4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310

[Docket No. FDA-2015-N-0101] (Formerly Docket No. FDA-1975-N-0012)

RIN 0910-AF69

Safety and Effectiveness of Health Care 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 antiseptic products intended for use by health care professionals in a hospital setting or other health care situations outside the hospital are generally recognized as safe and effective. In the 1994 TFM, certain antiseptic active ingredients were proposed as being generally recognized as safe for use in health care settings based on safety data evaluated by FDA as part of its ongoing review of OTC antiseptic drug products. However, in light of more recent scientific developments, we are now proposing that additional safety data are necessary to support the safety of antiseptic active ingredients for these uses. We also are proposing that all

health care antiseptic active ingredients have in vitro data characterizing the ingredient's antimicrobial properties and in vivo clinical simulation studies showing that specified log reductions in the amount of certain bacteria are achieved using the ingredient.

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

ADDRESSES: You may submit comments 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 Docket No. FDA-2015-N-0101 (formerly 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. Earlier FDA publications, public submissions, and other materials relevant to this rulemaking may also be found under Docket No. FDA-1975-N-0012 (formerly Docket No. 1975N-0183H) using the same procedures.

FOR FURTHER INFORMATION CONTACT: Michelle M. Jackson, 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 health care antiseptic active ingredients 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 we have identified and placed in the administrative file. These health care antiseptic products include health care personnel hand washes, health care personnel hand rubs, surgical hand scrubs, surgical hand rubs, and patient preoperative skin preparations.

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

Effectiveness

A determination that a drug product containing a particular active ingredient would be generally recognized as effective (GRAE) for a particular intended use requires consideration of the benefit-to-risk ratio for the drug for that use. New information on potential risks posed by the use of certain health care antiseptic products, as well as input from the Nonprescription Drugs Advisory Committee (NDAC) that met in March 2005 (the March 2005 NDAC), has prompted us to reevaluate the data needed for classifying health care antiseptic active ingredients as GRAE (see new information described in the Safety section of this summary). We continue to propose the use of surrogate endpoints (bacterial log reductions) as a demonstration of effectiveness for health care antiseptics combined with in vitro testing to characterize the antimicrobial activity of the ingredient. However, the log reductions required for the demonstration of effectiveness for health care antiseptics have been revised based on the recommendations of the March 2005 NDAC, comments received after the 1994 TFM, and other information that FDA reviewed.

We have evaluated the available literature and the data and other information that were submitted to the rulemaking on the effectiveness of health care antiseptic active ingredients, as well as the recommendations from the public meetings held by the Agency on antiseptics. We propose that the record should contain additional log reduction data to demonstrate the effectiveness of health care antiseptic 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 health care antiseptic active ingredients under the OTC Drug Review. Improved analytical methods now exist that can detect and more accurately measure these active ingredients at lower levels in the bloodstream and tissue. Consequently, we now know that, at least for certain health care antiseptic ingredients, systemic exposure is higher than previously thought (Refs. 1 through 5), and new information is available about the potential risks from systemic absorption and long-term exposure. New safety information also suggests that widespread antiseptic use could have an impact on the development of bacterial resistance. Currently, the significance of this new information is not known and we are unaware of any information that would lead us to conclude that any health care antiseptic active ingredient is unsafe (other than those that we proposed to be Category II in the 1994 TFM). The benefits of any active ingredient will need to be weighed against its risks once both the effectiveness and safety have been better characterized to determine GRAS/GRAE status.

The previously proposed generally recognized as safe (GRAS) determinations were based on safety principles that have since evolved significantly because of advances in technology, development of new test methods, and experience with performing test methods. The standard battery of tests that were used to determine the safety of drugs has changed over time to incorporate improvements in safety testing. To ensure that health care antiseptic active ingredients are GRAS, data that meet current safety standards are needed.

Based on these developments, we are now proposing that additional safety data are needed for each health care antiseptic active ingredient to support a GRAS classification. The

data described in this proposed rule are the minimum data necessary to establish the safety of antiseptic active ingredients used in health care antiseptic products in light of the new safety information. Health care practitioners may use health care antiseptics on a daily, long-term (i.e., chronic) basis. Patient preoperative skin preparations, on the other hand, are not usually used on any single patient on a daily basis. Nevertheless, an individual may be exposed to patient preoperative skin preparations (particularly those used for preinjection skin preparation) enough times over a lifetime to be considered a chronic use. The data we propose are needed to demonstrate safety for all health care antiseptic active ingredients fall into four broad categories: (1) Human safety studies described in current FDA guidance (e.g., maximal use trials or MUsT), (2) nonclinical safety studies described in current FDA guidance (e.g., developmental and reproductive toxicity studies and carcinogenicity studies), (3) data to characterize potential hormonal effects, and (4) data to evaluate the development of antimicrobial resistance.

We emphasize that our proposal for more safety and effectiveness data for health care antiseptic active ingredients does not mean that we believe that health care antiseptic products containing these ingredients are ineffective or unsafe, or that their use should be discontinued. However, now that we have enhanced abilities to measure and evaluate the safety and effectiveness of these ingredients, we believe we should obtain relevant data to support a GRAS/GRAE determination. Consequently, based on new information and improvements in safety testing and in our understanding of log reduction testing and the use of surrogate endpoints since our 1994 evaluation, we are requesting more safety and effectiveness data to ensure that these health care antiseptic active ingredients meet the updated standards to support a GRAS/GRAE classification. Considering the prevalent use of health care antiseptic products in

health care settings, it is critical that the safety and effectiveness of these ingredients be supported by data that meet the most current standards.

Active Ingredients

In the 1994 TFM, 27 antiseptic active ingredients were classified for three OTC health care antiseptic uses: (1) Patient preoperative skin preparation, (2) health care personnel hand wash, and (3) surgical hand scrub (59 FR 31402 at 31435) (for a list of all active ingredients covered by this proposed rule, see tables 4 through 7). Our detailed evaluation of the effectiveness and safety of the active ingredients for which data were submitted can be found in sections VI.A and VII.D. In the 1994 TFM, alcohol (60 to 95 percent) and povidone-iodine (5 to 10 percent), which are active ingredients that are being evaluated for use as a health care antiseptic in this proposed rule, were proposed to be classified as GRAS/GRAE (59 FR 31402 at 31435-31436) for patient preoperative skin preparation, health care personnel hand wash, and surgical hand scrub. Iodine tincture, iodine topical solution, and isopropyl alcohol were proposed to be classified as GRAS/GRAE for patient preoperative skin preparations (59 FR 31402 at 31435-31436). However, we now propose that the health care antiseptic active ingredients classified as GRAS/GRAE for use in health care antiseptics in the 1994 TFM need additional safety and effectiveness data to support a classification of GRAS/GRAE for health care antiseptic use.

Several health care antiseptic active ingredients evaluated in the 1994 TFM were proposed as GRAS, but not GRAE, for use in health care antiseptics because they lacked sufficient evidence of effectiveness for health care use (see tables 4 and 5). We are now proposing that these ingredients need additional safety data, as well as effectiveness data, to be classified as GRAS/GRAE.

The data available and the data that are missing are discussed separately for each active ingredient in this proposed rule. For those ingredients for which no data have been submitted since the 1994 TFM, we have not included a separate discussion section, but have indicated in table 10 that no additional data were submitted or identified.

In certain cases, manufacturers may have the data we propose as necessary in this proposed rule, but to date these data have not been submitted to the OTC Drug Review. Although currently we expect to receive the necessary data, if we do not obtain sufficient data to support monograph conditions for health care antiseptic products containing these active ingredients, these products may not be included in the future OTC health care antiseptic final monograph. Any health care antiseptic product containing the active ingredients being considered under this rulemaking that are not included in a future final monograph could obtain approval to market by submitting new drug applications (NDAs) under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355). After a final monograph is established, these products might be able to submit NDA deviations in accordance with § 330.11 (21 CFR 330.11), limiting the scope of review necessary to obtain approval.

Costs and Benefits

Benefits represent the monetary values associated with reducing the potential adverse health effects associated with the use of health care antiseptic products containing active ingredients that could potentially be shown to be unsafe or ineffective for their intended use. We estimate annual benefits to roughly range between $0 and $0.16 million. Total upfront costs are estimated to range between $64 and $90.8 million. Annualizing these costs over a 10-year period, we estimate total annualized costs to range from $7.3 and $10.4 million at a 3 percent discount rate to $8.5 and $12.1 million at a 7 percent discount rate. Potential one-time costs

include the expenditures to conduct various safety and effectiveness tests, and to reformulate and relabel products that contain nonmonograph ingredients.

Summary of Costs and Benefits of the Proposed Rule	Total Benefits Annualized Over 10 Years (in millions)	Total Costs Annualized Over 10 Years (in millions)	Total One-Time Costs (in millions)
Total……	$0.0 to $0.16	$7.3 to $10.4 at (3%) $8.5 to $12.1 at (7%)	$64.0 to $90.8

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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 health care 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), 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 health care antiseptic 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 hand wash, (3) patient preoperative skin preparation, (4) skin antiseptic, (5) skin wound cleanser, (6) skin wound protectant, and (7) surgical hand scrub (39 FR 33103 at 33140). FDA subsequently identified skin antiseptics, skin wound cleansers, and skin wound protectants as antiseptics used primarily by consumers for first aid use and referred to them collectively as "first aid antiseptics." We published a separate TFM covering the first aid antiseptics in the Federal Register of July 22, 1991 (56 FR 33644) (1991 First Aid TFM). Thus, first aid antiseptics are not discussed further in this document.

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

As we proposed in the consumer antiseptic wash proposed rule published in the Federal Register of December 17, 2013 (78 FR 76444) (the Consumer Wash PR), our evaluation of OTC antiseptic drug products is being 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 level of risk for infection. For example, in health care settings, the patient population is generally more susceptible to infection than the general U.S. consumer population (i.e., the population who use consumer antiseptic washes). Consequently, in the health care setting, the potential for spread of infection and the potential for serious outcomes of infection may be relatively higher than in the U.S. consumer

setting. Therefore, the safety and effectiveness should be evaluated separately for each intended use to support a GRAS/GRAE determination.

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. Patient preoperative skin preparations, which include products that are used for preparation of the skin prior to an injection (i.e., preinjection), may be used by patients outside the traditional health care setting. Some patients (e.g., diabetics who manage their disease with insulin injections) self-inject medications that have been prescribed by a health care professional at home or at other locations and use patient preoperative skin preparations prior to injection. 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 hand washes. (See 78 FR 76444for further discussion of the term "antimicrobial soaps.") In contrast, in the 1994 TFM, we proposed that both consumer antiseptic hand washes and health care personnel hand washes should have the same effectiveness testing and performance criteria. In response to the 1994 TFM, we received submissions from the public arguing that consumer products serve a different purpose and should continue to be distinct from health care antiseptics. We 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 outside the hospital.

The health care setting is different from the consumer setting in many ways. Among other things, health care facilities employ frequent, standardized disinfection procedures and stringent infection control measures that include the use of health care antiseptics. The use of these measures is critical to preventing the spread of infection within health care facilities. The

population in a hospital or health care facility also is different from the general consumer population. In addition, the microorganisms of concern are different in the health care and consumer settings. These differences have resulted in our proposing different effectiveness data requirements. (See section VI.B. about the different effectiveness data requirements.)

C. This Proposed Rule Covers Only Health Care Antiseptics

We refer to the group of products covered by this proposed rule as "health care antiseptics." In this proposed rule, FDA proposes the establishment of a monograph for OTC health care antiseptics that are intended for use by health care professionals in a hospital setting or other health care situations outside the hospital, but that are not identified as "first aid antiseptics" in the 1991 First Aid TFM. In this proposed rule, we use the term "health care antiseptics" to include the following products:

- health care personnel hand washes
- health care personnel hand rubs
- surgical hand scrubs
- surgical hand rubs
- patient preoperative skin preparations

This proposed rule covers products that are rubs and others that are washes. The 1994 TFM did not distinguish between products that we are now calling "antiseptic washes" and products we are now calling "antiseptic rubs." Washes are rinsed off with water, and include health care personnel hand washes and surgical hand scrubs. Rubs are sometimes referred to as "leave-on products" and are not rinsed off after use. Rubs include health care personnel hand rubs, surgical hand rubs, and patient preoperative skin preparations.

