ingredients will be addressed in future documents related to those other uses.

This proposal constitutes FDA's evaluation of submissions made in response to the 1994 TFM to support the safety and effectiveness of OTC consumer antiseptic wash active ingredients (Refs. 6 through 10). We reviewed the available literature and data and other comments submitted to the rulemaking and are proposing that adequate data for a determination of safety and effectiveness were not yet available for any consumer antiseptic wash active ingredient.

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

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

A. Eligibility for the OTC Drug Review

An OTC drug is covered by the OTC Drug Review if its conditions of use existed in the OTC drug marketplace on or before May 11, 1972 (37 FR 9464). Conditions of use include, among other things, active ingredient, dosage form and strength, route of administration, and specific OTC use or indication of the product (see 21 CFR 330.14(a)). To determine eligibility for the OTC Drug Review, FDA typically must have actual product labeling or a facsimile of

labeling that documents the conditions of marketing of a product prior to May 1972 (see § 330.10(a)(2)). FDA considers a drug that is ineligible for the OTC Drug Review to be a new drug that will require FDA approval through the new drug application (NDA) process. Ineligibility for use as a consumer antiseptic wash does not affect eligibility for other indications under the OTC Drug Review.

Based on a review of the labeling submitted to the Antimicrobial I Panel, the ingredients discussed in section III.B of this proposed rule currently do not have adequate evidence of eligibility for evaluation under the OTC Drug Review as a consumer antiseptic wash. Due to their lack of eligibility, effectiveness and safety information that has been submitted to the rulemaking for these antiseptic active ingredients are not discussed in this proposed rule. However, if documentation of the type described in this section is submitted, these active ingredients could be determined to be eligible for evaluation.

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

1. Chlorhexidine Gluconate

Previously, chlorhexidine gluconate 4 percent aqueous solution as a health care antiseptic was found to be ineligible for inclusion in the monograph and was not included in the 1994 TFM (59 FR 31402 at 31413). We have not received any new information since the 1994 TFM demonstrating that this active ingredient is eligible for the monograph. Consequently, we are not proposing to change the categorization of chlorhexidine gluconate from that of a new drug based on the lack of documentation demonstrating its eligibility as a consumer antiseptic wash, and we do not include a discussion of any safety or effectiveness data submitted for chlorhexidine gluconate.

2. Polyhexamethylene Biguanide; Benzalkonium Cetyl Phosphate; Cetylpyridinium Chloride; Salicylic Acid; Sodium Hypochlorite; Tea Tree Oil; Combination of Potassium Vegetable Oil Solution, Phosphate Sequestering Agent, and Triethanolamine

Following the publication of the 1994 TFM, FDA received submissions for the first time requesting that polyhexamethylene biguanide, benzalkonium cetyl phosphate, cetylpyridinium chloride, salicylic acid, sodium hypochlorite, tea tree oil, and the combination of potassium vegetable oil solution, phosphate sequestering agent, and triethanolamine be added to the monograph (Refs. 11 through 17). These compounds were not addressed in prior FDA documents related to the monograph and were not evaluated for antiseptic handwash use by the Antimicrobial I Panel. The submissions received by the Agency to date do not include documentation demonstrating the eligibility of any of these seven compounds for inclusion in the monograph (Ref. 18). Therefore, polyhexamethylene biguanide, benzalkonium cetyl phosphate, cetylpyridinium chloride, salicylic acid, sodium hypochlorite, tea tree oil, and the combination of potassium vegetable oil solution, phosphate sequestering agent, and triethanolamine have not been demonstrated to be eligible for the OTC Drug Review. Based on the information about eligibility that we have at this time, we propose to categorize them as new drugs, and we do not include a discussion of safety or effectiveness data submitted for them.

3. Alcohol (Ethyl Alcohol) and Isopropyl Alcohol

In the 1994 TFM, denatured ethyl alcohol (ethanol or alcohol) 60 to 95 percent by volume in an aqueous solution was one of two active ingredients classified as Category I for use as an antiseptic handwash or health care personnel handwash (59 FR 31402 at 31442). Isopropyl alcohol 70 to 91.3 percent was classified as Category III for use as an antiseptic handwash or health care personnel handwash. The only consumer products containing alcohol or isopropyl

alcohol that were submitted to the OTC Drug Review were products that were intended to be used without water (Ref. 19). Consequently, alcohol and isopropyl alcohol have not been demonstrated to be eligible for the OTC Drug Review for evaluation as consumer antiseptic wash drug products, which by definition are intended to be rinsed off with water. Based on the information we currently have about eligibility of these active ingredients, we propose to categorize alcohol and isopropyl alcohol intended for use as an antiseptic wash as new drugs, and we do not include a discussion of safety or effectiveness of alcohol or isopropyl alcohol for such use. This proposal relates to antiseptic washes and does not include consumer antiseptic hand rubs (commonly called hand sanitizers).

IV. Ingredients Previously Proposed as Not Generally Recognized as Safe and Effective (GRAS/GRAE)

FDA may determine that an active ingredient is not GRAS/GRAE (i.e., nonmonograph) because of lack of evidence of effectiveness or lack of evidence of safety or both. In the 1994 TFM (59 FR 31402 at 31435), FDA proposed that the active ingredients fluorosalan, hexachlorophene, phenol (greater than 1.5 percent), and tribromsalan be found not GRAS/GRAE for use as an antiseptic handwash or health care personnel handwash. The Agency did not classify hexachlorophene or tribromsalan in the 1978 TFM (43 FR 1210 at 1227) because it had already taken final regulatory action against hexachlorophene (21 CFR 250.250) and certain halogenated salicylamides, particularly tribromsalan (21 CFR 310.502). No substantive comments or new data were submitted to support reclassification of any of these ingredients to GRAS/GRAE status. Therefore, FDA is continuing to propose that these active ingredients be found not GRAS/GRAE for OTC consumer antiseptic hand or body washes as defined in this proposed rule and that any OTC consumer antiseptic hand or body wash drug product containing

any of these ingredients not be allowed to continue to be introduced or delivered for introduction into interstate commerce unless it is the subject of an approved application effective, except as otherwise provided in other regulations, as of 1 year after publication of the final monograph in the Federal Register.

V. Summary of Proposed Classifications of OTC Consumer Antiseptic Wash Active Ingredients

Tables 3 and 4 in this proposed rule list the classification proposed in the 1994 TFM for each OTC consumer antiseptic active ingredient and the classification being proposed in this proposed rule. The specific data that has been submitted to the public docket (the rulemaking) and evaluated by FDA and the description of data still lacking in the administrative record is described in detail for each active ingredient separately in section VII.D of this proposed rule.

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

Active Ingredient	1994 TFM	This Proposed Rule
Hexylresorcinol	III ^E ¹	III ^{SE}
Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)	III ^E	III ^{SE}
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)	III ^E	III ^{SE}
Nonylphenoxypoly (ethyleneoxy) ethanoliiodine	III ^E	III ^{SE}
Poloxamer iodine complex	III ^E	III ^{SE}
Povidone-iodine 5 to 10 percent	I ²	III ^{SE}
Secondary amylicresols	III ^E	III ^{SE}
Triclocarban	III ^E	III ^{SE}
Undecoylium chloride iodine complex	III ^E	III ^{SE}

¹ "III" denotes that additional data are needed. "E" denotes effectiveness data needed. "S" denotes safety data needed.

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

This proposed rule does not change the status of a number of antiseptic active ingredients previously proposed as lacking sufficient evidence of safety and effectiveness or the status of

several ingredients previously proposed as having been shown to be unsafe, ineffective, or both (see table 4 of this proposed rule).

Table 4.--OTC Consumer Antiseptic Active Ingredients With No Change in Classification in This Proposed Rule Compared to the 1994 TFM

Active Ingredient	No Change in Classification
Benzalkonium chloride	III ¹ SE
Benzethonium chloride	III ¹ SE
Chloroxylenol	III ¹ SE
Cloflucarban	III ¹ SE
Fluorosalan	II ²
Hexachlorophene	II
Methylbenzethonium chloride	III ¹ SE
Phenol (less than 1.5 percent)	III ¹ SE
Phenol (greater than 1.5 percent)	II
Sodium oxychlorosene	III ¹ SE
Tribromsalan	II
Triclosan	III ¹ SE
Triple dye ³	II

¹ "III" denotes that additional data are needed. "S" denotes safety data needed. "E" denotes effectiveness data needed.

² "II" denotes that an active ingredient has been shown to be unsafe, ineffective, or both.

³ Triple dye was proposed as Category II for antimicrobial soap due to a physical and/or chemical incompatibility in formulation and for skin antiseptic (except for use in neonatal ward) in the 1978 TFM (43 FR 1210 at 1227), and was not further evaluated as an antiseptic handwash in the 1994 TFM (59 FR 31402 at 31436). FDA has received no further information on triple dye for use as an antiseptic wash since the 1994 TFM.

VI. Effectiveness (Generally Recognized as Effective) Determination

OTC regulations (§ 330.10(a)(4)(ii)) define the standards for establishing an OTC active ingredient as GRAE. These regulations require controlled clinical trials of the kind described in § 314.126(b) (21 CFR 314.126(b)) as proof of the effectiveness of an active ingredient unless this requirement is waived. According to § 314.126(a), these clinical studies must be adequate and well-controlled studies that can distinguish the effect of a drug from other influences such as a spontaneous change in the course of the disease, placebo effect, or biased observation. In general, such studies include controls that are adequate to provide an assessment of drug effect,

adequate measures to minimize bias, and the use of adequate analytical methods to demonstrate effectiveness. For active ingredients being evaluated in the OTC Drug Review, this means that a demonstration of the contribution of the active ingredient to any effectiveness observed is required before an ingredient can be GRAE.

In the 1994 TFM, we proposed a log reduction standard (a clinical simulation standard) for establishing effectiveness of consumer and health care antiseptics (59 FR 31402 at 31448) for the proposed intended use of decreasing bacteria on the skin. The 1994 TFM log reduction standard for effectiveness is based on an unvalidated surrogate endpoint (i.e., number of bacteria removed from the skin), rather than a clinical outcome (e.g., reduction in the number of infections). Because of new concerns about the potential risks (e.g., resistance and hormonal effects) posed by the repeated daily use of consumer antiseptic washes (see section VII of this proposed rule), we are now proposing that a different type of effectiveness study is necessary to support the GRAE status of consumer antiseptic wash active ingredients. We are proposing that the use of antiseptic active ingredients to be used in consumer antiseptic wash products be supported by studies that demonstrate a direct clinical benefit (i.e., a reduction of infection). Data from these clinical outcome studies will help assure that any potential risk from consumer antiseptic wash products is balanced by a demonstrated clinical benefit.

This effectiveness requirement is consistent with NDAC's recommendations from the October 2005 meeting regarding consumer antiseptics (Ref. 4). NDAC unanimously agreed that in order to be considered effective, a demonstration that the drug removes bacteria is not enough and that consumer antiseptic products should provide a clinical benefit by reducing infections. They concluded that studies using surrogate endpoints would not be adequate to demonstrate this benefit and recommended studying the impact of these products on infections in specific

populations of consumers that use these products. NDAC also did not believe that it is possible to generalize from effectiveness in the health care environment to effectiveness in the consumer setting because of differences in populations and other risk factors.

NDAC concluded that it would be feasible to use clinical outcome studies to show a benefit of consumer antiseptic washes over and above washing with nonantibacterial soap. They pointed out that there are already studies in the community setting that have looked at clinical outcomes, such as the number of symptoms or infections over a given timeframe. NDAC concluded that it would not be unethical to run a placebo-controlled study of consumer antiseptic washes to demonstrate clinical benefit. NDAC also stated that it is important to know if there is any added benefit from the antiseptic active ingredient in consumer antiseptic wash products. We agree with NDAC's recommendations on this issue.

A coalition of trade organizations that represent antiseptic manufacturers submitted comments disagreeing with NDAC's conclusions. The comments state that clinical outcome studies in the consumer setting are not feasible because of the cost and considerable number of confounding factors that would make interpretation of the studies difficult (Refs. 5, 20, and 21). Some of these confounding factors identified in these comments included:

- Number and length of handwashes performed
- Amount of product used
- Compliance with handwashing technique and frequency
- Blinding of products
- Use of other (non-study) products when outside the home
- Type of infection
- Virulence of the infecting microorganism

- Generally low bacterial infection rate in the United States

NDAC found the studies by Luby et al. (Ref. 22) and Larson et al. (Ref. 23), which are discussed in section VI.A of this proposed rule, to be evidence that such clinical outcome studies are feasible. We agree. Although there are many confounding factors that must be addressed when designing a clinical outcome study of the effectiveness of antiseptic washes in the consumer setting, this is the case in any clinical outcome study. Despite this fact, well-designed clinical outcome studies are conducted for other types of drug products, and the most important factors can be addressed in an appropriately designed study. If effectiveness cannot be demonstrated in a clinical outcome study for consumer antiseptic washes, we should not rush to conclude that it is the confounding factors that limit our ability to detect a benefit; rather, if the study is appropriately designed, it is likely telling us that the consumer antiseptic wash does not provide a clinically significant benefit in a population at low risk to develop an infection, such as a healthy consumer.

As discussed later in this section of this proposed rule, we evaluated all the available effectiveness studies for consumer antiseptic washes to determine if the data supported effectiveness of consumer antiseptic active ingredients based on the 1994 TFM effectiveness criteria. We found that the available studies are not adequate to support a GRAE determination for any consumer antiseptic wash active ingredient under either the 1994 TFM effectiveness criteria or what we propose now.

A. Evaluation of Effectiveness Data

1. Clinical Simulation Studies

Most of the data available to support the effectiveness of consumer antiseptic washes are based on clinical simulation studies, such as the one described in the 1994 TFM (59 FR 31402 at

31444). The premise behind these studies is that bacterial reductions achieved in this type of study translate to a reduced risk for infection. However, there currently are no clinical data that demonstrate that the specific bacterial log reductions that we have relied upon as a demonstration of effectiveness lead to a specific reduction in infections. We now believe that the appropriate demonstration of effectiveness is a clinical outcome study. Moreover, clinical outcome studies are feasible in the consumer setting and may not give rise to ethical concerns such as those that could occur in studies in a hospital setting.

Although we are now proposing to require clinical outcome studies, we evaluated all clinical simulation studies that were submitted to the OTC Drug Review for evidence of antiseptic hand and body wash effectiveness demonstrated under the log reduction criteria proposed in the 1994 TFM (59 FR 31402 at 31448) (Ref. 6). We also searched the published literature for clinical simulation studies that assess antiseptic wash effectiveness also using the log reduction criteria in the 1994 TFM (Refs. 24, 25, and 26). Overall, when judged against the criteria in the 1994 TFM, the studies are not adequately controlled to allow an accurate assessment of the effectiveness of consumer antiseptic wash active ingredients for one or more reasons.

First, the majority of testing was conducted using a formulated product without adequate comparison to a vehicle control, which is needed to demonstrate the contribution of the antiseptic active ingredient, if any (43 FR 1210 at 1240). Second, many studies did not include an active control, which is needed to validate the conduct of the study (59 FR 31402 at 31450). Third, many studies lacked adequate documentation of neutralization (43 FR 1210 at 1244). Residual antiseptic remaining on the skin after rinsing, if not effectively neutralized, will continue its antimicrobial action and result in an exaggerated bacterial reduction that is not reflective of

product performance on the skin. Finally, none of the studies were of adequate size to assure a statistically valid demonstration of log reductions. The Agency's detailed evaluation of the data is on file at <http://www.regulations.gov> (see ADDRESSES) (Ref. 26). Only one submitted clinical simulation study was adequately designed and controlled to evaluate the contribution of the active ingredient to the observed bacterial log reductions (Ref. 27). This study compared a liquid soap containing 0.7 percent triclocarban to both the formulation without any antiseptic (placebo) and a 4 percent chlorhexidine gluconate active control. The triclocarban-containing soap was superior to placebo and met the 1994 TFM effectiveness criteria of a 2- \log_{10} reduction after the first wash and a 3- \log_{10} reduction after the eleventh wash (59 FR 31402 at 31448). The active control also met the 1994 TFM effectiveness criteria when tested against Serratia marcescens and validated the study conduct. Therefore, this was a valid, adequately controlled study that met the effectiveness criteria proposed in the 1994 TFM.

Although the 0.7 percent triclocarban soap met the standard for effectiveness proposed in the 1994 TFM, the log reduction differences compared to placebo were small (less than a 0.5-log reduction difference compared to placebo after the first wash and just over a 1-log reduction difference after the eleventh wash). Because we do not have any data that correlates specific bacterial log reductions with clinical outcomes, we have no basis to interpret the impact of these small log reductions on infections in a population at low risk for infection. Thus, even with an adequately designed and controlled clinical simulation study, the data do not provide sufficient evidence of a meaningful contribution of consumer antiseptic wash active ingredients relative to a placebo handwash.

2. Exposure-Response Studies

Although most clinical simulation studies submitted to the OTC Drug Review only evaluated bacterial log reductions, one study (Ref. 21) attempted to correlate the reduction of bacteria on the hands with a reduction in infection rate. The study was designed to compare the ability of a nonantibacterial handwash to the ability of an antiseptic (triclosan) handwash to reduce bacteria on the hands after a single use. The study also evaluated the impact of product use on the subsequent transfer of surviving bacteria from washed hands to a ready-to-eat food item, melon balls. The observed reduction in bacterial transfer was then used to estimate the potential reduction in infection risk from antiseptic use based on published bacterial exposure-response data for Shigella flexneri (S. flexneri). Here, exposure-response data refers to the correlation between the amount of S. flexneri ingested and the severity of clinical disease (e.g., diarrhea) that results from that ingestion. The rationale for this study design is that if ready-to-eat food was contaminated with bacteria left behind on washed hands and then eaten, those organisms would have the potential to cause illness. This scenario has the potential to occur in the consumer setting during domestic food preparation.

The antiseptic handwash met the 1994 TFM criteria for bacterial reduction after one wash; however, the study used a novel hand contamination method (Ref. 28) that has not been sufficiently validated. In addition, we believe this novel hand contamination method does not accurately reflect an antiseptic handwash's intended use because it ignores an important reservoir of bacteria on the hands (i.e., the area around and under the fingernails), which is evaluated when the whole hand contamination method is used. Further, although the study authors report that the transfer of bacteria to melon balls decreased with use of a consumer antiseptic handwash, it is not clear what factors other than the antiseptic may influence bacterial transfer from skin to ready-to-eat foods such as melon. Therefore, the results of this study do not demonstrate the

effectiveness of the consumer antiseptic handwash used in this study because of the novel and unvalidated methodology.

In addition, the data used by the study authors for the infection risk estimates have several limitations. First, the bacterial exposure-response data for S. flexneri are based on a small number of control subjects in human feeding studies (Refs. 29 through 33). Second, there is substantial variability in the exposure-response data. In cases where the same bacterial dose was fed to subjects in different studies, the number of subjects that became ill varied greatly (e.g., 33 to 86 percent) (Refs. 30 and 31). Third, investigators used different criteria to define illness in the various feeding studies (Refs. 29, 30, and 32). Depending on which parameter was examined, the percentage of subjects that were defined as having illness varied. In studies that examined both clinical symptoms and bacterial shedding or antibody response, there was no parameter that consistently appeared to be correlated with illness in all subjects. Finally, much of the feeding data comes from high-dose exposures. Consequently, the infection rates at low doses must be extrapolated, and there may be a high degree of uncertainty for these values. Furthermore, the bacterial exposure-response data from feeding studies are not linear, which means that an increase in the bacterial dose does not necessarily correlate with an increase in the number of subjects who become ill. Because of this, a statistical model must be used to create the bacterial exposure-response curve (Ref. 34). Use of different statistical models is likely to provide different results.

3. Clinical Outcome Studies

Unlike clinical simulation studies that evaluate effectiveness using unvalidated surrogate endpoints, adequate and well-controlled studies in the general population could more directly demonstrate the existence of any clinical benefit for consumer antiseptic washes. Although these

studies are complex because of the number of factors that need to be controlled for, we believe that they are feasible and are the most appropriate method of demonstrating the effectiveness of consumer antiseptic washes.

FDA evaluated all the clinical outcome studies that were submitted to the OTC Drug Review to look for evidence of a clinical benefit from the use of consumer antiseptic washes (Ref. 6). In addition, we searched the published literature for clinical outcome studies that would provide evidence of a clinical benefit from the use of consumer antiseptic washes (Refs. 25 and 26). We are defining a clinical benefit here as a reduction in the number of infections in the population that uses the consumer antiseptic wash.

We found only a few clinical outcome studies for consumer antiseptic washes. Overall, most of the studies were confounded, underpowered, and/or not properly controlled. Importantly, most of the studies did not include a vehicle control and, therefore, are not able to show the contribution of the antiseptic active ingredient to the observed clinical outcome.

Only two of the clinical outcome studies identified were randomized, blinded, and placebo-controlled with no major design flaws, and only one of these was designed to evaluate the effectiveness of a particular antiseptic active ingredient. These are the best available studies to evaluate the impact of consumer antiseptic washes on infections. Neither of these studies demonstrates a benefit from the use of the tested antiseptic active ingredient; however, their study designs can be used as a guide in the development of future clinical outcome studies of consumer antiseptic wash active ingredients.

The first study compared the household use of a 1.2 percent triclocarban-containing consumer antiseptic wash (bar soap) to placebo wash (nonantibacterial bar soap) or to standard practice in squatter neighborhoods in Pakistan (Ref. 22). Thirty-six neighborhoods were

randomized to 1 of 3 groups, with at least 300 households in each group. Fieldworkers visited households weekly for 1 year to encourage handwashing in the two soap groups and to record symptoms in all groups. The primary study outcomes were the incidence rates of diarrhea, impetigo, and acute respiratory tract infection. The authors report that handwashing with either soap significantly reduced diarrhea and acute lower respiratory tract infections, and handwashing in conjunction with daily bathing prevented impetigo. There was no difference between nonantibacterial soap and triclocarban-containing soap. Consequently, this study does not show a clinical benefit from the use of the consumer antiseptic wash over nonantibacterial soap and water, and does not support a GRAE finding for the active ingredient (triclocarban).

The second study, conducted in the United States, examined the use of triclosan-containing hand soap in the home (Ref. 23). This was a randomized, double-blind, placebo-controlled trial in 224 inner city households randomly assigned to use hand soap and household cleaning products with or without antimicrobial ingredients for 48 weeks. The authors measured infections by assessing the number of infectious disease symptoms during the course of the study (e.g., diarrhea). Test households received several antibacterial cleaning products: Liquid triclosan hand soap, quaternary ammonium hard surface and kitchen cleaner, and oxygenated bleach laundry detergent. Control households received similar nonantibacterial hand soap, hard surface and kitchen cleaner, and laundry detergent. Both groups received nonantibacterial liquid dish soap and bar soap. Adherence to the product regimen was assessed monthly by weighing the remainder of the products and inspecting the home for the presence of other products.

The participants in both groups experienced primarily respiratory symptoms (runny nose, sore throat, or cough). The differences between the intervention and control groups were not significant for any symptoms or for numbers of symptoms. The study did not show any

reduction in symptoms of infectious disease or disease transmission as a result of antimicrobial product use.

4. Antiseptic Body Wash Studies

Several studies were submitted to show a clinical benefit from the use of consumer antiseptic body washes in the prevention of skin infection (Ref. 25). In contrast to antiseptic handwashes, which are meant to work by removing transiently acquired microorganisms, antiseptic body washes are meant to reduce the number of resident bacteria on the skin. The majority of these studies describe the use of antiseptics for nonmonograph indications, such as for the treatment of atopic dermatitis or erythrasma. Furthermore, in most of the studies, the effectiveness of the antiseptic body wash was not the focus of the study. For example, often the antiseptic body wash was part of a treatment regimen that included antibiotics or corticosteroid creams, and the effectiveness of the treatment regimens as a whole were the primary focus of the investigation. Overall, these studies were not adequately controlled to assess the contribution of the antiseptic active ingredient, and these data are not sufficient to demonstrate a clinical benefit (Ref. 25).

B. In Vitro Studies to Support a Generally Recognized as Effective Determination

In the 1994 TFM we proposed that the effectiveness of antiseptic active ingredients could be supported by a combination of in vitro studies and in vivo clinical simulation testing as described in § 333.470 (59 FR 31402 at 31437). Today, we continue to believe that a GRAE determination for an antiseptic active ingredient should be supported by an adequate characterization of the antimicrobial activity of the ingredient. Extensive testing for this purpose was proposed in the 1994 TFM which included a determination of the in vitro spectrum of antimicrobial activity, minimum inhibitory concentration (MIC) testing against 25 fresh clinical

isolates and 25 laboratory strains, and time-kill testing against 10 laboratory strains (59 FR 31402 at 31444). Comments received in response to the 1994 TFM objected to the proposed in vitro testing requirements, stating that they were overly burdensome (Ref. 35). Consequently, submissions of in vitro data submitted to support the effectiveness of antiseptic active ingredients were far less extensive than proposed in the TFM (Ref. 6).

Based on our proposal for clinical outcome studies to support a GRAE determination and in consideration of comments on our in vitro testing proposal (Ref. 35), FDA has reevaluated its proposed testing standards. Because of the short exposure times for consumer antiseptic products, we no longer believe that MICs are relevant to the effectiveness of antiseptic active ingredients. We also now believe that a modified time-kill assay designed to provide an assessment of how rapidly an antiseptic active ingredient produces a bactericidal effect is a more efficient and less burdensome way of documenting in vitro antiseptic activity. Further, because clinical outcome studies are now needed to support a GRAE determination, we no longer believe that a demonstration of in vitro antiseptic activity against an extensive list of organisms is necessary.

Therefore, we now propose that data from a modified time-kill assay designed to provide an adequate assessment of how rapidly an antiseptic active ingredient produces a bactericidal effect and to estimate the antibacterial spectrum of an antiseptic active ingredient would be sufficient to characterize the in vitro antimicrobial activity of an antiseptic active ingredient. The assay should test the following reference strains and representative clinical isolates:

- Enterococcus faecalis (ATCC 19433 and ATCC 29212)
- Staphylococcus aureus (ATCC 6538 and ATCC 29213) and methicillin-resistant S. aureus (MRSA) (ATCC 33591 and ATCC 33592)

- Streptococcus pyogenes (ATCC 14289 and ATCC 19615)
- Listeria monocytogenes (ATCC 7644 and ATCC 19115)
- Campylobacter jejuni (ATCC 33291 and ATCC 49943)
- Escherichia coli (ATCC 11775 and ATCC 25922)
- Pseudomonas aeruginosa (ATCC 15442 and ATCC 27853)
- Salmonella enterica Serovar Enteritidis (ATCC 13076) and Serovar Typhimurium (ATCC 14028). Serovar refers to the subspecies classification of a group of microorganisms based on cell surface antigens.
- Shigella sonnei (ATCC 9290 and ATCC 25931)

The consumer antiseptic drug product will be considered bactericidal at the concentration and contact time that demonstrates a 3-log₁₀ (99.9 percent) or greater reduction in bacterial viability for all of the tested strains. This is the same performance criterion used by the Clinical and Laboratory Standards Institute (Ref. 36).

VII. Safety (Generally Recognized as Safe) Determination

In the 1994 TFM, 11 active ingredients were classified as GRAS for antiseptic handwash use (59 FR 31402 at 31435). There have since been a number of important scientific developments affecting our evaluation of the safety of these active ingredients and causing us to reassess the data necessary to support a GRAS determination. There is now new information regarding the potential risks from systemic absorption and long-term exposure to antiseptic active ingredients. The potential for widespread antiseptic use to promote the development of antibiotic-resistant bacteria also needs to be evaluated. Further, additional experience with and knowledge about safety testing has led to improved testing methods. Improvements include study designs that are more capable of detecting potential safety risks. Based on our

reassessment, we are proposing new GRAS data requirements for consumer antiseptic wash active ingredients. For our administrative record to be complete with regard to these new safety concerns, additional safety data will be necessary to support a GRAS determination for consumer antiseptic wash active ingredients.

A. New Issues

Since the 1994 TFM was published, new data have become available indicating that systemic exposure to topical antiseptic active ingredients may be more than previously thought. Systemic exposure refers to the presence of antiseptic active ingredients inside and throughout the body. For example, triclosan is an antiseptic active ingredient commonly found in consumer antiseptic hand and body wash products. It is absorbed through the skin and has been found in both human breast milk and urine (Refs. 37 and 38). Further, triclosan has been found at relatively consistent levels in urine samples collected from a representative sample of the U.S. population since sampling began in 2003 (Ref. 39). We believe that the consequences of this systemic exposure need to be assessed.

Given the prevalent use of consumer antiseptic wash drug products, systemic exposure may be commonplace (see Ref. 40 for a discussion of the consumer antiseptic wash market). While some systemic exposure data exist for triclosan, many of the other antiseptic wash active ingredients have not been evaluated in this regard. Currently there is also a lack of data to assess the impact of important drug use factors that can influence systemic exposure such as dose, application frequency, application method, duration of exposure (e.g., potentially a consumer's entire lifetime), product formulation, skin condition, and age.

The evaluation of the safety of drug products involves correlating findings from animal toxicity studies to the level of exposure to the drug obtained from pharmacokinetic studies in

animals and humans. Our administrative record lacks the data necessary to determine if there is an acceptable margin of safety for the repeated daily use of consumer antiseptic wash active ingredients. Thus, we are continuing to propose that this data is necessary for consumer antiseptic wash active ingredients. This information will help identify potential safety concerns and help determine if an adequate safety margin exists for OTC human use. One effect of systemic exposure to consumer antiseptic wash ingredients that has come to our attention since publication of the 1994 TFM is data suggesting that triclosan and triclocarban can cause alterations in thyroid, reproductive, growth, and developmental systems of neonatal and adolescent animals (Refs. 41 through 50). Hormonally active compounds have been shown to affect not only the exposed organism, but also subsequent generations (Ref. 51). These effects may not be related to direct deoxyribonucleic acid (DNA) mutation, but rather to alterations in factors that regulate gene expression (Ref. 52).

A hormonally active compound that causes reproductive system disruption in the fetus or infant may have effects that are not apparent until many years after initial exposure. There are also critical times in fetal development when a change in hormonal balance that would not cause any lasting effect in an adult could cause a permanent developmental abnormality in a child. For example, untreated hypothyroidism during pregnancy has been associated with cognitive impairment in the offspring (Refs. 53, 54, and 55).

Because consumer antiseptic washes are chronic use products and are used by sensitive populations such as children and pregnant women, evaluation of the potential for chronic toxicity and effects on reproduction and development should be included in the safety assessment. The designs of general toxicity and reproductive/developmental studies are often sufficient to identify developmental effects that can be caused by hormonally active compounds through the use of

currently accepted endpoints and standard good laboratory practice toxicology study designs. However, additional study endpoints may be needed to fully characterize the potential effects of drug exposure on the exposed individuals. In light of the preliminary findings for triclosan and triclocarban, it is particularly important that adequate analysis of all potential toxic effects of antiseptic active ingredients be conducted before their classification as GRAS. Section VII.C of this proposed rule describes the types of studies that can adequately evaluate an active ingredient's potential to cause developmental or reproductive toxicity, or adverse effects on the thyroid gland.

The potential of hormonally active antiseptic active ingredients to cause developmental or reproductive effects raises particular concerns for the safe use of these ingredients on children. Currently, there is a lack of data to assess the systemic exposure of antiseptic active ingredients in children. Additional data to support the safety of the use of consumer antiseptic active ingredients on children may be needed. The need for additional data in children would depend on the risks identified in the animal safety assessment. If studies in children are needed, we recommend that manufacturers discuss the types of studies needed with FDA before proceeding.

B. Antimicrobial Resistance

Since publication of the 1994 TFM, there is new information raising concerns about the impact of widespread antiseptic use on the development of antimicrobial resistance (Refs. 56 through 59). Bacteria use some of the same resistance mechanisms against both antiseptics and antibiotics. Thus, the use of antiseptic active ingredients with resistance mechanisms in common with antibiotics may have the potential to select for bacterial strains that are also resistant to clinically important antibiotics, adding to the problem of antibiotic resistance. Laboratory studies of some of the antiseptic active ingredients evaluated in this proposed rule demonstrate

the development of reduced susceptibility to antiseptic active ingredients and some antibiotics after growth in nonlethal amounts of the antiseptic (i.e., low-to-moderate concentrations of antiseptic) (Refs. 25 and 60 through 77). These studies provide ample evidence of bacterial resistance mechanisms that could select for antiseptic or antibiotic resistance in the natural setting.

The impact on bacterial resistance in the natural setting (rather than in the laboratory) has not been extensively evaluated. The existing data are very limited in scope. A few studies have not found evidence of such selective pressures occurring in the natural setting (Refs. 78 through 81). However, these data are limited by the small numbers and types of organisms, the brief time periods, and locations examined. More importantly, none of these consumer studies address the level of exposure to antiseptic active ingredients. Thus, the available data are not sufficient to support a finding that these mechanisms would not have meaningful clinical impact. Given the increasing evidence about the magnitude of the antibiotic resistance problem and the speed with which new antibiotic resistant organisms are emerging, it is important to assess this potential consequence of consumer antiseptic use (Ref. 82).