The 1994 TFM did not distinguish between consumer antiseptic washes and rubs, and health care hand washes and rubs. This proposed rule covers health care personnel hand washes and health care personnel hand rubs, as well as the other health care antiseptic categories previously listed in this section. This proposed rule does not cover consumer antiseptic washes or consumer antiseptic hand rubs.

Completion of the monograph for Health Care Antiseptic Products and certain other monographs for the active ingredient triclosan are 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.).

D. Comment Period

Because of the complexity of this proposed rule, we are providing a comment period of 180 days. Moreover, new data or information may be submitted to the docket via http://www.regulations.gov 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 to defer further rulemaking with respect to a specific active ingredient to allow the submission of new safety 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 defer rulemaking. In assessing whether to defer further rulemaking for a particular active ingredient to allow for additional time for studies to generate new data and information, FDA will consider the data already in the docket along with any information that is provided in any requests. FDA will determine whether

the sum of the data, if submitted in a timely fashion, is likely to be adequate to provide all the data that are necessary to make a determination of general recognition of safety and effectiveness.

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

II. Background

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

A. Significant Rulemakings Relevant to This Proposed Rule

A summary of the significant Federal Register publications relevant to this proposed rule is provided in table 1. Other 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 Health Care Antiseptic Drug Products

Federal Register Notice	Information in Notice
1974 ANPR (September 13, 1974, 39 FR 33103)	We published an advance notice of proposed rulemaking to establish a monograph for OTC topical antimicrobial drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Antimicrobial I Drug Products (Antimicrobial I Panel or Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class.
1978 Antimicrobial TFM (January 6, 1978, 43 FR 1210)	We published our tentative conclusions and proposed effectiveness testing for the drug product categories evaluated by the Panel. The 1978 TFM reflects our evaluation of the recommendations of the Panel and comments and data submitted in response to the Panel's recommendations.
1982 Alcohol ANPR (May 21, 1982, 47 FR 22324)	We published an advance notice of proposed rulemaking to establish a monograph for alcohol drug products for topical antimicrobial use, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class (Miscellaneous External Panel).

1991 First Aid TFM (July 22, 1991, 56 FR 33644)	We amended the 1978 TFM to establish a separate monograph for OTC first aid antiseptic products. In the 1991 First Aid TFM, we proposed that first aid antiseptic drug products be indicated for the prevention of skin infections in minor cuts, scrapes, and burns.
1994 Health-Care Antiseptic TFM (June 17, 1994, 59 FR 31402)	We amended the 1978 TFM to establish a separate monograph for the group of products that were referred to as OTC topical health care antiseptic drug products. These antiseptics are generally intended for use by health care professionals. In that proposed rule, we also recognized the need for antibacterial personal cleansing products for consumers to help prevent cross contamination from one person to another and proposed a new antiseptic category for consumer use: Antiseptic hand wash.
2013 Consumer Antiseptic Wash TFM (December 17, 2013, 78 FR 76444)	We issued a proposed rule to amend the 1994 TFM and to establish data standards for determining whether OTC consumer antiseptic washes are GRAS/GRAE. In that proposed rule, we proposed that additional safety and effectiveness data are necessary to support the safety and effectiveness of consumer antiseptic wash active ingredients.

B. Public Meetings Relevant to This Proposed Rule

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

Table 2.--Public Meetings Relevant to Health Care 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. 6 and 7)
March 2005 NDAC Meeting (February 18, 2005, 70 FR 8376)	The use of surrogate endpoints and study design issues for the in vivo testing of health care antiseptics (Ref. 8)
November 2008 Public Feedback Meeting	Demonstration of the effectiveness of consumer antiseptics (Ref. 9)
September 2014 NDAC Meeting (July 29, 2014, 79 FR 44042)	Safety testing framework for health care antiseptic active ingredients (Ref. 10)

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 health care antiseptics are discussed in this proposed rule, only those comments and data received in response to the 1994 TFM that are related to health care antiseptic active ingredients are addressed. We also received comments related to final formulation testing and labeling conditions proposed in the 1994 TFM. If in the future we determine that there are monograph health care antiseptic active ingredients that are GRAS/GRAE, we will address these comments. We invite further comment on the final formulation testing and labeling conditions proposed in the 1994 TFM, particularly in light of the conditions proposed in this proposed rule. Comments that were received in response to the 1994 TFM regarding other intended uses of the active ingredients are addressed in the Consumer Antiseptic Wash TFM (78 FR 76444), or will be addressed in future documents related to those other uses.

This proposed rule constitutes FDA's evaluation of submissions made in response to the 1994 TFM to support the safety and effectiveness of OTC health care antiseptic active ingredients (Refs. 11 and 12). 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 are not yet available for the health care antiseptic active ingredients.

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 health care antiseptic products.

A. Eligibility for the OTC Drug Review

An OTC drug is covered by the OTC Drug Review if its conditions of use existed in the OTC drug marketplace on or before May 11, 1972 (37 FR 9464).[1] Conditions of use include, among other things, active ingredient, dosage form and strength, route of administration, and specific OTC use or indication of the product (see § 330.14(a)). To determine eligibility for the OTC Drug Review, FDA typically must have actual product labeling or a facsimile of labeling that documents the conditions of marketing of a product prior to May 1972 (see § 330.10(a)(2)). FDA considers a drug that is ineligible for inclusion in the OTC monograph system to be a new drug that will require FDA approval through the NDA process. Ineligibility for use as a specific type of health care antiseptic (e.g., health care personnel hand wash or surgical hand scrub) does not affect eligibility for other indications under the health care antiseptic monograph (e.g., patient preoperative skin preparations) or under any other OTC drug monograph.

Section III.B discusses those ingredients that currently do not have adequate evidence of eligibility for evaluation under the OTC Drug Review based on a review of the labeling submitted to the Panel. Some ingredients are ineligible for any of the categories of health care antiseptics. Others are eligible for some, but not others. Because of their lack of eligibility, effectiveness and safety information that has been submitted to the rulemaking for these health care antiseptic active ingredients are not discussed in this proposed rule for such use(s). However, if documentation of the type described in this section is submitted, these active ingredients could be determined to be eligible for evaluation for such use(s).

[1] Also, note that drugs initially marketed in the United States after the OTC Drug Review began in 1972 and drugs without any U.S. marketing experience can be considered in the OTC monograph system based on submission of a time and extent application. (See § 330.14(c).)

B. Eligibility of Certain Active Ingredients for Certain Health Care Antiseptic Uses Under the OTC Drug Review

Table 3 lists the health care antiseptic active ingredients that have been considered under this rulemaking and shows whether each ingredient is eligible or ineligible for each of the five health care antiseptic uses: Patient preoperative skin preparation, health care personnel hand wash, health care personnel hand rub, surgical hand scrub, and surgical hand rub. After the table, we discuss the ineligibility of ingredients in this section of the proposed rule.

Table 3.--Eligibility of Antiseptic Active Ingredients for Health Care Antiseptic Uses[1]

Active Ingredient	Patient Preoperative Skin Preparation	Health Care Personnel Hand Wash	Health Care Personnel Hand Rub	Surgical Hand Scrub	Surgical Hand Rub
Alcohol 60 to 95 percent	Y[2]	N[3]	Y	N	Y
Benzalkonium chloride	Y	Y	Y	Y	N
Benzethonium chloride	Y	Y	N	Y	N
Chlorhexidine gluconate	N	N	N	N	N
Chloroxylenol	Y	Y	N	Y	N
Cloflucarban	Y	Y	N	Y	N
Fluorosalan	Y	Y	N	Y	N
Hexylresorcinol	Y	Y	N	Y	N
Iodine Active Ingredients:					
Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)	N	Y	N	Y	N
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)	Y	Y	N	Y	N
Iodine tincture USP	Y	N	N	N	N
Iodine topical solution USP	Y	N	N	N	N
Nonylphenoxypoly (ethyleneoxy) ethanoliodine	Y	Y	N	Y	N
Poloxamer-iodine complex	Y	Y	N	Y	N
Povidone-iodine 5 to 10 percent	Y	Y	N	Y	N
Undecoylium chloride iodine complex	Y	Y	N	Y	N
Isopropyl alcohol 70-91.3 percent	Y	N	Y	N	Y
Mercufenol chloride	Y	N	N	N	N

Methylbenzethonium chloride	Y	Y	N	Y	N
Phenol (less than 1.5 percent)	Y	Y	N	Y	N
Phenol (greater than 1.5 percent)	Y	Y	N	Y	N
Secondary amyltricresols	Y	Y	N	Y	N
Sodium oxychlorosene	Y	Y	N	Y	N
Triclocarban	Y	Y	N	Y	N
Triclosan	Y	Y	N	Y	N
Combinations:					
Calomel, oxyquinoline benzoate, triethanolamine, and phenol derivative	Y	N	N	N	N
Mercufenol chloride and secondary amyltricresols in 50 percent alcohol	Y	N	N	N	N
Triple dye	Y	N	N	N	N

[1] Hexachlorophene and tribromsalan are not included in this table because they are the subject of final regulatory action (see section IV).
[2] Y= Eligible for specified use.
[3] N= Ineligible for specified use.

1. Alcohols

a. Alcohol (ethanol or ethyl alcohol). In the 1994 TFM, alcohol (ethanol or ethyl alcohol) 60 to 95 percent by volume in an aqueous solution was evaluated for use as a health care personnel hand wash, surgical hand scrub, and patient preoperative skin preparation (59 FR 31402 at 31442). The only health care antiseptic products containing alcohol that were submitted to the OTC Drug Review were products that were intended to be used without water (i.e., rubs and skin preparations) (Ref. 13). Consequently, based on the information we currently have about eligibility, we propose to categorize as new drugs these health care antiseptic washes and surgical scrubs (both of which are washes and are by definition intended to be rinsed off with water) that contain alcohol as the active ingredient, and we do not include a discussion of safety or effectiveness of alcohol for such rinse-off uses in this proposed rule.

Alcohol, however, has been demonstrated to be eligible for the OTC Drug Review for use as a health care personnel hand rub, surgical hand rub, and patient preoperative skin preparation

(59 FR 31402 at 31435-31436). Thus, we include a discussion of the safety and effectiveness data for alcohol in this proposed rule for such uses.

b. Isopropyl alcohol. In the 1994 TFM, isopropyl alcohol 70 to 91.3 percent by volume in an aqueous solution (isopropyl alcohol) was classified for use as a health care personnel hand wash and surgical hand scrub (59 FR 31402 at 31435-31436). Isopropyl alcohol also was evaluated as a patient preoperative skin preparation (59 FR 31402 at 31442-31443). The only health care antiseptic products containing isopropyl alcohol that were submitted to the OTC Drug Review were products that were intended to be used without water (i.e., rubs and skin preparations) (Ref. 13). Consequently, isopropyl alcohol has not been demonstrated to be eligible for the OTC Drug Review for use as a health care personnel hand wash or a surgical hand scrub drug product, both of which are washes and by definition are intended to be rinsed off with water. Thus, we propose to categorize isopropyl alcohol for these uses as a new drug and do not include a discussion of safety or effectiveness of isopropyl alcohol for such rinse-off uses in this proposed rule.

Isopropyl alcohol, however, has been demonstrated to be eligible for the OTC Drug Review for use as a health care personnel hand rub, surgical hand rub, and patient preoperative skin preparation (59 FR 31402 at 31435-31436). Thus, we include a discussion of the safety and effectiveness data for isopropyl alcohol in this proposed rule for such uses.