FDA has been evaluating the role that consumer antiseptic products may play in the development of antibiotic resistance for quite some time, and has sought the advice from expert panels on this topic on two occasions. In 1997, a joint Nonprescription Drugs and Anti-Infective Drugs Advisory Committee concluded that the data were not sufficient to take any action on this issue at that time (Ref. 2). The joint Committee recommended that FDA work with industry to establish surveillance mechanisms to address antiseptic and antibiotic resistance. At the October 2005 NDAC meeting on antiseptics for consumer use, however, some NDAC members expressed concern about the societal consequences of the pervasive use of consumer antiseptic

wash products, including the potential for antiseptic use to lead to changes in bacterial susceptibilities to clinically important antibiotics (Ref. 4).

Reports of the persistence of low levels of some consumer antiseptic wash active ingredients in the environment (Refs. 83, 84, and 85) signal the need to better understand the impact of widespread use of consumer antiseptic washes. Section VII.C of this proposed rule describes the data that will help establish a better understanding of the interactions between antiseptic active ingredients and bacterial resistance mechanisms in consumer products and will provide the information needed to perform an adequate risk assessment for these consumer product uses. FDA recognizes that the science of evaluating the potential of compounds to cause bacterial resistance is evolving, and acknowledges the possibility that alternative data different from that listed in section VII.C may be identified as an appropriate substitute for evaluating resistance.

C. Studies to Support a Generally Recognized as Safe Determination

A GRAS determination for consumer antiseptic wash active ingredients should be supported by both nonclinical (animal) and clinical (human) studies. In order to issue a final monograph for these products, this safety data must be in the administrative record (i.e., rulemaking docket). In order to assist manufacturers or others who wish to pursue GRAS status for these active ingredients we are including specific information based in part on existing FDA guidance about the kinds of studies to consider conducting and submitting. We have published guidance documents describing the nonclinical safety studies that a manufacturer should perform when seeking to market a drug product under an NDA (Refs. 86 through 91). These guidance documents also provide suitable guidance for performing the studies necessary to determine GRAS status for a consumer antiseptic wash active ingredient. Because consumer antiseptic

washes may be used repeatedly over a lifetime and in sensitive populations, we propose that antiseptic active ingredients will need to be tested for carcinogenic potential, developmental and reproductive toxicity (DART), and other potential effects as described in more detail in this section.

1. Safety Studies Described in Existing FDA Guidances

NDA safety studies that are described in the existing FDA guidances (Refs. 86 through 91) provide a framework for the types of studies that are needed for FDA to assess the safety of each antiseptic active ingredient and make a GRAS determination. A description of each type of study and how we would use this information to determine safety is provided in table 5.

Table 5.--Requested Safety Data and Rationale for Studies

Type of Study	Study Conditions	What the Data Tell Us	How the Data Are Used
Animal pharmacokinetic absorption, distribution, metabolism, and excretion (ADME) (Refs. 88 and 92)	Both oral and dermal administration	Allows identification of the dose at which the toxic effects of an active ingredient are observed due to systemic exposure of the drug. ADME data provide: The rate and extent an active ingredient is absorbed into the body (e.g., AUC, C _{max} , T _{max}) ¹ ; where the active ingredient is distributed in the body; whether metabolism of the active ingredient by the body has taken place; information on the presence of metabolites; and how the body eliminates the original active ingredient (parent) and its metabolites (e.g., T _{1/2}) ²	Used as a surrogate to identify toxic systemic exposure levels that can then be correlated to potential human exposure via dermal pharmacokinetic study findings. Adverse event data related to particular doses and drug levels (exposure) in animals are used to help formulate a safety picture of the possible risk to humans.
Human pharmacokinetics (Ref. 93)	Dermal administration using multiple	Helps determine how much of the active ingredient penetrates the skin, leading	Used to relate the potential human exposure to toxic drug levels identified in

Type of Study	Study Conditions	What the Data Tell Us	How the Data Are Used
	formulations under maximum use conditions	to measurable systemic exposure	animal studies
Carcinogenicity (ICH S1A and S1B (Refs. 86, 87, and 90))	Minimum of one oral and one dermal study for topical products	Provides a direct measure of the potential for active ingredients to cause tumor formation (tumorigenesis) in the exposed animals	Identifies the systemic and dermal risks associated with drug active ingredients. Taken together, these studies are used to identify the type of toxicity, the level of exposure that produces this toxicity, and the highest level of exposure at which no adverse effects occur, referred to as the "no observed adverse effect level" (NOAEL). The NOAEL is used to determine a safety margin for human exposure.
Developmental toxicity (ICH S5 (Ref. 89))	Oral administration	Evaluates the effects of a drug on the developing offspring throughout gestation and postnatally until sexual maturation	
Reproductive toxicity (ICH S5 (Ref. 89))	Oral administration	Assesses the effects of a drug on the reproductive competence of sexually mature male and female animals	

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

² "T_{1/2}" denotes the half-life, which is the amount of time it takes to eliminate half the drug from the body or decrease the concentration of the drug in plasma by 50 percent.

Because the available data indicate that some antiseptic active ingredients are absorbed after topical application in humans and animals, it is necessary to assess the effects of long-term dermal and systemic exposure to these ingredients. It also is important that the human pharmacokinetic studies reflect maximal use conditions of consumer antiseptic washes using different formulations to fully characterize the active ingredient's potential for dermal penetration. Because consumer antiseptic active ingredients can be formulated into either hand or body washes and consumers may use both on a daily basis, studies examining maximal use conditions must take full body exposure into account.

The duration of the studies should be sufficient to reach steady-state levels of absorption (i.e., the concentration of active ingredient is unchanged by further application of the product because the amount of active ingredient being absorbed is equal to the amount being eliminated by the body). For a steady-state study, the measurement of total exposure would be the area under the concentration-time curve (AUC) for plasma, serum, or blood over the length of the dosing interval at steady-state. Steady-state must be demonstrated by an unchanged AUC or drug concentration on 3 consecutive days taken at the same time of day.

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

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

2. Studies to Characterize Hormonal Effects

We propose that data are also needed to assess whether antiseptic active ingredients have hormonal effects that could produce developmental or reproductive toxicity. A hormonally active compound is a substance that interferes with the production, release, transport, metabolism, binding, activity, or elimination of natural hormones, which results in a deviation from normal homeostasis, development, or reproduction (Ref. 94). Exposure to a hormonally

active compound early in development can result in long-term or delayed effects, including neurobehavioral, reproductive, or other adverse effects.

There are several factors common to antiseptic wash products that make it necessary to assess their full safety profile prior to classifying an antiseptic wash active ingredient as GRAS.

These are:

- Evidence of systemic exposure to several of the antiseptic active ingredients
- Consumer exposure to multiple sources of antiseptic active ingredients or other drugs that may be hormonally active compounds
- Exposure to antiseptic active ingredients throughout a consumer's lifetime starting in utero

Most antiseptic active ingredients have not been evaluated for these effects despite the fact that several of the ingredients have evidence of systemic absorption. For antiseptic active ingredients that have not been evaluated, in vitro receptor binding or enzyme assays can provide a useful preliminary assessment of the potential hormonal activity of an ingredient. However, such preliminary assays do not provide conclusive evidence that such an interaction will lead to a significant biological change (Ref. 95). Conversely, lack of binding does not rule out an effect (e.g., compounds could affect synthesis or metabolism of a hormone resulting in drug-induced changes in hormone levels indirectly).

a. Traditional studies. General toxicity and reproductive/developmental studies such as the ones described in this section are generally sufficient to identify potential hormonal effects on the developing offspring. Developmental and reproductive toxicity caused by hormonal effects will generally be identified using these traditional studies if the tested active ingredient

induces a detectable change in the hormone-responsive tissues typically evaluated in the traditional toxicity study designs.

Repeat-dose toxicity (RDT) studies. RDT studies typically include a variety of endpoints, such as changes in body weight gain, organ weights, gross organ changes, clinical chemistry changes, or histopathology changes, which can help identify adverse hormonal effects of the tested drug. The battery of organs typically collected for histopathological evaluation in RDT studies includes reproductive organs and the thyroid gland, which can indicate potential adverse hormonal effects. For example, estrogenic compounds can produce effects such as increased ovarian weight and stimulation, increased uterine weight and endometrial stimulation, mammary gland stimulation, decreased thymus weight and involution, or increased bone mineral density.

DART studies. Some developmental stages that are evaluated in DART studies, such as the gestational and neonatal stages, may be particularly sensitive to hormonally active compounds. Traditional DART studies capture gestational developmental time points effectively, but are less adequate for evaluation of effects on postnatal development. Endpoints in pre/postnatal DART studies that may be particularly suited at detecting hormonal effects include vaginal patency, preputial separation, anogenital distance, and nipple retention. Behavioral assessments (e.g., mating behavior) of offspring may also detect neuroendocrine effects.

Carcinogenicity studies. A variety of tumors that result from long-term hormonal disturbance can be detected in carcinogenicity assays. For example, the effect of a persistent disturbance of particular endocrine gland systems (e.g., hypothalamic-pituitary-adrenal axis) can be detected in these bioassays. Certain hormone-dependent ovarian and testicular tumors and

parathyroid hormone-dependent osteosarcoma also can be detected in rodent carcinogenicity bioassays.

b. Supplementary studies. If no signals are obtained in the traditional RDT, DART, and carcinogenicity studies, assuming the studies covered all the life stages at which a consumer may be exposed to such products (e.g., pregnancy, infancy, adolescence), then no further assessment of drug-induced hormonal effects are needed. However, if a positive response is seen in any of the animal studies and this response is not adequately understood, then additional studies, such as juvenile animal, pubertal animal, or multigeneration studies, may be needed (Ref. 96). Juvenile animal, pubertal animal, and multigeneration studies are designed to evaluate endocrine effects in developmental stages that supplement the information obtained from traditional DART studies (Refs. 97, 98, and 99).

Juvenile animal studies. Young animals are considered juveniles after they have been weaned. In traditional DART studies, neonatal animals (pups) are typically dosed only until they are weaned. If a drug is not secreted via the mother's milk, the DART study will not be able to test the direct effect of the drug on the pup. Furthermore, since pups are not dosed after weaning, they are not exposed to the drug during the juvenile stage of development. A juvenile animal toxicity study in which the young animals are dosed directly can be used to evaluate potential drug-induced effects on postnatal development for products intended for pediatric populations.

Pubertal animal studies. The period between the pup phase and the adult phase, referred to as the juvenile phase of development, includes the pubertal period where the animal reaches puberty and undergoes important growth landmarks. In mammals, puberty is a period of rapid morphological changes and endocrine activity. Studies in pubertal animals are designed to detect

alterations of pubertal development, thyroid function, and hypothalamic-pituitary-gonadal system maturation (Ref. 100).

Multigeneration studies. The multigeneration reproductive toxicity studies (Ref. 98) are conducted to assess the performance and integrity of the male and female reproductive systems and include assessment of gonadal function, the estrous cycle, mating behavior, conception, gestation, parturition, lactation, weaning, and growth and development of the offspring. The multigeneration study also provides information about the effects of the test substance on neonatal morbidity, mortality, target organs in the offspring, and data on prenatal and postnatal developmental toxicity.

In those cases where adverse effects are noted on the developing offspring due to a disturbance of any of the organ systems discussed previously in this proposed rule, a risk-benefit analysis should be conducted based on the dose-response observed for the findings and the animal-to-human exposure comparison. If such an assessment indicates a potentially significant risk, then the antiseptic active ingredient with such findings would not be suitable for inclusion in an OTC monograph. Consequently, such antiseptic active ingredients would require an approval via the NDA pathway prior to marketing.

3. Studies to Evaluate the Potential Impact of Antiseptics Active Ingredient on the Development of Resistance

Since the 1994 TFM published, the issue of antiseptic resistance and the potential for antibiotic cross-resistance has been the subject of much study and scrutiny. In particular, triclosan has been shown to cause changes in bacterial efflux activity at nonlethal concentrations (Refs. 62, 64, 66, 101, and 102). Efflux pumps are an important nonspecific bacterial defense mechanism that can confer resistance to a number of substances toxic to the cell, including

antibiotics. For this reason, the effects of triclosan's use as a preservative in cosmetic products on the development of resistance have been evaluated by a number of European Advisory Review Committees (Refs. 103 through 108). In general, these Advisory Review Committees have concluded that the data are not sufficient to conclude that the use of triclosan poses a public health risk. However, more recently, a number of data gaps have been identified that some Advisory Review Committees believe need to be addressed to allow for a complete risk assessment of the use of triclosan (Refs. 107 and 108).

Our own evaluation also found data gaps with respect to triclosan's impact on the development of resistance; however, based on the data available for other active ingredients, the need to evaluate potential resistance is not limited to triclosan. Further, because of the pervasive use of consumer antiseptic wash products we believe that it is necessary to assess this safety issue prior to classifying an antiseptic active ingredient as GRAS. Therefore, in addition to the preclinical data requirements (as discussed in this section of this proposed rule), data are also needed to clarify the effect of antiseptic active ingredients on the emergence of bacterial resistance.

Laboratory studies are a feasible first step in evaluating the impact of exposure to nonlethal amounts of antiseptic active ingredients on antiseptic and antibiotic bacterial susceptibilities. As discussed in section VII.D of this proposed rule, some of the active ingredients evaluated in this proposed rule have laboratory data demonstrating the development of reduced susceptibility to antiseptic active ingredients and antibiotics after exposure to nonlethal concentrations. However, the testing conducted thus far has been limited largely to human bacterial pathogens. Only limited data exist on the effects of antiseptic exposure on the bacteria that are predominant in the oral cavity, gut, skin flora, and the environment (Ref. 109).

These organisms represent pools of resistance determinants that are potentially transferable to human pathogens (Refs. 110 and 111). Broader laboratory testing would more clearly define the scope of the impact of antiseptic active ingredients on the development of resistance and provide a useful preliminary assessment of an antiseptic active ingredient's potential to foster the development of resistance.

Studies evaluating the impact of antiseptic active ingredients on the antiseptic and antibiotic susceptibilities of each of the following types of organisms could support a GRAS determination for antiseptic active ingredients intended for use in OTC consumer antiseptic wash products:

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

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

However, for antiseptic active ingredients that demonstrate an effect on antiseptic and antibiotic susceptibilities, additional data will be necessary to help assess the likelihood that changes in susceptibility observed in the preliminary studies would occur in the consumer setting. Different types of data could be used to assess whether or not ingredients with positive laboratory findings pose a public health risk. We do not anticipate that it will be necessary to

obtain data from multiple types of studies for each active ingredient to adequately assess the potential to affect resistance. Such studies include, but are not limited to the following:

- Information about the mechanism(s) of antiseptic action (for example, membrane destabilization or inhibition of fatty acid synthesis), and whether there is a change in the mechanism of action with changes in antiseptic concentration
- Information clarifying the mechanism(s) for the development of resistance or reduced susceptibility to the antiseptic active ingredient (for example, efflux mechanisms)
- Data characterizing the potential for reduced antiseptic susceptibility caused by the antiseptic active ingredient to be transferred to other bacteria that are still sensitive to the antiseptic
- Data characterizing the concentrations and antimicrobial activity of the antiseptic active ingredient in biological and environmental compartments (for example, on the skin, in the gut, and in environmental matrices)
- Data characterizing the antiseptic and antibiotic susceptibility levels of environmental isolates in areas of prevalent antiseptic use (for example, in the home, health care, food handler, and veterinary settings)

These data can help ascertain whether or not an antiseptic active ingredient is likely to induce nonspecific bacterial resistance mechanisms such as those that have been shown to occur with triclosan exposure. These data could also help determine the likelihood that changes in susceptibility would spread to other bacterial populations and whether or not concentrations of antiseptics exist in biological and environmental compartments that are sufficient to induce changes in bacterial susceptibilities. Data on the antiseptic and antibiotic susceptibilities of bacteria in areas of prevalent antiseptic use can help demonstrate whether or not changes in

susceptibility are occurring with actual use. Because actual use concentrations of consumer antiseptics are much higher than the MICs for these active ingredients, data from compartments where sublethal concentrations of biologically active antiseptic active ingredients may occur (e.g., environmental compartments) can give us a sense of the potential for change in antimicrobial susceptibilities in these compartments (Refs. 83, 84, and 112 through 115).

However, FDA recognizes that methods of evaluating this issue are an evolving science and that there may be other data appropriate to evaluate the impact of antiseptic active ingredients on the development of resistance. For this reason, FDA encourages interested parties to consult with FDA on the specific studies appropriate to address this issue.

In those cases where data of the type described in this proposed rule shows that changes in bacterial susceptibilities are likely to occur in the consumer setting, an analysis of the risk in relation to the effectiveness shown for the active ingredient would be conducted. Based on this evaluation, a determination would be made as to whether the antiseptic active ingredient would be suitable for inclusion in an OTC monograph.