2. Benzalkonium Chloride

Benzalkonium chloride has not been demonstrated to be eligible for the OTC Drug Review for use as a surgical hand rub. Based on the information we currently have about eligibility, we propose to categorize as a new drug benzalkonium chloride for use as a surgical hand rub. Benzalkonium chloride, however, has been demonstrated to be eligible for the OTC

Drug Review for use as a health care personnel hand wash, health care personnel hand rub, surgical hand scrub, and patient preoperative skin preparation (59 FR 31402 at 31435-31436). Thus, we include a discussion of the safety and effectiveness data for benzalkonium chloride in this proposed rule for such uses.

3. Chlorhexidine Gluconate

Previously, chlorhexidine gluconate 4 percent aqueous solution (chlorhexidine gluconate) was found to be ineligible for inclusion in the monograph for any health care antiseptic use and was not included in the 1994 TFM (59 FR 31402 at 31413). We have not received any new information since the 1994 TFM demonstrating that this active ingredient is eligible for the 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 health care antiseptic, and we do not include a discussion of any safety or effectiveness data submitted for chlorhexidine gluconate in this proposed rule.

4. Iodine and Iodine Complexes

a. Iodine topical solution USP and iodine tincture USP. Iodine topical solution and iodine tincture have not been demonstrated to be eligible for the OTC Drug Review for use as a health care personnel hand wash or rub or as a surgical hand scrub or rub. Neither iodine topical solution nor iodine tincture was evaluated for these uses in the1994 TFM (59 FR 31402 at 31435-31436), and we have not received any new information to demonstrate eligibility for these uses since publication of the 1994 TFM. Based on the information we currently have about eligibility of iodine topical solution and iodine tincture, we propose to categorize as new drugs these iodines intended for use as a health care personnel hand wash or rub or as a surgical hand

scrub or rub, and we do not include a discussion of safety or effectiveness of iodine solution or tincture for such uses in this proposed rule.

However, both iodine topical solution and iodine tincture have been demonstrated to be eligible for the OTC Drug Review for use as a patient preoperative skin preparation (59 FR 31402 at 31435-31436). Thus, we include a discussion of the safety and effectiveness of these iodines for this use in this proposed rule.

b. Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate). The only health care antiseptic products containing this iodine complex submitted to the OTC Drug Review were health care personnel hand washes and surgical hand scrubs intended to be used with water (Ref. 13). Consequently, iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate) has not been demonstrated to be eligible for the OTC Drug Review for evaluation as a health care personnel hand rub or a surgical hand rub, both of which are intended to be leave-on products used without water. This iodine complex also has not been demonstrated to be eligible for the OTC Drug Review for use as a patient preoperative skin preparation. It was not evaluated for use as a patient preoperative skin preparation in the 1994 TFM (59 FR 31402 at 31435-31436) and we have not received any new information to demonstrate eligibility for this use since publication of the 1994 TFM. Based on the information we currently have about eligibility of this active ingredient, we propose to categorize as a new drug iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate) intended for use as patient preoperative skin preparation as well. This iodine complex, however, has been demonstrated to be eligible for the OTC Drug Review for use as a health care personnel hand wash and surgical hand scrub (59 FR 31402 at 31435-31436).

c. Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol), nonylphenoxypoly (ethyleneoxy) ethanoliodine, poloxamer-iodine complex, and undecoylium chloride iodine complex. The only health care antiseptic products containing these iodine complexes that were submitted to the OTC Drug Review were health care personnel hand washes and surgical hand scrubs intended to be used with water, and patient preoperative skin preparations (Ref. 13). Consequently, iodine complex (phosphate ester of alkylaryloxy polyethylene glycol), nonylphenoxypoly (ethyleneoxy) ethanoliodine, poloxamer-iodine complex, and undecoylium chloride iodine complex have not been demonstrated to be eligible for the OTC Drug Review for evaluation as health care personnel hand rubs or surgical hand rubs (59 FR 31402 at 31418 and 31435-31436). Thus, we do not include a discussion of safety or effectiveness of these iodine complexes for these uses in this proposed rule.

These active ingredients, however, have been demonstrated to be eligible for the OTC Drug Review for use as a health care personnel hand wash, a surgical hand scrub, and a patient preoperative skin preparation (59 FR 31402 at 31435-31436). Thus, we include a discussion of the safety and effectiveness of these ingredients for these uses in this proposed rule.

d. Povidone-iodine 5 to 10 percent. The only health care antiseptic products containing povidone-iodine 5 to 10 percent submitted to the OTC Drug Review were health care personnel hand washes and surgical hand scrubs intended to be used with water (Ref. 13). Povidone-iodine 5 to 10 percent has not been demonstrated to be eligible for the OTC Drug Review for evaluation as a health care personnel hand rub or surgical hand rub, and we propose to categorize povidone-iodine for these uses as a new drug. However, povidone-iodine has been demonstrated to be eligible for the OTC Drug Review for use as a health care personnel hand wash, surgical hand scrub, and patient preoperative skin preparation (59 FR 31402 at 31423 and 31435-31436).

Thus, we include a discussion of the safety and effectiveness of povidone iodine for these uses in this proposed rule.

5. Mercufenol Chloride

Mercufenol chloride was evaluated for use only as a patient preoperative skin preparation in the 1994 TFM (59 FR 31402 at 31428-31429 and 31435-31436). Based on the information we currently have about eligibility, we propose to categorize as a new drug mercufenol chloride for use as a health care personnel hand wash or rub or as a surgical hand scrub or rub. Mercufenol chloride, however, has been demonstrated to be eligible for the OTC Drug Review for use as a patient preoperative skin preparation.

6. 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. 14 through 19). These compounds were not addressed in prior FDA documents related to the monograph and were not evaluated for any health care antiseptic use by the Antimicrobial I Panel. The submissions received by FDA to date do not include documentation demonstrating the eligibility of any of these seven compounds for inclusion in the monograph (Ref. 20). 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 we currently have about eligibility, we propose to categorize these compounds as new drugs and we do not include a discussion of safety or effectiveness data submitted for them in this proposed rule.

7. Other Individual Active Ingredients

In the 1994 TFM, each of the following ingredients was evaluated for use as a patient preoperative skin preparation, a health care personnel hand wash, and a surgical hand scrub (59 FR 31402 at 31435-31436):

- Benzethonium chloride
- Chloroxylenol
- Cloflucarban
- Fluorosalan
- Hexylresorcinol
- Methylbenzethonium chloride
- Phenol (less than 1.5 percent)
- Secondary amyltricresols
- Sodium oxychlorosene
- Triclocarban
- Triclosan

The only health care personnel hand wash or surgical hand scrub products containing any of these ingredients that were submitted to the OTC Drug Review were products that were intended to be used with water (i.e., rinse-off products) (Ref. 13). Consequently, based on the information we currently have about eligibility, we propose to categorize as a new drug each of

these ingredients for use as a health care personnel hand rub or a surgical hand rub, and we do not include a discussion of safety or effectiveness of these ingredients for these uses in this proposed rule.

Each of the listed ingredients, however, has been demonstrated to be eligible for the OTC Drug Review for use as a health care personnel hand wash, surgical hand scrub, and patient preoperative skin preparation.

8. Combination Active Ingredients

The combination active ingredients (1) calomel, oxyquinoline benzoate, triethanolamine, and phenol derivative; (2) mercufenol chloride and secondary amyltricresols in 50 percent alcohol; and (3) triple dye have not been demonstrated to be eligible for the OTC Drug Review for use as a health care personnel hand wash or rub or as a surgical hand scrub or rub (59 FR 31402 at 31435-31436). Consequently, based on the information we currently have about eligibility, we propose to categorize as a new drug each of these ingredients for use as a health care personnel hand wash, health care personnel hand rub, surgical hand scrub, or a surgical hand rub, and we do not include a discussion of safety or effectiveness of these ingredients for these uses in this proposed rule. However, each of the previously discussed active ingredients has been demonstrated to be eligible for the OTC Drug Review for use as a patient preoperative skin preparation.

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

FDA may determine that an active ingredient is not GRAS/GRAE for a given OTC use (i.e., nonmonograph) because of lack of evidence of effectiveness, lack of evidence of safety, or both. In the 1994 TFM (59 FR 31402 at 31435-31436), FDA proposed that the active ingredients fluorosalan, hexachlorophene, phenol (greater than 1.5 percent), and tribromsalan be

found not GRAS/GRAE for the uses referred to in the 1994 TFM as antiseptic hand wash and health care personnel hand wash. FDA 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, notably tribromsalan (21 CFR 310.502). No substantive comments or new data were submitted to the record of the 1994 TFM 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 health care antiseptic products as defined in this proposed rule and that any OTC health care antiseptic drug product containing any of these ingredients not be allowed 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 Health Care Antiseptic Active Ingredients

Tables 4 through 7 in this proposed rule list the classification proposed in the 1994 TFM for each OTC health care antiseptic active ingredient according to intended use 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 later described in detail for each active ingredient for which we have some data in section VII.D.

Tables 4 and 5 list ingredients for which a different status is being proposed in this proposed rule than was proposed in the 1994 TFM.

Table 4.--Classification of OTC Health Care Personnel Hand Wash and Surgical Hand Scrub Antiseptic Active Ingredients in This Proposed Rule and in the 1994 TFM

Active Ingredient	1994 TFM	This Proposed Rule
Alcohol 60 to 95 percent	I[1]	IIISE[2]
Hexylresorcinol	IIIE	IIISE
Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)	IIIE	IIISE
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)	IIIE	IIISE
Isopropyl alcohol 70 to 91.3 percent	IIIE	IIISE
Nonylphenoxypoly (ethyleneoxy) ethanoliodine	IIIE	IIISE
Poloxamer iodine complex	IIIE	IIISE
Povidone-iodine 5 to 10 percent	I	IIISE
Secondary amyltricresols	IIIE	IIISE
Triclocarban	IIIE	IIISE
Undecoylium chloride iodine complex	IIIE	IIISE

[1] "I" denotes a classification that an active ingredient has been shown to be safe and effective.
[2] "III" denotes a classification that additional data are needed. "S" denotes safety data needed. "E" denotes effectiveness data needed.

Table 5.--Classification of OTC Patient Preoperative Skin Preparation Antiseptic Active Ingredients in This Proposed Rule and in the 1994 TFM

Active Ingredient	1994 TFM	This Proposed Rule
Alcohol 60 to 95 percent	I[1]	IIISE[2]
Benzalkonium chloride	IIIE	IIISE
Benzethonium chloride	IIIE	IIISE
Chloroxylenol	IIIE	IIISE
Hexylresorcinol	IIIE	IIISE
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)	IIIE	IIISE
Iodine tincture USP	I	IIISE
Iodine topical solution USP	I	IIISE
Isopropyl alcohol 70 to 91.3 percent	I	IIISE
Mercufenol chloride	IIIE	IIISE
Methylbenzethonium chloride	IIIE	IIISE
Nonylphenoxypoly (ethyleneoxy) ethanoliodine	IIIE	IIISE
Phenol (less than 1.5 percent)	IIIE	IIISE
Poloxamer iodine complex	IIIE	IIISE
Povidone-iodine 5 to 10 percent	I	IIISE
Triclocarban	IIIE	IIISE
Triclosan	IIIE	IIISE
Undecoylium chloride iodine complex	IIIE	IIISE

[1] "I" denotes a classification that an active ingredient has been shown to be safe and effective.
[2] "III" denotes a classification that additional data are needed. "S" denotes safety data needed. "E" denotes effectiveness data needed.

This proposed rule does not change the status of a number of antiseptic active ingredients previously proposed as lacking sufficient evidence of safety or effectiveness or the status of several ingredients previously proposed as having been shown to be unsafe, ineffective, or both (see tables 6 and 7).