D. Review of Available Data for Each Antiseptic Active Ingredient

We have identified for each antiseptic active ingredient whether the studies outlined in section VII.C of this proposed rule are available. Table 6 of this proposed rule lists the types of studies available for each antiseptic active ingredient proposed as Category I or Category III in the 1994 TFM and indicates whether the currently available data are adequate to serve as the basis of a GRAS determination. Although we have data from submissions to the rulemaking and from information we have identified in the literature, our administrative record is incomplete for some types of safety studies for many of the active ingredients (see table 6 of this proposed rule).

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

Active Ingredient	Human Pharmacokinetic	Animal Pharmacokinetic (ADME)	Oral Carcinogenicity	Dermal Carcinogenicity	Reproductive Toxicity (DART)	Potential Hormonal Effects	Resistance Potential
Benzalkonium chloride			✓				✓
Benzethonium chloride		✓		✓✓	✓		✓
Chloroxylenol	✓	✓			✓		✓
Hexylresorcinol		✓	✓✓				
Iodophors:							
Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)			✓✓*		✓✓*	✓✓	
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)			✓✓*		✓✓*	✓✓	
Nonylphenoxypoly (ethyleneoxy) ethanoliiodine			✓✓*		✓✓*	✓✓	
Poloxamer-iodine complex			✓✓*		✓✓*	✓✓	
Povidone-iodine	✓✓		✓✓*		✓✓*	✓✓	
Undecylium chloride iodine complex			✓✓*		✓✓*	✓✓	
Methylbenzethonium chloride ²							
Phenol ²							
Secondary amylicresols ²							
Sodium oxychlorosene ²							
Triclocarban	✓	✓	✓✓		✓	✓	✓
Triclosan	✓✓	✓	✓✓		✓✓	✓	✓

¹ Empty cell indicates no data available; "✓" indicates some data available, but inadequate; "✓✓" indicates available data are adequate; * indicates based on studies of potassium iodide.

² These active ingredients are not discussed further because no safety data were submitted.

In the remainder of this section, we discuss the existing data and data gaps for each of the following antiseptic wash active ingredients that was proposed as GRAS in the 1994 TFM and explain why these active ingredients are no longer proposed as GRAS (i.e., why they are now proposed as Category III):

- Hexylresorcinol
- Iodophors (i.e., all iodine-containing ingredients)
- Triclocarban

We also discuss the following antiseptic active ingredients that were proposed as Category III in the 1994 TFM and for which there are some new data available and explain why these ingredients are still Category III:

- Benzalkonium chloride
- Benzethonium chloride
- Chloroxylenol
- Triclosan

We do not discuss the following antiseptic active ingredients that were proposed as Category III in the 1994 TFM because we are not aware of any safety data for these active ingredients:

- Methylbenzethonium chloride
- Phenol (less than 1.5 percent)
- Secondary amyltriclesols
- Sodium oxychlorosene

1. Hexylresorcinol

In the 1994 TFM, FDA proposed to classify hexylresorcinol as GRAS for use as an OTC antiseptic handwash based on the recommendations of the Panel, who concluded that the topical

application of hexylresorcinol is safe (39 FR 33103 at 33134). In support of its conclusion, the Panel cited hexylresorcinol's long history of use as an oral antihelmintic (a drug used in the treatment of parasitic intestinal worms) in humans and the lack of allergic reactions or dermatitis associated with topical use. The Panel noted that no information was provided regarding dermal or ophthalmic toxicity or absorption and blood levels attained after application to intact or abraded skin or mucous membranes, but concluded that the few animal toxicity studies submitted as summaries indicated a "low order" of toxicity (Ref. 116).

In light of the new safety information about the potential risks of systemic exposure to antiseptic active ingredients, the data relied on by the Panel no longer can be considered adequate to support a GRAS determination. Currently, there are only minimal data available to assess the safety of the repeated, daily, long-term use of hexylresorcinol.

a. Summary of available hexylresorcinol safety data.

Hexylresorcinol ADME data. There currently are no well characterized absorption studies in either humans or animals and only minimal ADME data by the oral route available. In one study (Ref. 117) male dogs were given single oral doses of 1 or 3 grams (g) of 4-hexylresorcinol. The majority of the administered dose was detected in its free form in the feces (67 to 80 percent) with some excretion in the urine (10 to 29 percent) primarily as conjugates. Urinary excretion was rapid, mainly in the first 6 hours, and levels were undetectable 12 hours after the 1 g dose and 24-36 hours after the 3 g dose.

In the only study in humans (Ref. 118), two men received oral doses of 1 g of 4-hexylresorcinol. An average of 18 percent of the dose was recovered in urine within the first 12 hours; thereafter, the compound was not detected in urine samples. Fecal excretion accounted

for 64 percent of the dose. It has been reported that hexylresorcinol is excreted via the urine mainly in the form of an ethereal sulfate conjugate (Ref. 119).

Overall, the animal ADME data are not adequate and additional pharmacokinetic data (e.g., AUC, Tmax, and Cmax) at steady-state levels continue to be necessary to bridge animal data to humans.

Hexylresorcinol carcinogenicity data. An adequate oral carcinogenicity study was conducted by the National Toxicology Program (NTP) in which hexylresorcinol was administered orally to groups of rats and mice of each sex 5 days per week for 2 years (Ref. 120). No evidence of carcinogenicity was found in rats. However, precancerous cells of the adrenal gland were observed at increased incidences in dosed male mice. A marginal upward trend in tumors of the adrenal gland was also observed in male mice. The increase of these two types of cancers was not statistically significant and was considered equivocal by the NTP.

FDA agrees that the findings in male mice should not be considered a positive carcinogenic signal. No changes were noted in the adrenal glands in 16- and 30-day subgroups included in the study. Also, the fact that the marginal increase in changes that occurred in male mice were not corroborated in earlier RDT studies in female mice, or in rats of either sex, makes the weight of the evidence for the male-only findings weak. In an 18-month intravaginal study (Ref. 121), injection of 1 percent hexylresorcinol dissolved in carbowax 1000 twice weekly in 20 female mice did not cause any genital tract tumors.

The submitted oral carcinogenicity data are adequate and show that hexylresorcinol does not pose a risk of cancer after repeated oral administration under the experimental conditions used; however, data from a dermal carcinogenicity study are lacking.

b. Hexylresorcinol safety data gaps. In summary, our administrative record for the safety of hexylresorcinol is incomplete with respect to the following:

- Human pharmacokinetic studies under maximal use conditions when applied topically, including documentation of validation of the methods used to measure hexylresorcinol and its metabolites
- Animal ADME
- Data to help define the effect of formulation on dermal absorption
- Dermal carcinogenicity
- DART studies
- 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 this proposed rule

2. Iodophors (iodine-containing ingredients)

Iodophor complexes are complexes formed between iodine, which is the active antimicrobial component, and a carrier molecule. Both surfactant and nonsurfactant compounds have been complexed with iodine. The rate of the release of “free” elemental iodine from the complex is a function of the equilibrium constant of the complexing formulation (39 FR 33103 at 33129). The following surfactant and nonsurfactant iodophor complexes were proposed as GRAS in the 1994 TFM for OTC antiseptic handwash use (59 FR 31402 at 31435):

- Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
- Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
- Nonylphenoxypoly (ethyleneoxy) ethaniodine

- Poloxamer-iodine complex
- Povidone-iodine 5 to 10 percent
- Undecylium chloride iodine complex

Iodine is found naturally in the human body and is essential for normal human body function. In the body, iodine accumulates in the thyroid gland and is a critical component of thyroid hormones. People obtain iodine through their food and water, which are often supplemented with iodine to prevent iodine deficiency. Because consumers are widely exposed to iodine, it has been the subject of comprehensive toxicological review by public health organizations (Refs. 122 and 123).

In the 1994 TFM, FDA stated that neither the medium nor large molecular weight size povidone molecules presented a safety risk when limited to the topical uses described in the monograph and that larger size molecules would not be absorbed under the TFM conditions of use (59 FR 31402 at 31424). We continue to believe that the larger size molecules pose no risk of absorption. However, data are lacking on the absorption of smaller molecular weight povidone molecules and for other carriers currently under consideration, e.g. poloxamer. Human absorption studies following maximal dermal exposure to these carriers can be used to determine the risk of systemic toxicity from the carrier molecule. For carrier molecules that are absorbed following dermal exposure, we propose that the following data are needed: Systemic toxicity of the carrier in animal studies that identify the target organ for toxicity, and characterization of the metabolic fate of the carrier as recommended by the Panel (39 FR 33103 at 33130).

a. Summary of iodophor safety data.

Iodophor human pharmacokinetics data. Several studies demonstrated that iodine applied to human skin was systemically absorbed to some extent (Ref. 122). The studies consistently

found raised blood concentrations of both organic (protein-bound) and inorganic (nonbound) iodine following topical application of iodine-containing antiseptics, indicating that iodine permeated the skin. However, the studies did not provide sufficient information to quantify typical amounts of iodine that can be absorbed from topically applied products containing iodine. In addition, the studies do not provide pharmacokinetic data at maximal exposure and steady-state levels.

Most of the absorption studies evaluated povidone-iodine. Significant iodine absorption was seen as a result of topical application of povidone-iodine either as a surgical scrub (Ref. 124) or as an antiseptic treatment of premature babies in a neonatal intensive care nursery (Ref. 125). Nobukuni et al. (Ref. 126) evaluated the effect of long-term topical povidone-iodine treatment on serum iodine levels and thyroid function in bedridden inpatients. Inpatients treated with povidone-iodine had higher blood concentrations of organic iodine compared to the control group, suggesting absorption of topically applied iodine. It is possible that steady-state levels may have been achieved in this study; however, this was not directly demonstrated.

Although these studies provide some information on absorption of topically applied povidone-iodine, they do not provide sufficient information to estimate typical amounts of iodine that could be absorbed from consumer antiseptic wash products containing povidone-iodine. Nor can the results of these studies be extrapolated to assess the potential dermal penetration of iodine from other iodophor complexes. Because the iodophor complex affects the release rate of iodine, absorption data are needed for each different complex.

Iodophor ADME data. In addition to human absorption data (described in the previous subsection), the distribution, metabolism, and excretion of iodine have been characterized in humans for oral exposures (Ref. 122). Because the distribution of absorbed iodine has been

shown to be similar regardless of the route of exposure, we can use data from oral exposures in assessing distribution, metabolism, and excretion of iodine from topical exposure. Most of the iodine from orally ingested sodium iodide accumulates in the thyroid (approximately 20 to 30 percent) as iodide or is excreted in the urine (30 to 60 percent) within 10 hours (Refs. 122 and 127). The elimination half-life of absorbed iodine is approximately 31 days in healthy adult males (Ref. 127), but has considerable variability (Ref. 128). Overall, the distribution, metabolism, and excretion of iodine have been adequately assessed in humans and no further animal ADME data is needed.

Iodophor carcinogenicity data. The oral carcinogenicity data indicate that iodine does not pose a risk of cancer in rats after repeated oral administration to rats under the experimental conditions used (Ref. 129). Overall, there was no significant increase in the incidence of tumors from iodine exposure. Although there was an increased incidence of squamous cell carcinomas in the submandibular salivary gland in the high dose group, this increase was not significant.

The ability of iodine to function as a tumor promoter (i.e., something that stimulates existing tumors to grow) also has been evaluated in rats. In a study by Takegawa et al. (Ref. 130), rats were pretreated with a chemical that can initiate tumors (DHPN). One group then received a high dose of potassium iodide (1,000 parts per million (ppm)) in their water while a control group received untreated water over 82 weeks. The iodine-treated group had a significantly higher incidence of follicular thyroid cancer compared to the control group, suggesting that iodine may be a tumor promoter for other carcinogens in the thyroid gland.

In another study (Ref. 131), rats were injected with either DHPN or saline and then received doses of potassium iodide in their drinking water to simulate conditions of iodine deficiency to iodine excess. For the two highest-dose groups, 5 of 20 rats and 2 of 20 rats

developed thyroid tumors, respectively. Although the authors concluded that excess iodine can promote thyroid tumor formation, these results were barely significant, and higher dosing did not correlate with increased tumor promotion activity. Therefore, some evidence suggests that very high oral doses of iodine may have tumor promoter activity. However, based upon the available data, oral doses of iodine do not significantly raise the risk of cancer in animals.

Iodophor DART data. The effects of iodine on embryo-fetal development and on fertility were studied in animals (Ref. 132). No fetal malformations were reported when the fetuses were exposed to iodine prenatally, nor were there any effects on fertility in adult animals that were exposed to iodine. The design of these studies, however, does not fit into current testing paradigms for an adequate evaluation of the reproductive and developmental toxicity of a drug.

One series of studies (Ref. 132) evaluated the effects of diets supplemented with high levels of iodine on reproduction, lactation, and survival in rats, hamsters, rabbits, and pigs. For the rats, excess iodine in the diet (2,500 ppm) was associated with an increase in the incidence of death in newborns and an increase in the time to give birth. In rabbits, a dose-dependent decrease in newborn survival was observed. There were no observed effects in hamsters or pigs. The results suggest a species difference in response to similar levels of excess iodine; however, the daily iodine intake per kilogram (kg) of body weight varied among species. Further, these studies do not evaluate all the necessary endpoints regarding fertility and embryo-fetal development.

Shoyinka, Obidike, and Ndumnego (Ref. 133) evaluated the effect of iodine on the male reproductive system of rats. A statistically significant ($p < 0.05$) increase in the average weights of the testes and epididymides, and approximately 12 percent decrease in epididymal sperm

counts were observed in the high dose-treated group. The authors suggest that excess iodine may reduce fertility by lowering epididymal sperm counts.

We found no information on reproductive effects in humans due to dermal iodine exposure. However, transient hypothyroidism (diminished production of thyroid hormones) in infants has been reported as a result of topical exposure to povidone-iodine (Refs. 134 through 138). Thyroid hormone deficiency from any cause at critical times of development may result in adverse effects, including abnormal pubertal development (Ref. 122). Although excess iodine may result in hypothyroidism, iodine deficiency is more likely to cause prenatal and postnatal hypothyroidism (Ref. 122).

Overall, the effect of iodine on development and reproductive toxicology are well characterized and additional DART studies are not needed.

Iodophor data on hormonal effects. We found no nonclinical studies that examine the effect of excess iodine or iodine deficiency on endocrine systems in animal models. However, clinical data indicate that at high doses iodine ingestion exerts a direct effect on the thyroid gland and on the regulation of thyroid hormone production and secretion (Ref. 122). The effects of iodine on the thyroid gland have been shown to include hypothyroidism, hyperthyroidism (excessive production or secretion of thyroid hormones), and inflammation of the thyroid. These conditions can adversely affect reproduction, growth, and developmental systems in humans.

The data demonstrating the thyroid effects of iodine are primarily from oral administration (Ref. 122). There is much less information on thyroid effects after topical administration of iodine. The majority of cases of thyroid hormone changes resulting from topical administration of iodine involve mothers and newborn infants. Studies have shown that topical povidone-iodine applied to pregnant and breast-feeding women causes transient

hypothyroidism in their newborns (Refs. 135, 136, 139, and 140). Iodine-induced hypothyroidism has been reported in nursing infants whose mothers used topical or vaginal iodine-containing antiseptics during pregnancy or after delivery (Refs. 135, 136, and 141). Other studies have shown hypothyroidism in infants after topical iodine exposure (Refs. 125, 134, 138, and 142). Elevated thyroid stimulating hormone (TSH) levels have been reported in full-term newborns after repeated topical application of povidone-iodine (Refs. 143 and 144).

Iodine readily crosses the placenta and is concentrated in the mammary gland and secreted in breast milk (Ref. 145). Although iodine-induced hypothyroidism is transient in newborns, even transient hypothyroidism should be avoided during this critical phase of brain development to prevent loss of intellectual capacity (Refs. 146, 147, and 148).

For adults, the association between topically applied iodine and hypothyroidism is unclear. One study in 27 bedridden inpatients treated continuously with povidone-iodine for 3 to 133 months showed changes in TSH levels (Ref. 126). However, these data are difficult to extrapolate to typical consumer antiseptic hand or body wash use because povidone-iodine was applied to damaged skin in this study. Another study in 16 nurses who used povidone-iodine regularly for handwashing and gargling (Ref. 149) found that thyroid hormone levels were not significantly different from control subjects who rarely used povidone-iodine, which suggests topical povidone-iodine does not significantly affect thyroid function.

Oral exposure to iodine has been demonstrated to cause significant thyroid effects (Refs. 122 and 123). Several clinical studies demonstrated that high oral doses of iodine can affect blood levels of thyroid hormones, but rarely did these effects seriously impair thyroid function. Oral iodine exposure exceeding 200 mg/day (2.8 mg/kg/day) during pregnancy can result in

congenital hypothyroidism (Ref. 122). Generally, however, adverse effects were only observed following very high oral doses that caused very high serum iodine concentrations.

Drawing conclusions from these studies is difficult because the studies have several limitations. Many of these studies lacked control groups, used small subject numbers, and/or did not record subjects' iodine status at baseline (iodine-deficient subjects may be more susceptible to thyroid effects caused by iodine exposure). The study results are also difficult to compare because the studies used different subject age groups, subject types, iodine formulations and amounts, durations and frequency of iodine treatment, and methods for measuring absorbed iodine levels or thyroid effects. Despite these deficiencies, we believe there are adequate data regarding the potential of iodine to cause changes in thyroid hormone levels and additional studies are not necessary.

b. Iodophor safety data gaps. In summary, our administrative record for the safety of iodophor complexes is 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 this section
- 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 section VII.C.3 of this proposed rule

3. Triclocarban

In the 1994 TFM, FDA proposed to classify triclocarban as GRAS for use as an OTC antiseptic handwash. This determination was based on safety data and information that were submitted in response to the 1978 TFM on triclocarban formulated as bar soap (Refs. 151 and 152). These data included blood levels, target organs for toxicity, and no effect levels and were discussed in the 1991 First Aid TFM (56 FR 33644 at 33664). The existing data, however, are no longer sufficient to fully evaluate the safety of triclocarban. New information regarding potential risks from systemic absorption and long-term exposure to antiseptic active ingredients is leading us to propose additional safety testing.

a. Summary of triclocarban safety data.

Triclocarban human pharmacokinetic data. Some human pharmacokinetic parameters were reported in a study where six male subjects received a single oral dose of ¹⁴C-labeled triclocarban: The maximum plasma concentration (i.e., C_{max}) was 3.7 nanomole (nmol)-equivalents of triclocarban per g of plasma (approximately 1,200 nanograms per milliliter (ng/mL)) and occurred at 2.8 hours (T_{max}) (Ref. 152). Although human pharmacokinetic parameters were reported in this study, triclocarban was administered orally. As a result, the exposure when applied topically under maximal use conditions and when steady-state levels were reached is unknown.

We found several studies in humans that examine the absorption of triclocarban after topical application (Refs. 153 through 156). Most of these studies evaluated absorption after a single topical exposure and used a small number of subjects. After a single exposure, blood levels of triclocarban ranged from below the limit of detection (10 ng/mL) to a C_{max} of 530 nanomolar (nM) (167 ng/mL) (Refs. 153, 154, and 155). Small amounts of triclocarban were also detectable in the urine and feces of subjects. The estimated total average recovery ranged

between 0.39 and 0.6 percent of the applied dose. Although small, these studies suggest that very little triclocarban is absorbed after a single topical exposure; however, steady-state levels were not evaluated.

Howes and Black (Ref. 156) examined absorption of triclocarban after repeated daily application in a 28-day bathing study. Twelve subjects bathed once daily using bar soap that contained 2 percent triclocarban. Each subject was exposed to approximately 260 mg of triclocarban per day. Triclocarban was below the limit of detection (25 ng/mL) in all samples at all time points. A manufacturer of triclocarban has suggested that steady-state levels were achieved in this study (Ref. 157), but this was not directly demonstrated.

In addition to systemic exposure as a result of dermal absorption, consumers may have prolonged exposure to those antiseptic active ingredients that remain bound to the skin after use (that is, substantive). Triclocarban has been shown to be substantive. North-Root et al. (Ref. 158) measured the amount of triclocarban that remained on the skin after a single application of bar soap in 12 human subjects. An average of 1.4 percent of the applied triclocarban remained on the skin. Substantive product remaining on the skin after rinsing may lead to additional absorption and systemic exposure.

Overall, the human pharmacokinetic studies are not adequate, and we propose that human pharmacokinetic studies using dermal administration under maximal use conditions are still needed to define the level of systemic exposure following repeated use. In addition, data are needed to help define the effect of formulation on dermal absorption.

Triclocarban ADME data. Triclocarban is readily metabolized in both humans and animals (Refs. 159 through 162). Birch et al. (Ref. 159) identified the metabolites of triclocarban in plasma and urine after oral exposure in rats, rhesus monkeys, and humans. The

principal metabolites common to all species were the sulfate and glucuronide conjugates of 2'-, 3'-, and 6-hydroxy-triclocarban. However, there were differences in triclocarban metabolism between rats and higher primates, and the monkey appears to be the more appropriate model for studying triclocarban pharmacokinetics in humans (Ref. 159).

Elimination of triclocarban metabolites from the plasma appears to be biphasic. In adult rhesus monkeys, elimination from the plasma occurs in two distinct phases: Rapid elimination of parent triclocarban and glucuronide conjugates, and slower elimination of sulfate conjugates (Ref. 160). Similarly, in humans, the major plasma metabolites are glucuronide conjugates, which were eliminated in urine with a half-life of about 2 hours (Ref. 152). Triclocarban sulfate conjugates are removed from plasma with a half-life of about 20 hours, presumably into the bile.

The majority of triclocarban and its metabolites are eliminated through the feces, with smaller amounts eliminated through the urine. In a human study where six male volunteers received a single oral dose of ¹⁴C-labeled triclocarban in corn oil, 70 percent of the dose was eliminated in the feces and elimination was complete after 120 hours (Ref. 152). Twenty-seven percent of the dose was eliminated in urine, and the urinary excretion of triclocarban and its metabolites was complete by 80 hours after dosing.

Although there are some ADME data on triclocarban after oral exposure, there are little data after topical exposure. Gruenke et al. (Ref. 163) analyzed plasma and urine samples from human subjects who used triclocarban-containing bar soap. The major plasma metabolite was a sulfate of hydroxy-triclocarban, with levels ranging from 0-20 ng/mL. The major metabolites found in the urine were triclocarban glucuronides, with typical levels averaging 30 ng/mL. The authors did not describe the frequency or length of time the subjects bathed with the soap; consequently, it is not known whether maximal exposure or steady-state levels were reached.

Overall, the animal ADME data are not adequate and additional pharmacokinetic data (e.g., AUC, Tmax, and Cmax) at steady-state levels continue to be necessary to bridge animal data to humans.

Triclocarban carcinogenicity data. A manufacturer submitted a 2-year oral carcinogenicity study of triclocarban in rats (Refs. 150 and 151). Based on this study, the no observed adverse effect level (NOAEL) for triclocarban in the rat is 25 mg/kg/day. Although no carcinogenicity findings were seen in this study, some noncarcinogenicity findings were noted. Male rats treated with 75 and 250 mg/kg/day doses of triclocarban exhibited male sex organ toxicity, including degeneration of the seminiferous tubules, enlargement of the epididymal secretory epithelium, and a decrease or absence of sperm in epididymal ducts.

No dermal carcinogenicity data have been submitted for triclocarban. Previously, we considered data from systemic exposure to represent a worst case scenario for topical products. Now, however, we recognize that topical products may affect the skin or be metabolized in the skin, which is not addressed in oral carcinogenicity studies.

The submitted oral carcinogenicity data are adequate and show that triclocarban does not pose a risk of cancer after repeated oral administration under the experimental conditions used; however, data from a dermal carcinogenicity study are lacking.

Triclocarban DART data. Our records indicate that a manufacturer submitted data regarding the reproductive toxicity of triclocarban to a triclocarban drug master file (Ref. 164). Safety data submitted to drug master files are not publicly available and, consequently, cannot be used to support a GRAS classification (§ 330.10(a)(4)(i)). For FDA to include these data in the administrative record for this rulemaking, they must be submitted to this rulemaking or be otherwise publicly available.

Triclocarban data on hormonal effects. Recent studies have demonstrated that triclocarban may have the ability to alter the activity of the androgen system (Refs. 41 and 42). Chen et al. (Ref. 42) reported that triclocarban enhanced the testosterone-induced androgen receptor-mediated response both in cell culture and in an in vivo rat model although triclocarban by itself had no activity. When castrated male rats were fed a diet containing 0.25 percent triclocarban and treated with testosterone propionate (0.2 mg/kg) for 10 days, all male sex accessory organs were significantly increased in size compared to rats treated with either triclocarban or testosterone alone. The implications of these findings on human health, especially for children, are not well understood.

The testicular effects seen in the 2-year oral carcinogenicity study (Refs. 150 and 151) also suggest a hormonal disturbance on the testes as a result of exposure to triclocarban. Our records indicate that additional studies to address possible testicular effects have been conducted and submitted to a triclocarban drug master file (Ref. 164). For FDA to include these data in the administrative record for this rulemaking, they must be submitted to the rulemaking or otherwise publicly available. Overall, the data submitted to the antiseptic rulemaking are not adequate to address concerns about hormonal effects of triclocarban. We propose that additional reproductive and developmental studies are necessary, which should include an assessment of any hormonal effects.

Triclocarban resistance data. We found one study that examined the potential for development of cross-resistance between triclocarban and antibiotics. Cole et al. (Ref. 78) described antibiotic and antiseptic susceptibilities of staphylococci isolated from the skin of consumers who used nonantibacterial or antiseptic body washes. Subjects were considered antiseptic body wash users if they used either bar soaps containing triclocarban (triclocarban

group) or liquid bath or shower products containing triclosan (triclosan group) on a regular basis for at least 30 days prior to study initiation. From a pool of 450 qualified subjects, 70 were randomly chosen for each treatment arm (non-user, triclocarban group, or triclosan group).

Bacterial skin samples were collected using a pre-validated method and were comprised of the combined samples from both forearms. Staphylococcus aureus and coagulase-negative Staphylococcus (CNS) were presumptively identified according to morphology, pigmentation, hemolysis, and other characteristics from these samples. One representative of each colony type from each sample was selected for further testing, for a total of 317 isolates: 16 S. aureus and 301 CNS.

All 317 Staphylococcus isolates were tested for susceptibility to 10 antibiotics, including the primary and secondary antibiotics of choice for treatment of Staphylococcus infections, by a commercial lab using an automated procedure. In addition, all isolates were tested for MIC of triclocarban and triclosan using a standard broth microdilution method.

The percentage of CNS isolates resistant to any of the 10 antibiotics was similar for all three groups (non-user, triclocarban, or triclosan group). When data from both user groups (triclocarban and triclosan) were pooled, there was no statistical difference in bacterial resistance patterns between users and non-users with the exception of tetracycline, which approached significance ($p = 0.052$). The authors did not provide the rationale for pooling triclocarban and triclosan user data in the analysis. Currently, there is no evidence to suggest that bacteria would use the same mechanisms of resistance against these two antiseptic active ingredients. When CNS susceptibility to antiseptics was examined, the MIC range for triclocarban was the same among all three groups (maximum MIC value of 0.750 (no units provided)). No patterns

emerged when the data were analyzed for cross-resistance between triclocarban or triclosan and antibiotics.

The authors conclude that this study shows no increase in antibiotic resistance from the regular use of triclocarban body wash. But, this study was not adequately designed to determine whether use of antiseptic body washes leads to changes in antibiotic or antiseptic susceptibilities. Given the limited number of isolates examined, it is not clear that the study was adequately powered to detect a difference in resistance patterns. Furthermore, the amount of antiseptic exposure was not defined. The length of time subjects has used antiseptic body washes (beyond the specified 30 days), the frequency of bathing, and the volume of antiseptic wash used per bath or shower was not reported. Finally, few bacterial isolates were examined. It is reasonable to examine the susceptibilities of Staphylococcus species; however, an average of only 1.5 isolates was obtained from each subject. Overall, the available data are not adequate to characterize triclocarban's potential to foster the development of cross-resistance with clinically important antibiotics and we propose that these studies are needed.

b. Triclocarban safety data gaps. In summary, our administrative record for the safety of triclocarban is incomplete with respect to the following:

- Human pharmacokinetic studies under maximal use conditions when applied topically, including documentation of validation of the methods used to measure triclocarban and its metabolites
- Animal ADME
- Data to help define the effect of formulation on dermal absorption
- Dermal carcinogenicity
- DART studies

- 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 this proposed rule

4. Benzalkonium Chloride

In the 1994 TFM, FDA categorized benzalkonium chloride in Category III because of a lack of adequate safety data for its use as OTC antiseptic handwash (59 FR 31402 at 31435). Because of its widespread use as an antimicrobial agent in cosmetics and as a disinfectant for hard surfaces in agriculture and medical settings, the safety of benzalkonium chloride has also been reviewed by the Environmental Protection Agency and an industry review panel (Cosmetic Ingredient Review (CIR)) (Refs. 165 and 166) and found to be safe for disinfectant and cosmetic uses, respectively. Both these evaluations have been cited by the comments in support of the safety of benzalkonium chloride as an antiseptic wash active ingredient (Ref. 167).

Each of these evaluations cites findings from the type of studies necessary to support the safety of benzalkonium chloride for repeated daily use. However, the data that are the basis of these safety assessments are proprietary and are publicly available only in the form of summaries. Consequently, these studies are not available to FDA and are precluded from a complete evaluation by FDA. In addition, the submitted safety assessments with study summaries do not constitute an adequate record on which to base a GRAS classification (§ 330.10(a)(4)(i)). For FDA to evaluate the safety of benzalkonium chloride for this rulemaking, these studies must be submitted to the rulemaking or otherwise be publicly available.

a. Summary of benzalkonium chloride safety data.

Benzalkonium chloride carcinogenicity data. Currently, no oral or dermal carcinogenicity data are publicly available. We found one short-term dermal toxicity study (Ref. 168). Mice were treated with a single topical application of 0.8, 3, 13, or 50 percent benzalkonium chloride aqueous solution and monitored for 1 month. Treatment with either the 13 or 50 percent solution (concentrations well above the actual use concentrations of 0.1 to 5 percent) caused death in 9 of 48 and 20 of 48 mice in each group, respectively. The surviving mice developed skin lesions at the application site. The low-dose groups (0.8 or 3 percent solutions) showed slightly lower body weights and rates of growth than the control group, suggesting a slight detrimental effect from dermal exposure to these low concentrations. The available data are not adequate to assess the carcinogenic potential of benzalkonium chloride. We propose that both oral and dermal carcinogenicity studies are needed for benzalkonium chloride.

Benzalkonium chloride resistance data. Several gram-negative bacteria (GNB) (Escherichia coli, Salmonella, and Pseudomonas) have been shown to readily adapt when grown in the presence of subinhibitory levels of benzalkonium chloride in laboratory studies (Refs. 60, 68, 70, 72, 169, and 170). These bacteria also displayed reduced susceptibility to antibiotics compared to the nonadapted parental strain (Refs. 60, 70, 72, 169, and 170). Four studies showed an association between reduced susceptibility to benzalkonium chloride and the antibiotic chloramphenicol (Refs. 70, 72, 79, and 170). This association was shown in three different bacteria; however, no common mechanism has been identified to explain this finding. There are data available suggesting that efflux pumps may not play a major role in the reduced susceptibility of Salmonella to benzalkonium chloride (Ref. 170).

In a study by Lambert and colleagues (Ref. 69), human clinical and industrial isolates and standard culture collection strains of P. aeruginosa were examined for reduced susceptibility to benzalkonium chloride, chlorhexidine, and eight antibiotics. No statistically significant association between benzalkonium chloride and antibiotic susceptibility (i.e., cross-resistance) was found in the industrial isolates. In contrast, there was a highly significant correlation between benzalkonium chloride and gentamycin resistance in the clinical isolates. In other words, strains that were resistant to gentamycin also tended to have reduced benzalkonium chloride susceptibility. Although the authors suggest that the clinical environment is responsible for cross-resistance, this study is not large enough to provide sufficient support for this theory.

In a second study, Lambert and colleagues found a positive correlation between benzalkonium chloride and six antibiotics (ciprofloxacin, erythromycin, oxacillin, clindamycin, amoxicillin/clavulanic acid, and sodium cefazolin) in MRSA clinical isolates. However, most of the statistically significant correlations found in this study were between two antiseptics or two antibiotics, rather than between an antiseptic and an antibiotic. In addition, there was also a negative correlation between benzalkonium chloride and ciprofloxacin in P. aeruginosa. The authors suggest that there are no correlations in resistance to benzalkonium chloride and resistance to antibiotics but believe a larger study is needed to confirm or change that conclusion.