Table 6.--OTC Health Care Personnel Hand Wash and Surgical Hand Scrub 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	IIISE[1]
Benzethonium chloride	IIISE
Chloroxylenol	IIISE
Cloflucarban	IIISE/II[2]
Fluorosalan	II[3]
Hexachlorophene	II
Methylbenzethonium chloride	IIISE
Phenol (less than 1.5 percent)	IIISE
Phenol (greater than 1.5 percent)	II
Sodium oxychlorosene	IIISE
Tribromsalan	II
Triclosan	IIISE

[1] "III" denotes a classification that additional data are needed. "S" denotes safety data needed. "E" denotes effectiveness data needed.
[2] Health care personnel hand wash proposed as IIISE and surgical hand scrub proposed as II.
[3] "II" denotes a classification that an active ingredient has been shown to be unsafe, ineffective, or both.

Table 7.--OTC Patient Preoperative Skin Preparation Antiseptic Active Ingredients With No Change in Classification in This Proposed Rule Compared to the 1994 TFM

Active Ingredient	No Change in Classification
Cloflucarban	II[1]
Fluorosalan	II
Hexachlorophene	II
Phenol (greater than 1.5 percent)	II
Secondary amyltricresols	IIISE[2]
Sodium oxychlorosene	IIISE
Tribromsalan	II
Calomel, oxyquinoline benzoate, triethanolamine, and phenol derivative	II
Mercufenol chloride and secondary amyltricresols in 50 percent alcohol	IIISE
Triple dye	II

[1] "II" denotes that an active ingredient has been shown to be unsafe, ineffective, or both.
[2] "III" denotes a classification that additional data are needed. "S" denotes safety data needed. "E" denotes effectiveness data needed.

VI. Effectiveness (Generally Recognized as Effective) Determination

OTC regulations (§§ 330.10(a)(4)(ii) and 314.126(b)) define the standards for establishing that an OTC drug containing a particular active ingredient would be GRAE for its intended use. These regulations provide that supporting investigations must be adequate and well-controlled, and able to distinguish the effect of a drug from other influences such as a spontaneous change in the course of the disease, placebo effect, or biased observation. In general, such investigations include controls that are adequate to provide an assessment of drug

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

In the 1994 TFM, we 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 a surrogate endpoint (i.e., number of bacteria removed from the skin), rather than a clinical outcome (e.g., reduction in the number of infections). In accordance with recommendations made by NDAC at its March 2005 meeting, we continue to propose a log reduction standard to demonstrate the general recognition of effectiveness of health care antiseptic active ingredients. See section VI.B for our current proposed log reduction standard.

Unlike the use of antiseptics in the consumer setting, the use of antiseptics by health care providers in the hospital setting is considered an essential component of hospital infection control measures (Refs. 21, 22, and 23). Hospital-acquired infections can result in prolonged hospital stays, additional medical treatment, adverse clinical outcomes, and increased health care costs (Refs. 24 through 27). The reliance on antiseptics in the clinical setting goes back over 150 years when, in the mid-1800s, Semmelweis observed that the mortality associated with childbed fever at the General Hospital in Vienna could be reduced by disinfection of physicians' hands with chlorine prior to patient care (Ref. 28). Around the same time, Lister demonstrated the effect of skin disinfection on surgical site infection rates (Ref. 28). This observational evidence of the effect of antiseptics on infection by Semmelweis and Lister form the basis for the current

role of antiseptics as a critical component of hospital infection control procedures. Adequate and well-controlled clinical trials demonstrating a definitive link between antiseptic use and a reduction in infection rates are lacking, however.

The March 2005 NDAC acknowledged the difficulty in designing clinical trials to demonstrate the impact of health care antiseptics on infection rates. This difficulty was one reason the committee advised against clinical outcome trials to demonstrate the effectiveness of health care antiseptics. Numerous factors contribute to hospital-acquired infections and, therefore, would need to be controlled for in the design of these types of studies. For example, some of the known risk factors for surgical site infection that must be controlled for include the following: Patient age, nutritional status, diabetes, smoking, obesity, coexistent infections at a remote body site, colonization with microorganisms, altered immune response, length of preoperative stay, duration of surgical scrub, preoperative shaving, preoperative skin prep, duration of the operation, inadequate sterilization of instruments, foreign material in the surgical site, surgical drain, and surgical technique (Ref. 22). There are also standard infection control measures such as gloving, isolation procedures, sterilization of instruments, and waste disposal that make it difficult to demonstrate the independent contribution of antiseptics to the reduction of the risk of hospital infection (Ref. 28).

Although we found a few studies that could serve as a basis for designing a clinical outcome study in the consumer setting (78 FR 76444 at 76450), we have not found any acceptable clinical outcome study designs for health care antiseptics. The March 2005 NDAC recommended that sponsors perform an array of trials to look simultaneously at the effect on the surrogate endpoint and the clinical endpoint to try to establish a link between the surrogate and clinical endpoints, but provided no guidance on possible study designs. We have not seen any

studies of this type. The March 2005 NDAC also believed that it would be unethical to perform a hospital trial using a vehicle control instead of an antiseptic. Although the NDAC thought that performing a placebo-controlled study for routine patients on the ward might be feasible, it stated that the Centers for Disease Control and Prevention hand hygiene guidelines and hospital accreditation requirements would prohibit such a practice. The NDAC also believed that an institutional review board would not approve a hospital trial that did not involve an antiseptic.

We agree that a clinical outcome study in the health care setting raises ethical concerns. For a clinical outcome study to be adequately controlled the study design would need to include a vehicle or negative control arm. However, the inclusion of such control arms in a clinical outcome study conducted in a hospital setting could pose an unacceptable health risk to study subjects (hospitalized patients and health care providers). In such studies a vehicle or negative control would be a product with no antimicrobial activity. The use of a nonantimicrobial product in a hospital setting (a setting with an already elevated risk of infections) could increase the risk of infection for both health care providers and their patients. Thus, it is generally considered unethical to perform placebo-controlled clinical studies to show the value of health care antiseptics (Ref. 8). Based on these considerations NDAC recommended the continued use of clinical simulation studies to validate the effectiveness of health care antiseptics.

FDA has relied upon clinical simulation studies to support the approval of health care antiseptics through the NDA process. Although it is not possible to quantify the contribution of NDA health care antiseptics to reduced hospital infection rates, in general, infection rates in the United States are low. For example, only 2 to 5 percent of over 40 million inpatient surgical procedures each year are complicated by surgical site infections (Ref. 29). We acknowledge that the use of surrogate endpoints to assess the effectiveness of these products is not optimal, but we

believe it is the best means available of assessing the effectiveness of health care antiseptic products.

Thus, we are continuing to rely on surrogate endpoints to evaluate the effectiveness of health care antiseptics while requiring data from clinical outcome studies to support the effectiveness of consumer antiseptics (78 FR 76444 at 76450). Unlike consumer antiseptics, however, health care antiseptics are considered an integral part of hospital infection control strategies (Refs. 21, 23, and 30). As is the case for consumer antiseptics, we lack clinical outcome data from adequate studies demonstrating the impact of health care antiseptics on infection rates. Given this, FDA faces the challenge of regulating this important component of current hospital infection control measures without methods to directly assess their clinical effect. We nonetheless need a practical means to assess the general recognition of effectiveness of health care products, such as the clinical simulation studies.

As discussed in section VI.A, we evaluated all the available effectiveness studies for health care antiseptics (i.e., health care personnel hand washes and rubs, surgical hand scrubs and rubs, and patient preoperative skin preparations) to determine whether the data supported finding the health care antiseptic active ingredient to be GRAE based on the 1994 TFM effectiveness criteria (which we are now proposing to update). We found that the available studies are not adequate to support a GRAE determination for any health care antiseptic active ingredient under the 1994 TFM effectiveness criteria (59 FR 31402 at 31445, 31448, and 31450).[2]

[2] We note that alcohol, isopropyl alcohol, and some iodine-containing active ingredients were proposed as GRAE in the 1994 TFM; however, the studies that supported that proposal do not meet our current standards for adequate and well-controlled studies. See discussion in section VI.A.1.

A. Evaluation of Effectiveness Data

1. Clinical Simulation Studies

Most of the data available to support the effectiveness of health care antiseptics are based on clinical simulation studies, such as the ones described in the 1994 TFM (59 FR 31402 at 31444). In vivo test methods, such as clinical simulation studies, and evaluation criteria proposed in the 1994 TFM are based on the premise that bacterial reductions achieved using tests that simulate conditions of actual use for each OTC health care antiseptic product category reflect the bacterial reductions that would be achieved under conditions of such use. For example, one of the intended purposes of a health care personnel hand wash is to reduce the risk of patient-to-patient cross contamination. Thus, the clinical simulation studies proposed in the 1994 TFM are designed to demonstrate effectiveness of a product in the presence of repeated bacterial challenge. The hands are artificially contaminated with a marker organism (bacteria), and the reduction from the baseline numbers of the contaminating organism is determined after use of the test product. This contamination and hand wash procedure is repeated several times, and bacterial reductions are measured at various time points. This aspect of the study design is intended to mimic the repeated use of the product (59 FR 31402 at 31448).

The testing proposed in the 1994 TFM for surgical hand scrubs and patient preoperative skin preparations involves testing against resident skin microflora (bacteria that normally colonize the skin), and there is no artificial contamination of the skin in these studies. Testing demonstrates that the resident bacterial load is highly variable among individuals within the general population (Refs. 31 and 32). Although the 1994 TFM methods specify a minimum bacterial count for individuals to be included in the assessment of surgical hand scrubs and patient preoperative skin preparations, there can be considerable intersubject variability. Similar

to the health care personnel hand washes, the testing of a surgical hand scrub proposed in the 1994 TFM involves multiple test product uses and the repeated measurement of bacterial reductions to determine both immediate and persistent antimicrobial activity (59 FR 31402 at 31445). The patient preoperative skin preparation test evaluates a single application of the product on a dry skin site (abdomen or back) and a moist skin site (groin or axilla) with higher numbers of resident bacteria (59 FR 31402 at 31450). The effectiveness criteria for patient preoperative skin preparations and surgical hand scrubs proposed in the 1994 TFM also require that bacterial growth be suppressed for 6 hours (59 FR 31402 at 31445 and 31450).

We evaluated all clinical simulation studies that were submitted to the OTC Drug Review for evidence of health care personnel hand antiseptic, surgical hand antiseptic, and patient preoperative skin preparation effectiveness demonstrated under the log reduction criteria proposed in the 1994 TFM (59 FR 31402 at 31445, 31448, and 31450) (Ref. 33). We also searched the published literature for clinical simulation studies that assess health care personnel hand antiseptic, surgical hand antiseptic, and patient preoperative skin preparation effectiveness using the log reduction criteria in the 1994 TFM (Refs. 33 through 36).

Overall, the studies used a variety of study designs, including nonstandard study designs. In some cases, such as for surgical hand antiseptics, data submitted to the OTC Drug Review was in the form of abstracts and technical reports. There is insufficient information to evaluate the scientific merit of studies described in abstracts and technical reports. Most importantly, none of the evaluated studies were adequately controlled to demonstrate the contribution of the active ingredient to the effectiveness observed in the studies (43 FR 1210 at 1240) and, therefore, cannot be used to demonstrate that the active ingredient tested is GRAE.