Similar to what has been observed with triclosan, exposure to benzalkonium chloride in the laboratory has resulted in changes to the antibiotic susceptibility profiles of some bacteria (Refs. 60, 70, 72, 79, 169, and 170). However, the data are limited in scope. The available studies have examined few bacterial species, provide no information on exposure levels, and are not adequate to define the potential for the development of resistance or cross-resistance. Additional laboratory studies are necessary to more clearly define the potential for the

development of resistance to benzalkonium chloride. Depending on the results of the laboratory studies, additional data of the type described in section VII.C of this proposed rule may also be needed to assess the level of risk posed by benzalkonium chloride.

b. Benzalkonium chloride safety data gaps. In summary, our administrative record for the safety of benzalkonium chloride is incomplete with respect to the following:

- Human pharmacokinetic studies under maximal use conditions when applied topically, including documentation of validation of the methods used to measure benzalkonium chloride and its metabolites
- Animal ADME
- Data to help define the effect of formulation on dermal absorption
- Oral carcinogenicity
- Dermal carcinogenicity
- DART studies
- Potential hormonal effects
- Data from laboratory studies that assess the potential for the development of resistance to benzalkonium chloride and cross-resistance to antibiotics in the types of organisms listed in section VII.C.3 of this proposed rule

5. Benzethonium Chloride

In the 1994 TFM, FDA classified benzethonium chloride as lacking sufficient evidence of safety for use as an antiseptic handwash (59 FR 31402 at 31435). Since FDA's proposed classification, two industry review panels (CIR and a second industry panel identified in a comment only as an "industry expert panel") and a European regulatory advisory board (Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers)

have evaluated the safety of benzethonium chloride when used as a preservative in cosmetic preparations and as an active ingredient in consumer hand soaps (Refs. 171, 172, and 173). These advisory bodies found benzethonium chloride to be safe for these uses. However, all of these safety determinations have largely relied on the findings of proprietary studies that are not publicly available. One of these evaluations, the findings of the unidentified industry expert panel, was submitted to the rulemaking to support the safety of benzethonium chloride (Ref. 174).

Some of the safety data reviewed by the unidentified industry expert panel represent the type of data that are needed to evaluate the safety of benzethonium chloride for use in consumer antiseptic wash products, e.g., ADME, DART, and oral carcinogenicity studies. The safety assessments used to support the unidentified industry expert panel's finding of safety, however, are publicly available only in the form of summaries. Consequently, these studies are not available to FDA and are precluded from a complete evaluation by FDA. Further, the submitted safety assessments with study summaries do not constitute an adequate record on which to base a GRAS classification (§ 330.10(a)(4)(i)). For FDA to include these studies in the administrative record for this rulemaking, they must be submitted to the rulemaking or otherwise publicly available.

a. Summary of benzethonium chloride safety data.

Benzethonium chloride ADME data. In 1988, NTP studied the extent of absorption following single and repeated once-daily dermal doses of benzethonium chloride and determined the pattern of tissue distribution and route of elimination of ¹⁴C-labeled benzethonium chloride in rats (Ref. 175). They also determined the kinetics of distribution and excretion following

intravenous administration. Under the conditions of the dermal studies, benzethonium chloride was readily absorbed following single or repeated dermal applications.

After a single application of ¹⁴C-labeled benzethonium chloride in ethanol to skin that was covered by a nonocclusive patch, total urinary excretion was 1 to 2 percent of the applied dose, and fecal excretion accounted for about 45 percent of the dose. The radiolabel was below the detection limit in blood and most tissues during the study, but low levels were measured in the liver. Some residual radiolabel could be accounted for in the epidermis at the site of application. When similar studies were performed with repeated once-daily dermal dosing, the total amount of radiolabel excreted up to 10 days following the last dose was about 25 percent, suggesting some accumulation with repeated dermal administration.

More recent data submitted to support the safety of benzethonium chloride have shown a much lower level of absorption. In response to the 1994 TFM, a manufacturer provided data from a preliminary rat dermal absorption study and an in vitro dermal absorption study (Ref. 176). In the rat study, an aqueous 1 percent solution of ¹⁴C-benzethonium chloride was applied to the shaved back of rats and covered with a nonocclusive patch. Blood, urine, and feces were collected for 48 hours after dosing. Little or no radioactivity was detected in blood or urine samples. Approximately 7 percent of the administered radioactivity was detected in the fecal samples. The remaining radioactivity was not accounted for.

The in vitro dermal absorption study compared the absorption of benzethonium chloride through rat and human skin (Ref. 176). Pieces of skin were obtained from rats and human plastic surgery patients. Total absorption was higher in rat compared to human skin. Under the conditions of this study, the total amount of benzethonium chloride maximally absorbed by

human skin during 24 hours was 4.14 percent. Accumulation of benzethonium chloride in the skin was less than 1 percent in human skin but was about 5 percent in rat skin.

The available data demonstrate that there is absorption of benzethonium chloride following dermal exposure. However, the level of absorption is not clearly defined. These data also suggest that the amount of dermal absorption varies by species and with formulation. The currently available animal data also lack other pharmacokinetic determinations, i.e., distribution and metabolism. Subsequent to the 1994 TFM, FDA had numerous discussions with a manufacturer interested in attaining a GRAS classification for benzethonium chloride (Refs. 174, 177, and 178). Topics covered in these discussions included the need for pharmacokinetic studies in animals following dermal exposure (Refs. 177 and 178). The available data are not adequate and data from ADME studies in animals continue to be necessary because of highly variable results in the submitted studies, the need to clearly define the level of dermal absorption, the effect of formulation on dermal absorption, and the distribution and metabolism of benzethonium chloride in animals. In addition, we lack human pharmacokinetic studies under maximal use conditions, which are needed to define the level of systemic exposure following repeated use.

Benzethonium chloride carcinogenicity data. In 1995, the NTP conducted dermal carcinogenicity studies of benzethonium chloride in an ethanol vehicle in rats and mice (Ref. 175). There were no treatment-related differences from control animals in survival, clinical signs (e.g., reddening or crusting of the skin), body weights, organ weights, or neoplastic lesions in either rats or mice. Histological evaluation revealed dose-related (minimal in low dose, moderate in high dose) epithelial hyperplasia in both rats and mice at doses greater than 0.15

mg/kg/day. In rats, epidermal ulceration was frequent in high dose females and in one high dose male.

There was no systemic toxicity or carcinogenicity at any dose level in either species. The no observed effect level (NOEL) for systemic toxicity was 1.5 mg/kg/day based on systemic toxicity and carcinogenicity. While we agree with NTP's analysis of the systemic toxicity, we disagree with the NOEL for dermal toxicity because epithelial hyperplasia and reddening of the skin were noted at all doses greater than 0.15 mg/kg/day. Therefore, we consider the NOEL for dermal toxicity to be 0.15 mg/kg/day.

The submitted dermal carcinogenicity data are adequate and show that benzethonium chloride does not pose a risk of cancer after repeated dermal administration under the experimental conditions used; however, data from an oral carcinogenicity study are lacking.

Benzethonium chloride DART data. A manufacturer submitted summaries of four teratology studies (three rat and one rabbit) and one perinatal and postnatal study in rats (Ref. 174). In two of the rat teratology studies, the rats showed delayed bone tissue formation (ossification) and soft tissue and skeletal malformation at the high dose. Only delayed ossification was noted in the third rat study and in the rabbit study. These findings suggest that benzethonium chloride is a teratogen at high doses when administered orally. However, without the complete study reports, we are unable to fully assess the significance of these findings.

An embryo-fetal rat study with sufficient detail for evaluation was submitted (Ref. 174). In this study, pregnant female rats were administered benzethonium chloride on gestational days 6 through 15. Maternal toxicity was noted among the high dose-treated females. In the other dose groups, toxicity findings were sporadic and not dose-related. There were no treatment-related gross necropsy findings or reproductive endpoint changes caused by the treatment. The

incidence of delayed sternal ossification and/or nonossified sternal centrae was noted in all treatment groups and was statistically significant. However, this finding is not considered biologically significant as the incidence was not dose-related, the litter incidence values did not differ significantly, and the values were within the range of historical values. The maternal NOAEL is 100 mg/kg/day based on body weight changes and deaths at the dose of 170 mg/kg/day.

Overall, the DART data are not adequate to characterize all aspects of reproductive toxicity and we propose that studies are needed to assess the effect of benzethonium chloride on male and female fertility and on pre- and postnatal endpoints (e.g., the number of live or dead offspring, body weight at birth, physical growth and development, neurodevelopmental effects, and fertility of the pups).

Benzethonium chloride resistance data. We found two studies that examined bacterial susceptibility profiles for both benzethonium chloride and antibiotics. One study (Ref. 179) provided the data collectively, so no associations between reduced susceptibility to benzethonium chloride and specific antibiotics could be determined. The second study (Ref. 180) found a positive correlation between reduced susceptibility to benzethonium chloride and ciprofloxacin or oxacillin in clinical isolates of MRSA. There were no associations between benzethonium chloride and antibiotic resistance in the other tested organisms (methicillin-sensitive S. aureus or P. aeruginosa).

Overall, the available studies are limited in scope. They examine few bacterial species, provide no information on the level of benzethonium chloride exposure, and are not adequate to define the potential for the development of resistance and cross-resistance to antibiotics. Additional laboratory studies are necessary to more clearly define the potential for the

development of resistance to benzethonium chloride. Depending on the results of the laboratory studies, additional data of the type described in section VII.C of this proposed rule may also be needed to assess the level of risk posed by benzethonium chloride.

b. Benzethonium chloride safety data gaps. In summary, our administrative record for the safety of benzethonium chloride is incomplete with respect to the following:

- Human pharmacokinetic studies under maximal use conditions when applied topically, including documentation of validation of the methods used to measure benzethonium chloride and its metabolites
- Animal ADME
- Data to help define the effect of formulation on dermal absorption
- Oral carcinogenicity
- DART studies (fertility and embryo-fetal testing)
- Potential hormonal effects
- Data from laboratory studies that assess the potential for the development of resistance to benzethonium chloride and cross-resistance to antibiotics in the types of organisms listed in section VII.C.3 of this proposed rule

6. Chloroxylenol

There are limited safety data to support the long-term use of chloroxylenol in OTC consumer antiseptic hand and body wash products. Chloroxylenol is absorbed after topical application in both humans and animals. However, studies conducted in humans and animals are inadequate to fully characterize the extent of systemic absorption after repeated topical use or to demonstrate the effect of formulation on dermal absorption. The administrative record also lacks other important data to support a GRAS determination for this antiseptic active ingredient.

a. Summary of chloroxylenol safety data.

Chloroxylenol human pharmacokinetic data. The dermal absorption of chloroxylenol has been studied in humans following single and repeated bathing (10 minutes daily for 1 to 10 days) and following a single 30-minute percutaneous application to the back of one subject (Refs. 181 and 182). The studies were conducted with few subjects and a single formulation, and as shown in table 7 of this proposed rule, produced inconsistent results.

Table 7.--Results of Human Absorption Studies of Chloroxylenol

Study	No. of Subjects	Bath	Absorption ¹	
			Milligrams	Percent
Jordan, Nichols, and Rance, Preliminary Bathing Study (Ref. 181)	1	1st	5.74	0.5
Jordan, B. J., et. al., Repeat Bathing Study (Ref. 182)	4	1st	2.4 to 4.4	0.2 to 0.37
		10th	2.4 to 6.4	0.2 to 0.5
Jordan, B. J., et. al., Dermal ADME under Occlusion Study (Ref. 182)	1	N/A	7.2	15.7

¹ Based on amounts in urine.

The wide variation in the study findings may be due to the much lower concentration of chloroxylenol used in bathing studies (1:4,000 and 1:4,800 dilution of a 4.8 percent product versus 1 mL of the same product undiluted). However, the small sample size and disparate study results make it difficult to draw any meaningful conclusions on the level of dermal absorption following single or repeated use.

The percutaneous absorption study (Ref. 182) also provides some limited information on the elimination of chloroxylenol in humans. Assays of urine samples revealed that all

chloroxylenol was excreted as conjugated metabolites. No unchanged chloroxylenol was found in the urine at any time point, and most of the drug was excreted in the first 8 hours after application.

Overall, the human pharmacokinetic studies are not adequate and we propose that human pharmacokinetic studies using dermal administration under maximal use conditions are still needed to define the level of systemic exposure following repeated use. In addition, data is needed to help define the effect of formulation on dermal absorption.

Chloroxylenol animal ADME data. Dermal ADME studies in rats and mice are available (Refs. 183 and 184). In a study conducted by Sved (Ref. 184), increasing doses of ¹⁴C-labeled chloroxylenol were applied to the shaved backs of mice as a single or repeated dose (once daily for 14 or 28 days). Absorption was apparent at all time points and increased with increasing length of exposure. Approximately 50 percent of the applied dose was absorbed at 24 hours after a single dose and approximately 65 percent at 24 hours after 14 and 28 days of daily dosing. The amount of chloroxylenol absorbed was proportional to the administered dose. The plasma half-life for chloroxylenol was 18, 22, and 12 hours for low, mid, and high dose males, respectively, and 70, 9, and 12 hours for low to high dose females, respectively. The half-life in skin was longer at lower doses of chloroxylenol.

After dermal application chloroxylenol has been found in the following tissues: Kidney, lung, liver, adrenal glands, skin, heart, ovary, ovarian fat, skeletal muscle, skull, spinal cord, spleen, eyes, femur, and brain (Refs. 183 and 184). Tissue concentrations increased with repeated dosing, up to 1.8-fold in the kidney, up to 3.8-fold in the liver, and up to 8.9-fold in the brain (Ref. 183). Concentrations in tissue also increased with dose. Unlike the concentrations in the liver and kidney, chloroxylenol levels in the brain did not appear to reach steady-state

concentrations after 28 days of dosing, particularly at the lower chloroxylenol concentrations (Ref. 183). The relevance of these findings from a chronic use perspective cannot be evaluated without long-term animal studies.

The majority of chloroxylenol is excreted in the urine, and this is largely as polar conjugated metabolites. Only traces of unchanged chloroxylenol are present in urine. Havler identified a minor metabolite of chloroxylenol, hydroxylated chloroxylenol, which represents 10 to 15 percent of the metabolites found in urine (Ref. 183). Both chloroxylenol and the minor metabolite are excreted as a mixture of glucuronide and sulfate conjugates (Ref. 183). Excretion is largely complete 24 hours after a single dermal application.

Overall, these data demonstrate that absorption of chloroxylenol occurs after dermal application in humans and animals. However, the extent of this absorption and the resulting systemic exposure has not been adequately characterized. In the 1994 TFM, FDA stated that data from human studies characterizing the absorption, distribution, and metabolism of chloroxylenol conducted under maximal exposure conditions were needed (59 FR 31402 at 31415). The administrative record for this active ingredient still lacks data to characterize the rate and extent of systemic absorption, the similarities and differences between animal and human metabolism of chloroxylenol under maximal use conditions, and data to help establish the relevance of findings observed in animal toxicity studies to humans.

Chloroxylenol carcinogenicity data. In the 1994 TFM, FDA stated that a lifetime dermal carcinogenicity study (up to 2 years) in mice was needed to assess the dermal toxicity of chloroxylenol (59 FR 31402 at 31415). In response to this request, data from a 13-week dose ranging dermal toxicity study in mice were submitted (Ref. 185).

The study results show dose-related dermal adverse effects that may be indicative of dermal toxicity, such as erythema (skin redness), edema (swelling), and exfoliation (skin peeling). Microscopic changes consistent with a mild dermal irritant were also noted. These changes included hyperplasia (abnormal multiplication of skin cells) and hyperkeratosis of the epidermis (overgrowth of outermost layer of the skin) in all dosed animals, inflammation of the superficial dermis (a deeper layer of the skin) in most treated animals, crust formation, and necrosis (degradation) of epidermal cells. There were also dose-dependent lesions that increased in significance with dose. Hyperplasia of bone marrow and increased extramedullary hematopoiesis (formation of red blood cells outside the bone marrow) in the spleen consistent with an increasing inflammatory reaction were observed in the high dose group. The NOEL was 15 percent chloroxylenol and the NOAEL was less than 30 percent.

To adequately assess the significance of these study findings, a long-term dermal carcinogenicity study is needed. In addition, because of potential systemic exposure, an oral carcinogenicity study is also necessary to characterize the systemic effects from long-term exposure.

Chloroxylenol DART data. Data are available from a teratology study in rats that adequately characterizes chloroxylenol's potential effects on embryo and fetal development (Ref. 186). The maternal NOEL in this study was 100 mg/kg/day. The maternal lowest observed effect level was 500 mg/kg/day based on decreased food consumption and decreased body weight gain. The NOEL for developmental toxicity was 1,000 mg/kg/day. However, this study is not sufficient to characterize effects on other aspects of reproduction. Additional studies are necessary to assess the effect of chloroxylenol on fertility and early embryonic development and on pre- and postnatal development.

Chloroxylenol resistance data. We found no published studies that examine the changes in bacterial susceptibilities that may occur after exposure to nonlethal amounts of chloroxylenol. The few studies that are available assess antibiotic susceptibility in chloroxylenol-tolerant bacteria. In one study Lambert and colleagues determined the MICs of 8 antiseptics and at least 7 antibiotics for 256 clinical isolates of S. aureus (including MRSA) and 111 clinical isolates of P. aeruginosa (Ref. 180). Although most of the statistically significant correlations were between two antiseptics or between two antibiotics rather than between an antiseptic and an antibiotic, the authors found a significant positive correlation between chloroxylenol and gentamycin resistance in P. aeruginosa, but a negative correlation between chloroxylenol and ciprofloxacin resistance. They found no correlations between chloroxylenol and antibiotic resistance for S. aureus.

In a pair of studies (Refs. 79 and 80), Lear and colleagues collected, identified, and measured antimicrobial susceptibilities of bacteria from industrial sources. The authors saw no difference in the antibiotic susceptibility patterns of the industrial and standard strains of P. aeruginosa. Overall, there were few changes in antibiotic resistance patterns between the standard and industrial strains.

While these studies provide little evidence of cross-resistance to antibiotics, they are limited in scope. They examine few bacterial species, provide no information on the level of chloroxylenol exposure, and are not adequate to define the potential for the development of resistance to chloroxylenol and cross-resistance to antibiotics. If the data from initial laboratory studies indicate a potential for the development of chloroxylenol resistance and antibiotic cross-resistance, additional data such as the type described in section VII.C of this proposed rule will be necessary to assess the level of risk posed by chloroxylenol.

b. Chloroxylenol safety data gaps. In summary, our administrative record for the safety of chloroxylenol is incomplete with respect to the following:

- Human pharmacokinetic studies under maximal use conditions when applied topically that includes documentation of validation of the methods used to measure chloroxylenol and its metabolites
- Animal ADME at toxic exposure levels
- Data to help define the effect of formulation on dermal absorption
- Dermal carcinogenicity
- Oral carcinogenicity
- DART studies defining the effects of chloroxylenol on fertility and pre- and postnatal development
- Potential hormonal effects
- Data from laboratory studies that assess the potential for the development of resistance to chloroxylenol and cross-resistance to antibiotics in the types of organisms listed in section VII.C.3 of this proposed rule

7. Triclosan

A large number of studies have been conducted to characterize the toxicological and metabolic profile of triclosan using animal models. Most of these studies have focused on understanding the fate of triclosan following exposure to a single source of triclosan via the oral route of administration. However, dermal studies in both humans and animals are also available. These studies show that triclosan is absorbed through the skin, but to a lesser extent than oral absorption.

a. Summary of triclosan safety data.

Triclosan human pharmacokinetics data. Although much of the human data relates to oral exposure, there are some human studies that examine triclosan pharmacokinetics after dermal exposure on the hands or body (Refs. 187, 188, and 189). The dermal absorption of triclosan has been estimated or characterized using a variety of formulations and techniques, as described in this subsection. The available data show that dermal absorption of triclosan is low. Consequently, additional human pharmacokinetic studies are not necessary.

In one multiple exposure handwash study (Ref. 187), 13 human subjects washed their hands 6 times a day with 1 percent triclosan liquid soap for 20 days. Dermal absorption of triclosan was demonstrated by an increase in the levels of triclosan in plasma after handwash use; however, the percentage of the applied dose that was absorbed through the skin was not provided or estimated. Steady-state levels of free and total triclosan were achieved within approximately 1 week (days 6-8). The highest plasma concentrations achieved by any subject during the study were 69.9 ng/mL for free triclosan and 229 ng/mL for total triclosan. Although this study provides a picture of the steady-state levels of triclosan from repeated handwash use, it does not provide C_{max}, T_{max} or AUC values for humans.

Despite the lack of individual concentration-time data, this study provides a basis on which to estimate the mean steady-state concentrations that would result if a multiple-application body wash study were to be conducted. From the reported study results, it is possible to calculate the cumulative amount of product used by each subject, and to relate this amount to the amount that would be used as a body wash. Assuming a concentration of 1 g triclosan/mL of soap, the mean of all subjects in the handwash study was 3.6 mL/wash. Multiplying this value by six washes per day gives a total mean volume of 21.6 mL/day.

Using a reported industry estimate (Ref. 190) that a 10 ounce (295.5 mL) bottle contains enough body wash for 29 washes, the estimated amount of body wash per use would be 10.2 mL ($295.5 \text{ mL}/29 \text{ washes} = 10.2 \text{ mL/wash}$). Assuming that an individual bathes twice a day with a 1 percent triclosan-containing body wash, the total mean volume estimate would be approximately 20.4 mL. This is less than the mean amount used in the handwash study (21.6 mL/day). Based on the pharmacokinetic data provided, steady-state was achieved during the study, indicating that the study was of sufficient length to evaluate the pharmacokinetics of chronically administered triclosan.

Another of the available studies (Ref. 188) addresses triclosan exposure as a result of multiple product use. Two groups of 84 subjects were enrolled in this 13-week study. One group used triclosan toothpaste twice a day plus triclosan bar soap for face and handwashing twice a day plus triclosan deodorant once a day. The other group used triclosan toothpaste twice a day plus placebo soap and deodorant. Blood was drawn before product usage and at 3, 6, and 13 weeks.

At baseline, there was no significant difference in the mean triclosan plasma concentrations between groups. After product use, however, the mean triclosan plasma concentrations were significantly higher in the multiple triclosan-containing product group (highest achieved concentration: 31.04 ng/mL) than in the toothpaste only group (highest achieved concentration: 22.47 ng/mL) for all three time points. This suggests that the use of multiple triclosan-containing products can lead to higher triclosan exposure than from use of a single product. The concentrations observed in this study are substantially lower than the range of concentrations at steady-state that were observed in the handwashing study (Ref. 187). The substantial increase in triclosan concentration from baseline to 3 weeks indicates that the

majority of the absorbed triclosan in this study was due to the use of the triclosan-containing toothpaste.

There have been several studies that attempted to estimate the absorption of triclosan following topical application in a variety of different formulations (Refs. 189, 191, 192, and 193). In these studies triclosan was delivered as a solution, in toothpaste, as a mouthwash, or in a cream. Despite the different properties of the dosage forms and vehicles used, the estimated absorption was approximately in the range of 5 to 15 percent of the applied dose. Based on these data, the impact of different formulations on the dermal absorption of triclosan appears to be minimal.

In summary, human absorption of triclosan has been adequately characterized and no further human pharmacokinetic studies are needed.

Triclosan ADME data. Triclosan is readily metabolized in both humans and animals to two main parent conjugates, triclosan glucuronide and triclosan sulfate. Several other minor metabolites have been detected in animal studies (Refs. 194 through 197); however, the relevance of these minor metabolites to humans is unknown. In humans after oral or oral plus dermal triclosan exposure, triclosan glucuronide is the primary circulating metabolite in plasma (Ref. 188). After a single oral exposure to 4 mg of triclosan, the triclosan levels in human plasma increased rapidly and reached maximum concentration within 1 to 3 hours (Ref. 198). In this study, the majority of the triclosan in plasma was conjugated; the unconjugated fraction of triclosan in plasma was 30 to 35 percent. Triclosan was cleared from the plasma at a rate of 2.9 L/hour.

There also are some data to suggest that triclosan is metabolized during passage through the skin. Moss, Howes, and Williams (Ref. 191) examined dermal metabolism of triclosan in

vivo in the rat and in vitro using rat or human skin in flow-through diffusion cells. In both species, triclosan was metabolized during passage through the skin to triclosan glucuronide and triclosan sulfate. Triclosan was more readily metabolized to the glucuronide conjugate, which was also more readily removed from the skin than the sulfate conjugate.

The elimination pattern of triclosan varies depending on the species. Triclosan is excreted mainly via urine in humans (Ref. 198) and hamsters (Ref. 195), while it is eliminated mainly through feces in mice (Ref. 196) and rats (Ref. 199). After a single oral administration of 4 mg of triclosan to human subjects, the majority of the triclosan was excreted in urine within the first 24 hours (Ref. 198). There was considerable variability among subjects; between 24 and 83 percent of the dose was excreted within 4 days after exposure. The urinary excretion half-life ranged from 7 to 17 hours, and excretion approached baseline levels by 8 days after exposure.

In the multiple exposure handwash study (previously described in this section (Ref. 187)), the mean elimination half-life for total triclosan after multiple dermal exposures was 33 hours. This is longer than the elimination half-life calculated after a single oral exposure (12 hours). The authors suggest the reason for this difference is that absorption through the skin takes longer than absorption from the gastrointestinal tract.

It is well documented that triclosan in aqueous solution can be degraded into 2,8-dichlorodibenzo-p-dioxin and other degradation products by heat or ultraviolet irradiation (i.e., photodegradation) (Refs. 200 through 206). Although the data support photodegradation in aqueous solution, we found no data regarding whether photodegradation of triclosan can occur on human skin. It is not known whether photodegradation products would be formed on human skin after topical application of triclosan-containing antiseptics and, if so, whether they would be absorbed or affect the skin. Because of this new information regarding photodegradation of

triclosan, we propose that data are needed regarding the potential for formation of triclosan photodegradation products on human skin as a result of consumer antiseptic use and, if present, their effects on the skin.

Overall, the animal ADME data are not adequate and additional pharmacokinetic data (e.g., AUC, Tmax, and Cmax) at steady-state levels continue to be necessary to bridge animal data to humans. In addition, data regarding the potential for formation of photodegradation products on human skin and their effects on the skin are needed.

New triclosan findings. A recent study evaluated the physiological effects of triclosan treatment on muscle function in mice and fish (Ref. 207). The authors observed a negative effect on both cardiac and skeletal muscle function as a result of a single triclosan treatment and identified a mechanism to explain the observed effect. While this finding suggests a previously unidentified toxicity of triclosan, it is a preliminary finding that has not been duplicated. Further, the mice were treated by injecting triclosan into the abdomen (i.e., intraperitoneal administration), rather than through a more relevant route of administration, such as the oral or dermal route. We invite comment on what these findings tell us about triclosan's potential impact on human health and the submission of additional data on this subject.

Triclosan carcinogenicity data. A 2-year oral carcinogenicity study in hamsters was submitted to the rulemaking (Ref. 208). The study was conducted in Syrian hamsters because the elimination pattern of triclosan is similar in hamsters and humans. Although some treatment-related noncancerous lesions were seen in the kidneys, epididymides, testes, and stomach, there were no tumor findings in any of the organs examined. The NOAEL for triclosan in this hamster study is 75 mg/kg/day. The study included additional (satellite) groups to assess triclosan plasma levels at week 53 and at study termination (Ref. 209). At both time points, plasma levels

increased with increasing doses and significantly higher triclosan plasma levels were seen in males compared to females ($p < 0.001$). This increase over time suggests that triclosan is accumulating in the animals; however, the effect of this accumulation is unknown.

In contrast to the oral data, there are little data regarding dermal toxicity of triclosan. Short-term dermal toxicity studies in rats (Ref. 210) and mice (Refs. 211 and 212) show dose-related dermal adverse effects following a 14-day treatment period. Similar dermal effects were seen in a 90-day subchronic dermal toxicity study in rats (Ref. 213). A long-term dermal carcinogenicity study could be used to assess the relevance of the short-term dermal toxicity findings to a chronic use situation; however, currently no long-term dermal carcinogenicity data are available. Because these data are not available but are needed to fully evaluate the safety of triclosan, FDA nominated triclosan to NTP for toxicological evaluation (Ref. 214). The NTP studies will evaluate the dermal carcinogenicity potential following chronic dermal exposure to triclosan (Refs. 215 and 216). These studies are ongoing; however, results of these studies are not expected to be available for several years, and we do not intend to delay the antiseptic rulemaking to wait for these study results.

The submitted oral carcinogenicity data are adequate and show that triclosan does not pose a risk of cancer after repeated oral administration under the experimental conditions used; however, data from a dermal carcinogenicity study are still needed.

Triclosan DART data. In the 1994 TFM, we stated that we were evaluating the data from a two-generation study of the reproductive toxicity of triclosan in rats (Ref. 217). In this study, rats that were exposed to a high dose (3,000 ppm) of triclosan in utero showed lower neonatal survival and lower mean body weights compared to untreated controls. The offspring of these rats (i.e., F2 pups) had a lower rate of survival to weaning compared to untreated controls.

Based on the findings from this two-generation study, we recommended that a segment II study should be conducted to address the decreased survival among the high dose-treated litters.

Since that time, additional segment II reproductive toxicity studies have been submitted showing that triclosan is not teratogenic in mice, rats, or rabbits (Ref. 218). No treatment-related mortality was observed, and pregnancy rates and the number of litters for treated animals were comparable to controls. The oral NOAELs from these studies are listed in table 8 of this proposed rule.

Table 8.--Oral No Observed Adverse Effect Levels (NOAEL) From Reproductive Toxicity Studies of Triclosan

Species	Oral NOAEL (mg/kg/day)	
	Maternal Toxicity	Developmental Toxicity
Mouse	25	25
Rat	50	50
Rabbit	50	150

Overall, the triclosan DART data are adequate and additional traditional DART studies are not necessary. However, as discussed in the subsection of this proposed rule on drug-induced hormonal effects, we propose that additional reproductive and developmental testing will be needed to address concerns about these effects.

Triclosan data on hormonal effects. Recent studies have demonstrated that triclosan has effects on the thyroid, estrogen, and testosterone systems in several animal species, including mammals (Refs. 41, 43 through 47, 50, and 219). In addition, effects were also seen in the hamster carcinogenicity study (e.g., a reduction or absence of spermatozoa, abnormal spermatogenic cells, and partial depletion of one or more generations of germ cells in male testes in the high dose-treated group) (Ref. 220). The implications of these findings on human health, especially for children, are still not well understood.

At this time, no adequate long-term (i.e., more than 30 days) in vivo animal studies have been conducted to address the consequences of these hormonal effects on functional endpoints of growth and development (e.g., link of preputial separation to sexual differentiation and fertility, link of decreased thyroxine/triiodothyronine to growth and neurobehavioral development) in exposed fetuses or pups. Studies in juvenile animals (of the type described in section VII.C.2 of this proposed rule) could address the consequences of short-term thyroid and reproductive findings on the fertility, growth, and development of triclosan-exposed litters.

Triclosan resistance data. Much of the recent data looking at cross-resistance between antiseptic active ingredients and antibiotics involve an evaluation of triclosan. Several bacterial species that showed reduced susceptibility to triclosan were also resistant to one or more of the tested antibiotics (Refs. 60 through 66, 71, and 73 through 77). This trend was seen for both gram-negative (E. coli, Pseudomonas aeruginosa, Salmonella enterica, Stenotrophomonas maltophilia, Acinetobacter, and Campylobacter) and gram-positive (Staphylococcus aureus, including MRSA) organisms. Although the clinical relevance of these studies is not clear, the possibility that triclosan contributes to changes in antibiotic susceptibility warrants further evaluation.

One of our concerns stems from the observation that triclosan exposure can lead to changes in bacterial efflux pump activity. Several studies (Refs. 62, 64, 66, and 102) suggest that an efflux mechanism is responsible for the observed reduced triclosan susceptibility. In addition, overexpression of efflux pump regulatory genes also leads to reduced triclosan susceptibility in E. coli (Ref. 101).

In addition to bacterial efflux activity, other mechanisms have been documented that may also contribute to reduced antiseptic susceptibility and cross-resistance, e.g., changes in bacterial

membrane (Ref. 67). This type of nonspecific mechanism, in theory, could work against multiple antibiotics or antiseptics.

Other data suggest that different mechanisms of action may occur at different triclosan concentrations. In the laboratory, at low concentrations triclosan has a specific action against a bacterial enzyme (FabI), while high concentrations act against less specific targets, such as the cell membrane (Ref. 109). Currently, there is not enough information to know which scenarios, if any, could occur under actual use conditions.

Although numerous studies have evaluated the antiseptic and antibiotic susceptibility profiles of clinical or culture collection strains, there are few studies that evaluate the susceptibility profiles of bacterial isolates from nonhospital or consumer settings. In a pair of studies (Refs. 79 and 80), Lear and colleagues collected, identified, and measured antimicrobial susceptibilities of bacteria from industrial sources. Samples were taken from a factory and laboratories of companies that manufacture products containing triclosan, where it was likely that the organisms were exposed to this ingredient. Of approximately 100 industrial isolates, two triclosan-tolerant isolates were chosen for further study (*Acinetobacter johnsonii* and *Citrobacter freundii*).

The authors then determined the antibiotic susceptibility profiles of the two industrial isolates compared to standard culture collection strains (Ref. 79). The authors saw no difference in the antibiotic susceptibility patterns of the industrial and standard strains of *A. johnsonii*. In contrast, the *C. freundii* industrial isolate was more resistant to 12 of 14 antibiotics tested. These changes in antibiotic susceptibility were quite modest, however. While this industrial isolate showed only modest changes in susceptibility for most of the tested antibiotics, it still demonstrates a change in the antibiotic susceptibility pattern after triclosan exposure.

Unfortunately, the number of sites that were sampled was low (50 total sites), only two isolates were studied, and the time and extent of triclosan exposure is unknown.