In general, the evaluated studies also had other deficiencies. Each study had at least one of the following deficiencies:

- Some studies that were described as using a standardized method (American Society for Testing and Materials (ASTM) or 1994 TFM) varied from these methods without explanation or validation, and the majority of studies did not provide sufficient information about critical aspects of the study conduct.
- Many studies did not include appropriate controls; for example, some studies did not include a vehicle control or an active control (59 FR 31402 at 31446, 31448, and 31450), and some studies that included an active control failed to use the control product according to its labeled directions (59 FR 31402 at 31446, 31448, and 31450).
- Many studies did not provide sufficient detail concerning neutralizer use (43 FR 1210 at 1244) or validation of neutralizer effectiveness.
- The studies evaluated a small number of subjects (59 FR 31402 at 31446, 31449, and 31451).
- Some studies did not sample at all of the time points specified by the test method (59 FR 31402 at 31446, 31448, and 31450).
- In the case of patient preoperative skin preparation studies, some studies used subjects with baseline values that were too low and other studies did not provide baseline values at all (59 FR 31402 at 31451). Many of the studies only tested one type of test site (dry or moist), but the 1994 TFM (as well as the testing proposed here) requires testing of both dry and moist test sites to demonstrate effectiveness (59 FR 31402 at 31450).

FDA's detailed evaluation of the data is filed in Docket No. FDA-2015-N-0101, available at http://www.regulations.gov (Refs. 33 through 36).

2. Clinical Outcome Studies

Although we are not currently proposing to require clinical outcome studies to support a GRAE determination in this proposal, FDA has 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 health care antiseptics (Ref. 33). In addition, we searched the published literature for clinical outcome studies that would provide evidence of a clinical benefit from the use of a health care antiseptic (Ref. 37). Most of these studies were designed to evaluate health care worker compliance with hand hygiene protocols, and thus, were not adequately controlled to demonstrate a reduction of infection rates. Most importantly, none of the studies used a vehicle control. In general, the studies had additional design flaws such as the following:

- A small sample size.
- A lack of randomization, blinding, or both.
- Inadequate statistical power and, in some cases, a failure to analyze results for statistical significance.
- Inadequate description of methodology and data collection methods.
- Inadequate documentation of proper training in hand wash or rub, surgical hand scrub or rub, or patient preoperative skin preparation technique.
- Failure to observe and document hand washing technique.
- Inadequate controls to address the multifactorial nature of surgical site infection.
- Some patients received antibiotic treatment and others did not.
- Some studies addressed nonmonograph indications.

As discussed in section VI, the March 2005 NDAC agreed that there are currently no clinical trials presented that showed any clinical benefit. The committee stated that conducting such a study in the hospital setting would be unethical, especially considering the need to introduce a placebo or vehicle control to show contribution of an antiseptic drug product. This would put the subjects' health at risk.

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

In the 1994 TFM, we proposed that the effectiveness of antiseptic active ingredients could be supported by a combination of in vitro studies and in vivo clinical simulation testing as described in 21 CFR 333.470 (59 FR 31402 at 31444). In vitro studies are designed to demonstrate the product's spectrum and kinetics of antimicrobial activity, as well as the potential for the development of resistance associated with product use. In vivo test methods and evaluation criteria are based on the premise that bacterial reductions can be adequately demonstrated using tests that simulate conditions of actual use for each OTC health care antiseptic product category and that those reductions are reflective of bacterial reductions that would be achieved during use. (See discussion in section B.2.) Given the limitations of our ability to study these active ingredients in a clinical outcome study in a health care setting, a GRAE determination for a health care antiseptic active ingredient should be supported by an adequate characterization of the antimicrobial activity of the ingredient through both in vitro testing and in vivo clinical simulation testing.

1. In Vitro Studies

The 1994 TFM proposed that the antimicrobial activity of an active ingredient could be demonstrated in vitro by a determination of the in vitro spectrum of antimicrobial activity,

minimum inhibitory concentration (MIC) testing against 25 fresh clinical isolates and 25 laboratory strains, and time-kill testing against 23 laboratory strains (59 FR 31402 at 31444). Comments received in response to the 1994 TFM objected to the proposed in vitro testing requirements, stating that they were overly burdensome (Ref. 38). Consequently, submissions of in vitro data submitted to support the effectiveness of antiseptic active ingredients were far less extensive than what was proposed in the 1994 TFM (Ref. 39). Although we agree that the in vitro testing proposed in the 1994 TFM is overly burdensome for testing every final formulation of an antiseptic product that contains a GRAE ingredient, we continue to believe that a GRAE determination for a health care antiseptic active ingredient should be supported by adequate in vitro characterization of the antimicrobial activity of the ingredient. In addition, we now propose the option of assessing the minimum bactericidal concentration (MBC) as an alternative to testing the MIC to demonstrate the broad spectrum activity of the antiseptic. The ability of an antiseptic to kill microorganisms, rather than inhibit them, is more relevant for a topical product. Because the determination of GRAE status is a very broad statement that can apply to many different formulations of an active ingredient, we continue to propose that an evaluation of the spectrum and kinetics of antimicrobial activity of a health care antiseptic active ingredient should include the following:

- A determination of the in vitro spectrum of antimicrobial activity against recently isolated normal flora and cutaneous pathogens (59 FR 31402 at 31444).
- MIC or MBC testing of 25 representative clinical isolates and 25 reference (e.g., American Type Culture Collection) strains of each of the microorganisms listed in the 1994 TFM (59 FR 31402 at 31444).

- Time-kill testing of each of the microorganisms listed in the 1994 TFM (59 FR 31402 at 31444) to assess how rapidly the antiseptic active ingredient produces its effect. The dilutions and time points tested should be relevant to the actual use pattern of the final product.

Despite the fact that the in vitro data submitted to support the effectiveness of antiseptic active ingredients were far less extensive than proposed in the 1994 TFM, manufacturers may have data of this type on file from their own product development programs that has not been submitted to the rulemaking. Furthermore, published data may be available that would satisfy some or all of this data requirement.

2. In Vivo Studies

Based on the recommendations of NDAC at its March 23, 2005, meeting, we are continuing to propose the use of bacterial log reductions as a means of demonstrating that health care antiseptics are GRAE (Ref. 8). The 1994 TFM also proposed final formulation testing for health care personnel hand washes (59 FR 31402 at 31448), surgical hand scrubs (59 FR 31402 at 31445), and patient preoperative skin preparations (59 FR 31402 at 31450). We do not discuss final formulation testing here because we are not proposing that any of the active ingredients are GRAS/GRAE. Although these proposed test methods are intended to evaluate the effectiveness of antiseptic final formulations, this type of clinical simulation testing when adequately controlled also can be used to demonstrate that an active ingredient is GRAE for use in a health care antiseptic product. Based on our experience with the approval of NDA antiseptic products and input from the March 2005 NDAC, we recommend that the bacterial log reduction studies used to demonstrate that an active ingredient is GRAE for use in health care antiseptic drug products include the following:

- A vehicle control to show the contribution of the active ingredient to effectiveness. The test product should be statistically superior to the vehicle control for the clinical simulation to be considered successful at showing that the test product is effective for use in health care antiseptic products. Products with vehicles that have antimicrobial activity should consider using a negative control, such as nonantimicrobial soap or saline, rather than a vehicle control.
- An active control to validate the study conduct to assure that the expected results are produced. For the results to be valid, the active control should meet the appropriate log reduction criteria.
- A sample size large enough to show statistically significant differences from the results achieved using the vehicle, and meeting the threshold of at least a 70 percent success rate for the health care antiseptic, including justification that the number of subjects tested is adequate for the test.
- Use of an appropriate neutralizer in all recovery media (i.e., sampling solution, dilution fluid, and plating media) and a demonstration of neutralizer validation. The purpose of neutralizer validation is to show that the neutralizer used in the study is effective against the test and control products, and that it is not toxic to the test microorganisms. If a test product can be neutralized through dilution, this should be demonstrated in the neutralizer validation study.
- An analysis of the proportion of subjects who meet the log reduction criteria based on a two-sided statistical test for superiority to vehicle and a 95 percent confidence interval approach.

To establish that a particular active ingredient is GRAE for use in health care antiseptics, clinical simulation studies using the parameters described in this section should be evaluated using log reduction criteria similar to those proposed in the 1994 TFM (59 FR 31402 at 31445, 31448, and 31450). Our current criteria are laid out in table 8. We have revised the log reduction criteria proposed for health care personnel hand washes and rubs, and surgical hand scrubs and rubs based on the recommendations of the March 2005 NDAC and comments to the 1994 TFM that argued that the demonstration of a cumulative antiseptic effect for these products is unnecessary. We agree that the critical element of effectiveness is that a product must be effective after the first application because that represents the way in which health care personnel hand washes and rubs and surgical hand scrubs and rubs are used. For these indications, log reduction criteria are proposed only for a single-product application rather than multiple-product applications. Given that we are no longer requiring a cumulative antiseptic effect, the log reduction criteria were revised to reflect this single product application and fall between the log reductions previously proposed for the first and last applications. The GRAE criteria proposed for all the health care antiseptic indications are based on log reductions achieved by antiseptics as shown in the published literature and evaluated under the NDA process. In addition, based on the timeframes within which patient preoperative skin preparations are commonly used, we are recommending that these products also be able to demonstrate effectiveness at 30 seconds because we believe that injections and some incisions might be made as soon as 30 seconds after skin preparation. The log reductions that we would expect an effective health care antiseptic active ingredient to meet to show that it is GRAE are shown in table 8.

Table 8.--Clinical Simulation Testing Bacterial Log Reduction Effectiveness Criteria in This Proposed Rule and in the 1994 TFM

Indication	1994 TFM	This Proposed Rule
Health care personnel hand wash or health care personnel hand rub	• reduction of 2 $\log_{10}$ on each hand within 5 minutes after the first wash, and • reduction of 3 $\log_{10}$ on each hand within 5 minutes after the tenth wash	reduction of 2.5 $\log_{10}$ on each hand within 5 minutes after a single wash or rub
Surgical hand scrub or surgical hand rub	• reduction of 1 $\log_{10}$ on each hand within 1 minute after the first wash on day 1, and • does not exceed baseline at 6 hours on day 1, and • reduction of 2 $\log_{10}$ on each hand within 1 minute after the last wash on day 2, and • reduction of 3 $\log_{10}$ on each hand within 1 minute after the last wash on day 5	• reduction of 2 $\log_{10}$ on each hand within 1 minute after a single wash or rub, and • does not exceed baseline at 6 hours
Patient preoperative skin preparation	• reduction of 2 $\log_{10}$ per square centimeter on abdominal site within 10 minutes after use, and • reduction of 3 $\log_{10}$ per square centimeter on groin site within 10 minutes after use, and • does not exceed baseline at 6 hours	• reduction of 2 $\log_{10}$ per square centimeter on abdominal site within 30 seconds after use, and • reduction of 3 $\log_{10}$ per square centimeter on groin site within 30 seconds after use, and • does not exceed baseline at 6 hours

VII. Safety (Generally Recognized as Safe) Determination

In the 1994 TFM, 11 active ingredients were classified as GRAS for both health care personnel hand wash and surgical hand scrub use, and 18 active ingredients were classified as GRAS for patient preoperative skin preparation use (59 FR 31402 at 31435). As described in section I.C., health care personnel hand rubs and surgical hand rubs were not separately addressed in the 1994 TFM. 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 systemic exposure to antiseptic active ingredients (Refs. 1 through 5). The potential for widespread antiseptic use to promote the development of antibiotic-resistant bacteria also needs to be evaluated. 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 standards for health care antiseptic active ingredients. In order to fully address these new safety concerns, additional safety data will be necessary to support a GRAS determination for all health care antiseptic active ingredients.

Many of the safety considerations for the five health care antiseptic uses are the same because each use is considered a "chronic" use as that term is defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[3] A use is considered chronic if the drug will be used for a period of at least 6 months over the user's lifetime, including repeated, intermittent use (Ref. 40). Health care personnel washes and rubs are used on a frequent daily basis, as are surgical hand scrubs and rubs. Health care authorities list a variety of situations in which health care workers should perform hand hygiene, such as before and after touching a patient, after contact with body fluids, and after removing gloves (Refs. 21 and 23). Patient preoperative skin preparations also are used daily by many users. For example, many people with type I diabetes require three to four insulin injections a day (Ref. 41) and use these products prior to each injection. Accordingly, we are proposing the same safety testing for each active ingredient be done to support a GRAS determination, regardless of the proposed health care antiseptic use.