In addition to laboratory data, there are also a few studies that examined the potential for development of cross-resistance in bacterial isolates taken from the skin of consumer antiseptic users. Cole et al. (Ref. 78) described antibiotic and antiseptic susceptibilities of staphylococci isolated from the skin of consumers who used antiseptic or nonantibacterial body washes. This study also evaluated triclocarban and is described in detail in section VII.D.3.a of this proposed rule.

When CNS susceptibility to antiseptics was examined, the maximum MIC value was the same for all three groups (2.020 (no units provided)); however, the minimum MIC value differed between triclosan users (0.008) and non-users (0.120). Because antiseptic MICs do not correlate with clinical endpoints, it is not clear what this difference in MIC means. No patterns emerged when the data were analyzed for cross-resistance between triclosan or triclocarban and antibiotics.

The authors conclude that this study shows no increase in antibiotic resistance from the regular use of antiseptic body washes. But, this study was not adequately designed to determine whether use of antiseptic body washes leads to changes in antibiotic or antiseptic susceptibilities. Given the limited number of isolates examined, it is not clear that the study was adequately powered to detect a difference in resistance patterns. Furthermore, the amount of antiseptic exposure was not defined. The length of time subjects had used antiseptic body washes (beyond the specified 30 days), the frequency of bathing, and the volume of antiseptic wash used per bath or shower was not reported. Finally, few bacterial isolates were examined. It is reasonable to

examine the susceptibilities of Staphylococcus species; however, an average of only 1.5 isolates was obtained from each subject.

Aiello et al. (Ref. 81) looked for a possible association between antibiotic and triclosan susceptibilities among staphylococci and GNB isolated from the hands of consumers who used nonantibacterial or 0.2 percent triclosan-containing antiseptic handwashes for 1 year. Two hundred twenty-four inner city households were randomized to use soap and cleaning products with or without antibacterial ingredients. The products were blinded and were delivered to each household monthly. During the study period, the households were required to use only the assigned home hygiene products and were asked not to change any of their other normal hygiene practices. To assess prior exposure to antimicrobials, including antiseptics, a survey of the antibacterial cleaning and hygiene products used within the home was conducted at baseline.

The hands of the primary caregiver in the home were sampled for bacteria at baseline and 1 year later. Only the most commonly isolated bacterial species, defined as at least 38 isolates of a single species from all samples, were analyzed further. A total of 628 isolates were examined for their triclosan MICs and susceptibilities to selected antibiotics. Staphylococci were tested against oxacillin to determine methicillin resistance. The GNB were tested against three to six antibiotics, based on clinical relevance. There were no significant differences in the observed proportions of isolates that were antibiotic resistant at baseline versus the end of the year except for Enterobacter cloacae, which was significantly higher at baseline (36 percent) than at the end of the year (0 percent) ($p = 0.016$).

The MICs of triclosan ranged from 0.03 to 4.00 $\mu\text{g/mL}$; however, two thirds of the isolates had triclosan MICs over 1 $\mu\text{g/mL}$. The median triclosan MICs for the gram negative species varied widely. In contrast, the staphylococcus median values were very similar, except

for S. aureus, which was 2 µg/mL at baseline and 0.03 µg/mL at the end of the year. There was no statistically significant association between triclosan MICs and susceptibility to antibiotics.

A randomly chosen subset of seven GNB organisms with triclosan MICs of at least 32 µg/mL was retested with agar containing triclosan concentrations in the range of 64 to 1,024 µg/mL. The subset contained Klebsiella pneumoniae, Acinetobacter baumannii, Enterobacter cloacae, and P. fluorescens isolates. All of the isolates grew on agar containing 1,024 µg/mL triclosan, suggesting that they may survive the triclosan concentrations used in some consumer products.

This study did not show an association between high triclosan MICs and antibiotic resistance after 1 year of triclosan handwash use. However, the authors note that the triclosan MICs seen for many of the isolates in this study are higher than those reported previously. They suggest that general levels of decreased susceptibility to triclosan seem to be increasing in the community, regardless of whether triclosan-containing products are used in the home or not. The authors also concluded that the absence of a statistically significant association between elevated triclosan MICs and reduced antibiotic susceptibility may indicate that such a correlation does not exist or that it is relatively small among the isolates that were studied. Still, they theorized that a relationship may emerge after longer term or higher dose exposure of bacteria to triclosan in the community setting.

Overall, the administrative record for triclosan is complete on the following aspects of the resistance issue:

- Laboratory studies demonstrate triclosan's ability to alter antibiotic susceptibilities (Refs. 60 through 66, 71, and 73 through 77)

- Data define triclosan's mechanisms of action and demonstrate that these mechanisms are dose dependent (Ref. 109)
- Data demonstrate that exposure to triclosan changes efflux pump activity, a common nonspecific bacterial resistance mechanism (Refs. 62, 64, 66, and 102)
- Data show that low levels of triclosan may persist in the environment (Refs. 85, 113, 114, 115, and 221 through 224).

However, the administrative record is not complete with respect to data that would clarify the potential public health impact of the currently available data. Examples of the type of information that could be submitted to complete the record include the following:

- Data to characterize the concentrations and antimicrobial activity of triclosan in various biological and environmental compartments (e.g., on the skin, in the gut, and in environmental matrices);
- Data to characterize the antiseptic and antibiotic susceptibility levels of environmental isolates in areas of prevalent antiseptic use, e.g., in the home, health care, food handler, and veterinary settings; and
- Data to characterize the potential for the reduced antiseptic susceptibility caused by triclosan to be transferred to other bacteria that are still sensitive to triclosan.

b. Triclosan safety data gaps. In summary, our administrative record for the safety of triclosan is incomplete with respect to the following:

- 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

VIII. Proposed Effective Date

Based on the currently available data, this proposed rule finds that consumer antiseptic wash active ingredients can be considered neither safe nor effective for use in OTC consumer antiseptic wash drug products. Accordingly, consumer antiseptic wash active ingredients would be nonmonograph in any final rule based on this proposed rule. We recognize, based on the scope of products subject to this monograph, that manufacturers will need time to comply with a final rule based on this proposed rule. However, because of the potential safety considerations raised by the data for some antiseptic active ingredients evaluated, we believe that an effective date later than 1 year after publication of the final rule would not be appropriate or necessary. Consequently, any final rule that results from this proposed rule will be effective 1 year after the date of the final rule's publication in the Federal Register. On or after that date, any OTC consumer antiseptic wash drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not GRAS/GRAE or to be misbranded, could not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application or abbreviated new drug application. Any OTC consumer antiseptic wash drug product subject to the final rule that is repackaged or relabeled after the effective date of the final rule would be required to be in compliance with the final rule, regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce.

IX. Summary of Preliminary Regulatory Impact Analysis

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

A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). This proposed rule would be an economically significant regulatory action as defined by Executive Order 12866.

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

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$141 million, using the most current (2012) Implicit Price

Deflator for the Gross Domestic Product. FDA expects this proposed rule to result in a 1-year expenditure that would meet or exceed this amount.

B. Summary of Costs and Benefits

The costs and benefits of the proposed rule are summarized in table 9 of this proposed rule entitled "Economic Data: Costs and Benefits Statement." As table 9 shows, the primary estimated benefits come from reduced exposure to antiseptic active ingredients by 2.2 million pounds per year. Using the primary estimates, the combined total consists of a reduction in triclosan exposure by 799,426 pounds per year, triclocarban exposure by 1.4 million pounds per year, chloroxylenol exposure by 231.9 pounds per year, and benzalkonium chloride by 63.8 pounds per year. Limitations in the available data characterizing the health effects resulting from widespread long-term exposure to such 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 \$28.6 million at a 7 percent discount rate. These costs consist of total one-time costs of relabeling and reformulation ranging from \$112.2 to \$368.8 million. Estimates of the cost of relabeling and reformulating may be overstated if manufacturers produce data consistent with the monograph changes in this proposed rule and do not need to relabel or reformulate. In such a scenario, the costs of producing the data would be incurred instead. Under the proposed rule, we estimate that each pound of reduced exposure to antiseptic active ingredients would cost \$3.86 to \$43.67 at a 3 percent discount rate and \$4.69 to \$53.04 at a 7 percent discount rate.

Manufacturers are expected to incur most product reformulation and relabeling costs with the impact to relabelers, repackers, and distributors being considerably less. The impact on a

manufacturer can vary considerably depending on the number and type of products it produces. For the estimated 707 affected establishments that would qualify as small¹, our estimate of the average one-time cost of compliance ranges from \$0.10 million to \$0.33 million, which would be approximately 0.33 percent to 1.10 percent of the average annual value of shipments for a small business. In its Initial Regulatory Flexibility Analysis, the Agency assesses a pair of regulatory options that would reduce the proposed rule's burden on small entities: (1) Exempting small businesses from the rule and (2) longer compliance period, allowing 18 months (rather than 12 months).

Table 9.--Economic Data: Costs and Benefits Statement

Category	Primary Estimate	Low Estimate	High Estimate	Units			Notes
				Year Dollars	Discount Rate	Period Covered	
Benefits							
Annualized Monetized \$millions/year					7%	Annual	
					3%	Annual	
Annualized Quantified	2,198,033	989,922	3,406,145		7%	Annual	Reduced antiseptic active ingredient exposure (in pounds)
	2,198,033	989,922	3,406,145		3%	Annual	
Qualitative							
Costs							
Annualized Monetized \$millions/year	\$28.6	\$16.0	\$52.5	2010	7%	Annual	Annualized costs of relabeling and reformulation. Range of estimates captures uncertainty.
	\$23.6	\$13.2	\$43.2	2010	3%	Annual	
Annualized Quantified					7%		
					3%		
Qualitative							
Transfers							
Federal Annualized Monetized \$millions/year					7%		None.
					3%		

¹ FDA notes that the analysis was conducted using data at the establishment level rather than at the firm level. This makes the implicit assumption that the typical manufacturing establishment is roughly equivalent to the typical small manufacturing firm. However, if market is dominated by a few large firms with a large number of small establishments, our estimated number of small entities, may be an overestimate of the actual number of businesses with fewer than 750 employees.

Table 9.--Economic Data: Costs and Benefits Statement

Category	Primary Estimate	Low Estimate	High Estimate	Units			Notes
				Year Dollars	Discount Rate	Period Covered	
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 \$0.01-\$0.04 million, which would represent 0.04-0.13 percent of annual shipments.							
Wages: No estimated effect							
Growth: No estimated effect							

X. Paperwork Reduction Act of 1995

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

XI. 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.

XII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, would have a preemptive effect on State law. 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.” Section 751 of the Federal Food, Drug and Cosmetic Act (the FD&C Act) (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the FD&C Act (21 U.S.C. 379r(a)) provides that “no State or political subdivision of a State may establish or continue in effect any requirement--(1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 et seq.), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.)” Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. (See section 751(b) through (e) of the FD&C Act for the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.)

This proposed rule, if finalized as proposed, would require data from clinical outcome studies to demonstrate the effectiveness of consumer antiseptic active ingredients. Any final rule would have a preemptive effect in that it would preclude States from issuing requirements related to OTC consumer antiseptics that are different from, in addition to, or not otherwise identical with a requirement in the final rule. This preemptive effect is consistent with what Congress set forth in section 751 of the FD&C Act. Section 751(a) of the FD&C Act displaces both State legislative requirements and State common law duties. We also note that even where the express preemption provision is not applicable, implied preemption may arise (see Geier v. American Honda Co., 529 U.S. 861 (2000)).

FDA believes that the preemptive effect of the proposed rule, if finalized, would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that “when an agency proposed to act through adjudication or rulemaking to preempt State law, the agency

shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.” FDA is providing an opportunity for State and local officials to comment on this rulemaking.

XIII. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) under Docket No. FDA-1975-N-0012 (formerly 1975N-0183H) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified all Web site addresses in this reference section, but we are not responsible for any subsequent changes to the Web sites after this proposed rule publishes in the Federal Register.)

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3. Transcript of the March 23, 2005, Meeting of the Nonprescription Drugs Advisory Committee, <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4098T1.pdf>, 2005.
4. Transcript of the October 20, 2005, Meeting of the Nonprescription Drugs Advisory Committee, <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4184T1.pdf>, 2005.
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6. Comment Nos. C7, C10, C11, C12, C14, C18, C22, C25, C32, C34, C35, C36, C40, C43, C44, C45, C47, C48, C53, C54, C55, C56, C57, C60, C61, C63, C64, C77, C80, C81, C82, C83, C85, C89, CP3, CP4, CP6, CP7, CP11, CP14, CP15, CP16, LET11, LET13, LET15, LET18, LET43, RPT3, RPT5, SUP1, SUP2, SUP3, SUP5, SUP6, and SUP7 in Docket No. 1975N-0183H.

7. Comment Nos. C1, C8, C11, C14, C18, C19, C20, C23, C32, C34, C35, C36, C38, C42, C43, C45, C48, C50, C51, C52, C58, C60, C61, C70, C76, C79, C82, C84, C85, C89, C93, CP1, CP3, CP4, CP7, CP9, CP12, CP14, CP17, LET1, LET12, LET13, LET16, LET17, LET43, PR1, PR3, PR4, PR5, PR6, PR7, PR9, RPT4, SUP3, SUP4, SUP5, SUP7, SUP12, and SUP13 in Docket No. 1975N-0183H.

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11. Comment No. C4 in Docket No. 1975N-0183H.

12. Comment No. C42 in Docket No. 1975N-0183H.

13. Comment No. C20 in Docket No. 1975N-0183H.

14. Comment No. CP8 in Docket No. 1975N-0183H.

15. Comment No. CP1 in Docket No. 1996P-0312.

16. Comment No. CP1 in Docket No. 1975N-0183H.

17. Comment No. C30 in Docket No. 1975N-0183H.

18. Comment No. LET23 in Docket No. 1975N-0183H.

19. Product labels in OTC Vol. 02CAWASHTFM.
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List of Subjects

21 CFR Part 310

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

21 CFR Part 333

Labeling, Over-the-counter drugs, Incorporation by reference.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 310 and 333 be amended as follows:

PART 310--NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.

2. Amend § 310.545 by removing from paragraph (d) introductory text the number "(d)(39)" and adding in its place the number "(d)(40)"; and by adding paragraphs (a)(27)(iii), (a)(27)(iv), and (d)(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 handwash drug products. Approved as of [DATE 1 YEAR AFTER DATE OF PUBLICATION OF THE FINAL RULE IN THE FEDERAL REGISTER].

Benzalkonium chloride

Benzethonium chloride

Chloroxylenol

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) ethanoliiodine

Phenol

Poloxamer iodine complex

Povidone-iodine

Secondary amyltr cresols

Sodium oxychlorosene

Tribromsalan

Triclocarban

Triclosan

Undecoylium chloride iodine complex

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

Benzalkonium chloride

Benzethonium chloride

Cloflucarban

Fluorosalan

Hexachlorophene

Hexylresorcinol

Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)

Iodine tincture

Methylbenzethonium chloride

Nonylphenoxypoly (ethyleneoxy) ethanoliiodine

Parachlorometaxylenol (chloroxylenol)

Phenol

Poloxamer iodine complex

Povidone-iodine

Tribromsalan

Triclocarban

Triclosan

Undecoylium chloride iodine complex

* * * * *

(d)* * *

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

PART 333--TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 333 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

§ 333.403 [Amended]

4. As proposed to be added June 17, 1994 (59 FR 31442), § 333.403 is further amended in paragraph (c)(1) by removing the phrase "Antiseptic handwash or health-care" from the paragraph heading and adding in its place "Health-care".

§ 333.410 [Amended]

5. As proposed to be added June 17, 1994 (59 FR 31442), § 333.410 is further amended by removing the phrase "Antiseptic handwash or health-care" from the section heading and adding in its place "Health-care".

§ 333.455 [Amended]

6. As proposed to be added June 17, 1994 (59 FR 31443), § 333.455 is further amended by:

- a. Removing from the section heading the phrase "antiseptic handwash or";
 - b. Removing from paragraph (a) the phrase " 'antiseptic handwash,' or";
 - c. Removing and reserving paragraph (b)(2);
 - d. Removing from the paragraph (b)(3) paragraph heading the phrase "either antiseptic or" and adding in its place the word "a";
 - e. Removing from paragraph (c)(1) the paragraph designation and paragraph heading;
- and
- f. Removing paragraph (c)(2).

§ 333.470 [Amended]

7. As proposed to be added June 17, 1994 (59 FR 31444), § 333.470 is further amended in paragraph (a) introductory text and paragraph (b)(2) heading and introductory text by removing the phrase "an antiseptic handwash or" and adding in its place the word "a"; and in paragraph (b)(2)(iii) introductory text by removing the phrase "antiseptic or".

8. Add and reserve subpart F to read as follows:

Subpart F--Consumer Antiseptic Drug Products [Reserved]

Dated: December 11, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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