[3] FDA is a member of the ICH Steering Committee, the governing body that oversees the harmonization activities, and contributed to the development of ICH guidelines.

A. New Issues

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

Given the frequent repeated use of both health care personnel hand washes and rubs and surgical hand scrubs and rubs, systemic exposure may occur. For some patients, the same may be true for patient preoperative skin preparations. Although some systemic exposure data exist for alcohol and triclosan, many of the other health care antiseptic 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, 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 drug exposure obtained from pharmacokinetic studies in animals and humans. Our administrative record lacks the data necessary to define a margin of safety for the potential chronic use of health care antiseptic active ingredients. Thus, we are continuing to propose that both animal and human pharmacokinetic data are necessary for health care

antiseptic active ingredients. This information will help identify any potential safety concerns and help determine the safety margin for OTC human use.

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

A hormonally active compound that causes reproductive system disruption in the fetus or infant may have effects that are not apparent until many years after initial exposure. There are also critical times in fetal development when a change in hormonal balance that would not cause any lasting effect in an adult could cause a permanent developmental abnormality in a child. For example, untreated hypothyroidism during pregnancy has been associated with cognitive impairment in the offspring (Refs. 54, 55, and 56).

Because health care antiseptics are chronic use products and are used by sensitive populations such as pregnant women, evaluation of the potential for chronic toxicity and effects on reproduction and development should be included in the safety assessment. The designs of general toxicity and reproductive/developmental studies are often sufficient to identify developmental effects that can be caused by hormonally active compounds through the use of currently accepted endpoints and standard good laboratory practice toxicology study designs. As followup in some cases, additional study endpoints may be needed to fully characterize the

potential effects of drug exposure on the exposed individuals. Section VII.C 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.

B. Antimicrobial Resistance

Since publication of the 1994 TFM, there is new information available concerning the impact of widespread antiseptic use on the development of antimicrobial resistance (Refs. 57 through 60). 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. In the health care setting where infection-control practices are multifaceted and include the use of antiseptics, antibiotics, and frequent disinfection, it is difficult to identify the source of antimicrobial resistance or to quantify the impact of antiseptics on the selection, survival, and spread of antimicrobial resistant bacterial strains.

Laboratory studies of some of the antiseptic active ingredients evaluated in this proposed rule demonstrate that bacteria can develop 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. 61 through 78). These studies indicate that further data needs to be gathered regarding whether bacterial resistance mechanisms exist that could select for cross-resistance in the health care setting.

Laboratory studies examining the antiseptic and antibiotic susceptibilities of clinical isolates of Staphylococcus aureus and methicillin-resistant S. aureus (MRSA) have found strains of these organisms with reduced susceptibilities to both antiseptics and antibiotics (Refs. 67 and

79 through 83). However, the impact of such dual tolerances in the clinical setting is unclear. Studies of the impact of such tolerance in S. aureus and Escherichia coli in the clinical setting have yielded mixed results (Refs. 84 through 87). Interpretation of these data is further limited by the fact that only S. aureus and E. coli have been studied. All of the organisms studied constitute a very small subset of the organisms of concern, and one of these organisms (MRSA) is already resistant to some antimicrobials. Thus, the available data are not sufficient to support a finding that these mechanisms of reduced susceptibility would have meaningful clinical impact in a setting where extensive infection control measures that include antibiotic use and frequent disinfection are the norm. In other words, bacteria in the health care setting will be exposed to multiple sources of antimicrobials--regardless of the use of health care antiseptics--which may lessen the impact of the role of health care antiseptics in the development of bacterial resistance.

FDA has been evaluating the role that all antiseptic products, including health care 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. 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. 6). The joint Committee recommended that FDA work with industry to establish surveillance mechanisms to address antiseptic and antibiotic resistance. FDA also plays a major role on the Interagency Task Force on Antimicrobial Resistance and helped draft the Public Health Action Plan to Combat Antimicrobial Resistance (Ref. 88). The Action Plan discusses how to sufficiently implement the surveillance, prevention and control, and research elements of the Action Plan.

Reports of the persistence of low levels of some antiseptic active ingredients in the environment (Refs. 89, 90, and 91) signal the need to better understand the impact of all

antiseptics, including health care antiseptic drug products. Although it is important to consider the relative contribution of the use of health care antiseptic products to any possible environmental impact, it is also important to consider the benefits of these products. Hospital-acquired infections can result in prolonged hospital stays, additional medical treatment, adverse clinical outcomes, and increased health care costs. The use of health care antiseptics is considered an important component of the multifaceted approach that hospitals use to keep hospital acquired infection rates low (Refs. 21 and 23). Furthermore, in situations where there is extensive use of antibiotics, exposure to antibiotics, rather than exposure to antiseptics, plays a dominant role in emerging antibiotic resistance. This makes it difficult to determine whether antiseptics play a significant role in the development of antimicrobial resistance in the hospital setting. Despite this, the use of antiseptics in health care settings may also contribute to the selection of bacterial genera and species that are less susceptible to both antiseptics and antibiotics. We are requesting additional data and information to address this issue. Section VII.C describes the data that will help establish a better understanding of the interactions between antiseptic active ingredients and bacterial resistance mechanisms in health care antiseptic products and will provide the information needed to perform an adequate risk assessment for these health care 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 health care antiseptic active ingredients must be supported by both nonclinical (animal) and clinical (human) studies. To issue a final monograph for these products, this safety data must be in the administrative record (i.e., rulemaking docket).[4]

To assist manufacturers or others who wish to provide us with the information we expect will establish GRAS status for these active ingredients, we are including specific information, based in part on existing FDA guidance, about the other kinds of studies to consider conducting and submitting. We have published guidance documents describing the nonclinical safety studies that a manufacturer should perform when seeking to market a drug product under an NDA (Refs. 40 and 92 through 98). These guidance documents also provide relevant guidance for performing the nonclinical studies necessary to determine GRAS status for a health care antiseptic active ingredient. Because health care antiseptics may be used repeatedly and in sensitive populations, we propose that health care 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. FDA Guidances Describing Safety Studies

The safety studies that are described in the existing FDA guidances (Refs. 40 and 92 through 98) provide a framework for the types of studies that are needed for FDA to assess the safety of each antiseptic active ingredient according to modern scientific standards and make a GRAS determination. A description of each type of study and how we would use this

[4] At the 2014 NDAC meeting, FDA received comments referencing data or other information that appears to be relevant to the safety assessment of health care antiseptic active ingredients, but the referenced data and information were not submitted to the docket for this rulemaking and we are not aware that it is otherwise publicly available. The Agency will consider only material that is submitted to the docket for this rulemaking or that is otherwise publicly available in its evaluation of the GRAS/GRAE status of a relevant ingredient. Information about how to submit such data or information to the docket is set forth in this document in the ADDRESSES section.

information to improve our understanding of the safety of health care antiseptic active ingredients is provided in table 9.

Table 9.--FDA Guidance Documents Related to Requested Safety Data and Rationale for Studies

Type of Study	Study Conditions	What the Data Tell Us	How the Data Are Used
Animal pharmacokinetic absorption, distribution, metabolism, and excretion (ADME) (Refs. 93 and 99)	Both oral and dermal administration	Allows identification of the dose at which the toxic effects of an active ingredient are observed as a result of systemic exposure of the drug. ADME data provide: The rate and extent an active ingredient is absorbed into the body (e.g., AUC, Cmax, Tmax)[1]; where the active ingredient is distributed in the body; whether metabolism of the active ingredient by the body has taken place; information on the presence of metabolites; and how the body eliminates the original active ingredient (parent) and its metabolites (e.g., T½).[2]	Used as a surrogate to identify toxic systemic exposure levels that can then be correlated to potential human exposure via dermal pharmacokinetic study findings. Adverse event data related to particular doses and drug levels (exposure) in animals are used to help formulate a safety picture of the possible risk to humans.
Human pharmacokinetics (MUsT) (Ref. 97)	Dermal administration using multiple formulations under maximum use conditions	Helps determine how much of the active ingredient penetrates the skin, leading to measurable systemic exposure.	Used to relate the potential human exposure to toxic drug levels identified in animal studies.
Carcinogenicity (ICH S1A, S1B, and S1C (Refs. 40, 92, and 95))	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 (tumorogenesis) in the exposed animals.	Identifies the systemic and dermal risks associated with drug active ingredients. Taken together, these studies are used to identify the type(s) of toxicity, the level of exposure that produces these toxicities, and the highest level of exposure at which no adverse effects occur, referred to as the "no observed adverse effect level" (NOAEL). The NOAEL is used to determine a safety margin for human exposure.
Developmental toxicity (ICH S5 (Ref. 94))	Oral administration	Evaluates the effects of a drug on the developing offspring throughout gestation and postnatally until sexual maturation.	
Reproductive toxicity (ICH S5 (Ref. 94))	Oral administration	Assesses the effects of a drug on the reproductive competence of sexually mature male and female animals.	
Hormonal effects (Ref. 98)	Oral administration	Assesses the drug's potential to interfere with the endocrine system.	Used in hazard assessment to determine whether the drug has the capacity to induce a harmful effect at any exposure level without regard to actual human exposures.

[1] "AUC" denotes the area under the concentration-time curve, a measure of total exposure or the extent of absorption. "Cmax" denotes the maximum concentration, which is peak exposure. "Tmax" denotes the time to reach the maximum concentration, which aids in determining the rate of exposure.
[2] "T½" denotes the half-life, which is the amount of time it takes to eliminate half the drug from the body or decrease the concentration of the drug in plasma by 50 percent.

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

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

2. Studies to Characterize Maximal Human Exposure

Because the available data indicate that some dermal products, including at least some antiseptic active ingredients, are absorbed after topical application in humans and animals, it is necessary to assess the effects of long-term dermal and systemic exposure to these ingredients. Based on input from the 2014 NDAC meeting, the Agency has also determined that results from a human pharmacokinetic (PK) maximal usage trial (MUsT) are needed to support a GRAS determination. This trial design is also referred to as a maximal use PK trial and is described in FDA's 2005 draft guidance for industry on developing drugs for treatment of acne vulgaris (Ref. 97). The purpose of the MUsT is to evaluate systemic exposure under conditions that would maximize the potential for drug absorption in a manner consistent with possible "worst-case"

real world use of the product. In a MUsT, the collected plasma samples are analyzed, and the resulting in vivo data could be used to estimate a safety margin based on animal toxicity studies.

A MUsT to support a determination that an active ingredient is GRAS for use in health care antiseptics is conducted by obtaining an adequate number of PK samples following administration of the active ingredient. For studies of active ingredients to be used in topically applied products like these that are used primarily on adults, for which there is less information available and for which crossover designs are not feasible, a larger number of subjects are required compared to studies of orally administered drug products. A MUsT using 50 to 75 subjects should be sufficient to get estimates of the PK parameters from a topically applied health care antiseptic. The MUsT should attempt to maximize the potential for drug absorption to occur by considering the following design elements (Ref. 100):

- Adequate number of subjects (steps should be taken to ensure that the target population (for example, age, gender, race) is properly represented);
- frequency of dosing (e.g., number of hand rub applications during the study);
- duration of dosing (e.g., dosing to represent an 8- to 12-hour health care worker shift);
- use of highest proposed strength (e.g., 95 percent alcohol);
- total involved surface area to be treated at one time (e.g., hands and arms up to the elbow for surgical hand scrubs and rubs);
- amount applied per square centimeter
- method of application (e.g., hand rub or hand wash); and
- sensitive and validated analytical methods.

It also is important that the MUsT reflect maximal use conditions of health care antiseptics (Ref. 101) using different formulations to fully characterize the active ingredient's potential for dermal penetration. Since real-world exposure from health care personnel hand wash and rub and surgical hand scrub and rub use is likely to be greater than from patient preoperative skin preparation use, MUsT data on an active ingredient for either of these indications also would be sufficient to fulfill the MUsT requirement for a patient preoperative skin preparation.

3. Studies to Characterize Hormonal Effects

We propose that data are also needed to assess whether health care 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. 102). 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 products that make it necessary to assess their full safety profile prior to classifying an antiseptic active ingredient as GRAS for use in health care antiseptic products. These factors are as follows:

- Evidence of systemic exposure to several of the antiseptic active ingredients.
- Exposure to multiple sources of antiseptic active ingredients that may be hormonally active compounds, in addition to exposure to health care antiseptic products.
- Exposure to antiseptic active ingredients may be long-term for some health care professionals.

Most antiseptic active ingredients have not been evaluated for hormonal 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, these preliminary assays do not provide conclusive evidence that such an interaction will lead to a significant biological change (Ref. 103). 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 nonclinical 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, changes in organ weights, gross organ changes, clinical chemistry changes, or histopathology changes, which can help identify adverse hormonal effects of the tested drug. Also, 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. Note, however, that 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 for 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 health care antiseptic user 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 these animal studies and this response is not adequately understood, then additional studies, such as mechanistic studies involving alternative animal models, may be needed (Refs. 98, 104, 105, and 106). For example, juvenile animal studies can help address the long-term hormonal effects from acute or continuous exposure to drugs that are administered to neonates and children, when these effects cannot be adequately predicted from existing data. As

an alternative to, or in addition to, supplemental nonclinical assessment of hormonal effects, inclusion of endocrine endpoints (e.g., hormone levels) in clinical studies can be important to clarify the relevance of adverse hormonal effects identified in nonclinical studies.

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 in which 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. 107).

In those cases where adverse effects are noted on the developing offspring, FDA intends to conduct a risk-benefit analysis based on the dose-response observed for the findings and the animal-to-human exposure comparison. If such an assessment indicates a potential risk to humans, then we will include that risk in our risk-benefit analysis in order to determine whether the antiseptic active ingredient at issue is suitable for inclusion in an OTC monograph.

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

Since the 1994 TFM published, the issue of antiseptic resistance and whether bacteria that exhibit antiseptic resistance have the potential for antibiotic cross-resistance has been the subject of much study and scrutiny. One of the major mechanisms of antiseptic and antibiotic cross-resistance is changes in bacterial efflux activity at nonlethal concentrations of the antiseptic (Refs. 66, 69, 76, 108, 109, and 110). Efflux pumps are an important nonspecific bacterial defense mechanism that can confer resistance to a number of substances toxic to the cell, including antibiotics (Refs. 111 and 112). The development of bacteria that are resistant to antibiotics is an important public health issue, and additional data may tell us whether use of antiseptics in health care settings may contribute to the selection of bacteria that are less susceptible to both antiseptics and antibiotics. Therefore, we are requesting additional data and information to address this issue.

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, some of the active ingredients evaluated in this proposed rule have laboratory data demonstrating that bacteria have developed reduced susceptibility to antiseptic active ingredients and antibiotics after exposure to nonlethal concentrations of the antiseptic active ingredient. However, only limited data exist on the effects of antiseptic exposure on the bacteria that are predominant in the oral cavity, gut, skin flora, and the environment (Ref. 113). These organisms represent pools of resistance determinants that are potentially transferable to human pathogens (Refs. 114 and 115). Broader laboratory testing of each health care antiseptic active ingredient would more clearly define the scope of the impact of

antiseptic active ingredients on the development of antibiotic 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 help support a GRAS determination for antiseptic active ingredients intended for use in OTC health care antiseptic drug 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; and
- nonpathogenic organisms and opportunistic pathogens from relevant environmental sources (e.g., patient rooms, surgical suites).

If the results of these studies show no evidence of changes in antiseptic or antibiotic susceptibility, then we propose that 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 health care setting. Different types of data could be used to assess whether or not ingredients with positive laboratory findings pose a public health risk (Ref. 291). We do not anticipate that it will be necessary to obtain data from multiple types of studies for each active ingredient to adequately assess its potential to affect resistance. Such types of data could include, but are not limited to, the following:

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

These data can help ascertain whether or not a health care antiseptic active ingredient is likely to induce nonspecific bacterial resistance mechanisms. These data could also help determine the likelihood that changes in susceptibility would spread to other bacterial populations and whether or not concentrations of health care antiseptics exist in relevant 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 health care antiseptic use can help demonstrate whether or not changes in susceptibility are occurring with actual use. Because actual use concentrations of health care 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. 116, 117, and 118). FDA recognizes, however, that methods of evaluating this issue are an evolving science and that there may be other data appropriate to evaluate the impact of health care antiseptic active ingredients on the development of resistance. For this reason, FDA encourages interested parties to consult with the Agency on the specific studies appropriate to address this issue for a particular active ingredient.

D. Review of Available Data for Each Antiseptic Active Ingredient

We have identified for each health care antiseptic active ingredient whether the studies outlined in section VII.C are publicly available. Table 10 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 some data from submissions to the rulemaking and from information we have identified in the literature, our administrative record is incomplete for at least some types of safety studies for each of the active ingredients (see table 10). As noted previously in this document, only information that is part of the administrative record for this rulemaking can form the basis of a GRAS/GRAE determination.

We recognize that data and information submitted in response to the 2013 Consumer Wash PR may be relevant to this proposed rule for those active ingredients eligible for use as both consumer and health care antiseptics. At the time of publication of this proposed rule, FDA's review of all submissions made to the 2013 Consumer Wash PR had not been completed.

To be considered in this rulemaking, any information relevant to health care antiseptic active ingredients must be resubmitted under this docket (FDA-2015-N-0101) for consideration.

Table 10.--Safety Studies Available for Health Care Antiseptic Active Ingredients[1]

Active Ingredient[2]	Human Pharmaco-kinetic (MUsT)	Animal Pharmaco-kinetic (ADME)	Oral Carcino-genicity	Dermal Carcino-genicity	Reproductive Toxicity (DART)	Potential Hormonal Effects	Resistance Potential
Alcohol	○	●	●	●	●	●	●
Benzalkonium chloride			○				○
Benzethonium chloride		○		●	○		○
Chloroxylenol	○	○			○		○
Hexylresorcinol		○	●				
Simple iodine solutions:							
Iodine tincture USP	○	●	●[3]		●[3]	●	
Iodine topical solution USP	○	●	●[3]		●[3]	●	
Iodine complexes:							
Povidone-iodine	○[4]	●[5]	●[3]		●[3]	●	
Isopropyl alcohol	○	○		○	●	○	●
Triclocarban	○	○	●		○	○	
Triclosan	○[4]	○	●		●	○	○

[1] Empty cell indicates no data available; "○" indicates incomplete data available; "●" indicates available data are sufficient to make a GRAS/GRAE determination.
[2] The following active ingredients are not included in the table because no safety data were submitted or identified since the 1994 TFM: Cloflucarban; combination of calomel, oxyquinoline benzoate, triethanolamine, and phenol derivative; combination of mercufenol chloride and secondary amyltricresols in 50 percent alcohol; fluorosalan; iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate); iodine complex (phosphate ester of alkylaryloxy polyethylene glycol); mercufenol chloride; methylbenzethonium chloride; nonylphenoxypoly (ethyleneoxy) ethanoliodine; phenol (less than 1.5 percent); phenol (greater than 1.5 percent); poloxamer-iodine complex; secondary amyltricresols; sodium oxychlorosene; triple dye; and undecoylium chloride iodine complex.
[3] Based on studies of potassium iodide.
[4] The change in classification from sufficient data to incomplete data compared to the Consumer Wash PR (78 FR 76444 at 76458) is a reflection of the higher frequency of use in the health care setting.
[5] Applies to povidone molecules greater than 35,000 daltons.

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

- Alcohol
- Hexylresorcinol
- Iodine tincture USP
- Iodine topical solution USP
- Isopropyl alcohol
- Povidone-iodine
- 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 new safety data for these active ingredients:

- Cloflucarban
- Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
- Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
- Mercufenol chloride
- Mercufenol chloride and secondary amyltricresols in 50 percent alcohol
- Methylbenzethonium chloride

- Nonylphenoxypoly (ethyleneoxy) ethanoliodine
- Phenol (less than 1.5 percent)
- Poloxamer-iodine complex
- Secondary amyltricresols
- Sodium oxychlorosene
- Undecoylium chloride iodine complex

1. Alcohol

In the 1994 TFM, FDA proposed to classify alcohol as GRAS for all health care antiseptic uses based on the recommendation of the Miscellaneous External Panel, which concluded that the topical application of alcohol is safe (47 FR 22324 at 22329 and 59 FR 31402 at 31412). FDA is now proposing to classify alcohol as Category III. Extensive studies have been conducted to characterize the metabolic and toxic effect of alcohol in animal models. Although the impetus for most of the studies has been to study the effects of alcohol exposure via the oral route of administration, some dermal toxicity studies are available and have shown that, although there is alcohol absorption through human skin, it is much lower than absorption via the oral route. Overall, there are adequate safety data to make a GRAS determination for alcohol, with the exception of human pharmacokinetic data under maximal use conditions.

a. Summary of alcohol safety data

Alcohol human pharmacokinetic data. Some published data are available to characterize the level of dermal absorption and expected systemic exposure in adults as a result of topical use of alcohol-containing health care antiseptics. As shown in table 11, a variety of alcohol-based hand rub product formulations and alcohol concentrations have been used in these studies. Based on the available data, which represents moderate hand rub use (7.5 to 40 hand rub

applications per hour, studied for 30 to 240 minutes), the highest observed exposure was 1,500 milligrams (mg) of alcohol (Ref. 4), which is the equivalent of 10 percent of an alcohol-containing drink.[5] (See also the discussion of occupational exposure to alcohol via the dermal route (Ref. 119) in the alcohol carcinogenicity section of this proposed rule.) Although the available data suggest that dermal absorption of alcohol as a result of health care antiseptic use is relatively low, these studies do not reflect the amount of exposure that may occur during a regular 8- to 12-hour work shift in a health care facility. Consequently, human pharmacokinetics data under maximal use conditions as determined by a MUsT are still needed to make a GRAS determination.

Table 11.--Results of Alcohol Hand Rub Absorption Studies in Humans

Study	No. of Subjects	Amount of Alcohol in Hand Rub (Percent)	Volume of Hand Rub Used (Milliliter (mL))	No. of Hand Rub Applications During the Study	Total Length of Assessment	Highest Blood Alcohol Level Detected (Milligram/ Deciliter (mg/dL))
Kramer, et al. (Ref. 4)	12	95	4	20	30 minutes	2.10
Kramer, et al. (Ref. 4)	12	95	4[1]	10	80 minutes	1.75
Kramer, et al. (Ref. 4)	12	85	4	20	30 minutes	1.15
Kramer, et al. (Ref. 4)	12	85	4[1]	10	80 minutes	3.01
Kirschner, et al. (Ref. 120)	14	74.1	20[2]	One 10-minute application	10 minutes	~0.175
Brown, et al. (Ref. 121)	20	70	1.2-1.5	30	1 hour	1.2
Ahmed-Lecheheb, et al. (Ref. 122)	86	70	3	Average of 9[3]	4 hours	0.022
Miller, et al. (Ref. 5)	5	62	5	50	4 hours	< 5
Miller, et al. (Ref. 123)	1	62	5	25	2 hours	< 5
Kramer, et al. (Ref. 4)	12	55	4	20	30 minutes	0.69
Kramer, et al. (Ref. 4)	12	55	4[1]	10	80 minutes	0.88

[5] One alcohol-containing drink is equivalent to approximately 14 grams of alcohol (Ref. 290).

Bessonneau, V. and O. Thomas (Ref. 124)	1	70	3	5	NA[4]	1.43[5]
Bessonneau, V. and O. Thomas (Ref. 124)	1	70	3 mL x 2[1]	5	NA	2.02[5]

[1] Product applied using a surgical scrub procedure.
[2] Product applied to the subject's back rather than to the hands to exclude any significant interference of inhaled uptake of evaporated alcohol.
[3] Assessed under actual use conditions in a hospital.
[4] Not available because of different study design.
[5] Alcohol concentration measured in air collected from the subject's breathing zone.

Alcohol ADME data. Animal absorption studies have been conducted both in vitro (Ref. 125) and in vivo in several species (Refs. 126 through 129). After absorption, alcohol is metabolized primarily in the liver by alcohol dehydrogenase to acetaldehyde. Acetaldehyde, in turn, is rapidly metabolized to acetic acid by aldehyde dehydrogenase. These data are sufficient to show that about 5 percent of consumed alcohol is excreted in breath and another 5 percent in urine, with negligible amounts excreted in sweat and feces. Overall, the available animal ADME data are adequate to make a GRAS determination.

Alcohol carcinogenicity data. The carcinogenicity of alcohol has been studied by both the dermal and oral routes of administration in animals and by the oral route of administration in humans. These studies are sufficient to characterize the risk of carcinogenesis from the use of alcohol-containing health care antiseptics. Based on two adequate and well-controlled trials, chronic dermal application of alcohol does not appear to be carcinogenic in animals and no further dermal carcinogenicity data are needed to make a GRAS determination (Refs. 130 and 131).

Dermal carcinogenicity data have been obtained from studies where alcohol was used as a vehicle control in 2-year studies. For example, a study performed by the National Toxicology Program (NTP) evaluated the carcinogenic potential of diethanolamine by the dermal route of

administration in rats and mice (Ref. 130). Each species had a vehicle control group that was treated with alcohol only. The skin of F334/N rats (50/sex/group) and B6C3F1 mice (50/sex/group) was treated with 95 percent alcohol for 5 days per week for 103 weeks. The amount of alcohol administered corresponds to a daily dose of 442 mg/kilogram(kg)/day and 1,351 mg/kg/day in rats and mice, respectively. None of the alcohol-treated rats or mice showed any skin tumors; however, every mouse group, including the alcohol-alone treatment, showed high incidences of liver tumors. It is unclear whether the high liver tumor incidence was caused by background incidence or by the chronic topical application of alcohol. Dermal administration of alcohol to the skin did not result in skin tumors under the conditions of this study.

Another study performed by the NTP evaluated the carcinogenic potential of benzethonium chloride by the dermal route of administration in rats and mice (Ref. 131). Each species had a vehicle control group that was treated with 95 percent alcohol only. The rats and mice were treated for 5 days per week for 103 weeks. There was no evidence of an increased incidence of skin tumors in the alcohol-treated rats or mice.

In another study, alcohol was used as a vehicle control in the dermal administration of 9,10-dimethyl-1,2-benzanthracene (DMBA), a known carcinogen (Ref. 132). Application of 0.02 mL alcohol alone on the skin of mice 3 times per week for 20 weeks did not cause any tumors. Despite the fact that this study did not cover the entire lifespan of the mice, it provides additional support that alcohol is not tumorigenic to skin after prolonged dermal administration.

In contrast, chronic administration of orally ingested alcohol has been associated with carcinogenicity in both animals and humans (Ref. 133). In animals, alcohol treatment increased tumor incidences in multiple organs (Refs. 134, 135, and 136). In humans, drinking around 50,000 mg of alcohol per day increases the risk for cancers of the oral cavity, pharynx, larynx,

esophagus, liver, colon, and rectum in both men and women, and breast cancer in women (Refs. 119 and 137). However, no significant increases in cancer risk for any of these types of cancer appear to be associated with less than one alcoholic drink (about 14,000 mg of alcohol) per day. Based on currently available human absorption data, the highest observed alcohol exposure was 1,500 mg after use equivalent to 40 rubs per hour (Ref. 4), which is far below the alcohol levels that have been shown to be associated with cancer.

Bevan and colleagues evaluated the potential cancer risk from occupational exposures to alcohol via the inhalation and dermal routes, including the risk to health care workers (Ref. 119). They estimated that under a "worst-case scenario" of a hospital worker disinfecting both hands and lower arms with alcohol 20 times per day, dermal uptake would be approximately 600 mg alcohol/day. When a more realistic worst-case estimate of 100 hand rubs per day is used (Ref. 101), systemic alcohol exposure may be as high as 6,825 mg/day, assuming bioavailability remains at 2.3 percent for 95 percent alcohol (Ref. 4). Ultimately, systemic exposure data from a human MUsT are needed to fully assess the risk to health care workers.

Alcohol DART data. The developmental and reproductive toxicity profile of orally administered alcohol is well characterized. In many animal species, exposure to alcohol during pregnancy can result in retarded development and structural malformations of the fetus. In humans, consumption of even small amounts of alcohol in pregnant women may result in fetal alcohol spectrum disorders (FASD) and other major structural malformations; therefore, according to the Centers for Disease Control and Prevention, there is no known level of safe alcohol consumption during pregnancy (Ref. 138). The most severe form of FASD, fetal alcohol syndrome, has been documented in infants of mothers who consumed large amounts of alcohol throughout pregnancy (Ref. 292). Based on available absorption data, however, it is highly

unlikely that the levels of alcohol absorbed as a result of health care antiseptic use would approach the levels that cause fetal alcohol syndrome.

Alcohol data on hormonal effects in animals. Alcohol exposure affects the level of a number of different hormones in animals. In vitro studies have shown that alcohol at a concentration of 280 to 300 mg/dL increased production of human chorionic gonadotropin and progesterone by cultured trophoblasts (Ref. 139), and at concentrations of at least 2,500 mg/dL, decreased the ability of rat Leydig cells to secrete testosterone by up to 44 percent (Ref. 140). There are also many in vivo studies of the effects of alcohol on hormone levels in animals after oral administration. Alcohol exposures are associated with suppression of the hypothalamic pituitary gonadal (HPA) axis in male rats. For example, in an alcohol feeding study where adult rats were treated for 5 weeks with 6 percent alcohol, resulting in blood alcohol levels of 110 to 160 mg/dL, the serum and testicular testosterone concentrations of the alcohol group were significantly lower than in untreated controls ($P < 0.01$) (Ref. 141). The serum luteinizing hormone concentration of alcohol-treated rats was significantly higher than that of diet controls ($P < 0.01$), but the pituitary luteinizing hormone, the serum and pituitary follicle-stimulating hormone, and the prolactin concentrations did not differ. When the effect of alcohol exposure was compared in prepubescent and adult rats, treatment with 500 to 4,000 mg alcohol/kg decreased serum testosterone levels in adult rats as expected (Ref. 293). In contrast, the opposite effect was observed in prepubescent male rats (25-30 days old) where alcohol treatment produced dose-dependent increases in serum testosterone levels. Serum luteinizing hormone levels in alcohol-treated rats were either unchanged or only modestly decreased in all ages tested. Results of this study suggest that alcohol at serum levels of greater than 200 mg/dL exerts age-dependent effects on the synthesis and secretion of testosterone throughout sexual maturation in

rats. Overall, the effects of alcohol on hormones in animals have been well characterized and no additional data are needed to make a GRAS determination.

Alcohol data on hormonal effects in humans. The effects of alcohol on human hormones are multiple and complex. Several variables, including the type, length, and pattern of alcohol exposure, and coexisting medical problems, such as malnutrition and liver dysfunction, must be considered when assessing the impact of alcohol on hormonal status (Ref. 142). Pregnant health care workers are a potentially vulnerable population given that alcohol is a teratogen, and alcohol-containing antiseptic hand rubs are used frequently in health care settings. Alcohol in the maternal bloodstream crosses readily into the placenta and the fetal compartment (Ref. 143). This results in similar blood alcohol concentrations in the mother, the fetus, and the amniotic fluid (Ref. 143). The fetus has very limited metabolic capacity for alcohol primarily because of low to absent hepatic activity for the metabolism of alcohol (Ref. 144). Although both the placenta and fetus have some capacity to metabolize alcohol, the majority of alcohol metabolism occurs in maternal metabolic systems outside of the fetal compartment (Ref. 143).

Maternal alcohol use (by ingestion) is the leading known cause of developmental and cognitive disabilities in the offspring, and is a preventable cause of birth defects (Ref. 145). However, based on available absorption data, it is highly unlikely that the levels of alcohol absorbed as a result of health care antiseptic use would approach the levels that cause fetal alcohol syndrome. Nonetheless, children exposed to lower levels of alcohol in utero may be vulnerable to more subtle effects. Currently, the levels of alcohol exposure that cause more subtle effects are unknown.

Unlike the abundance of data from oral exposure, there are no data on the effects of systemic exposure to alcohol during pregnancy from the use of alcohol-containing hand rubs.

There are, however, some pharmacokinetic data on alcohol absorption after hand rub use in the nonpregnant population (described in the human pharmacokinetic subsection of this section of the proposed rule). As noted previously, the available data suggest that with moderate health care antiseptic hand rub use (e.g., evaluations of the amount of alcohol in the blood at up to 4 hours of use), systemic alcohol exposure is relatively low, but may be as high as 10 percent of an alcohol-containing drink. However, health care workers who use these products chronically and repetitively may be required to use alcohol-containing hand rubs in situations such as prior to and following contact with patients or contact with body fluids, and therefore may be exposed to these products a hundred times or more per day (Ref. 101). Consequently, additional human pharmacokinetic data are needed to determine the level of alcohol exposure following maximal use of health care antiseptics (i.e., MUsT) to determine the level of risk from the use of these products.

Alcohol resistance data. The antimicrobial mechanism of action of alcohol is considered nonspecific. It is believed that alcohol has multiple toxic effects on the structure and metabolism of microorganisms, primarily caused by denaturation and coagulation of proteins (Refs. 146 through 149). Alcohol's reactive hydroxyl (-OH) group readily forms hydrogen bonds with proteins, which leads to loss of structure and function, causing protein and other macromolecules to precipitate (Ref. 148). Alcohol also lyses the bacterial cytoplasmic membrane, which releases the cellular contents and leads to bacterial inactivation (Ref. 146). Because of alcohol's speed of action and multiple, nonspecific toxic effects, microorganisms have a difficult time developing resistance to alcohol. Of note, researchers have been attempting to develop alcohol-tolerant bacteria for use in biofuel production and beverage biotechnology applications. One of the most alcohol-tolerant bacteria, Lactobacillus, has been shown to grow in the presence of up to 13

percent alcohol, which is far lower than the alcohol concentrations present in health care antiseptic products (Ref. 150). Health care antiseptic products contain at least 60 percent alcohol (59 FR 31402 at 31442), and bacteria are unable to grow in this relatively high concentration of alcohol. Furthermore, alcohol evaporates readily after topical application, so no significant antiseptic residue is left on the skin that could contribute to the development of resistance (Refs. 146 and 148). Consequently, the development of resistance as a result of health care antiseptic use is unlikely, and additional data on the development of antimicrobial resistance to alcohol are not needed to support a GRAS determination.

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

- Human pharmacokinetic studies under maximal use conditions when applied topically (MUsT), including documentation of validation of the methods used to measure alcohol and its metabolites and
- data to help define the effect of formulation on dermal absorption

2. 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 both a health care personnel hand wash and surgical hand scrub (59 FR 31402 at 31435). FDA continues to propose benzalkonium chloride as Category III. 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. 151 and 152) 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 a health care antiseptic wash active ingredient (Ref. 153).

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 (see generally § 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 made publicly available.

In addition to these summaries, as discussed in the 2013 Consumer Wash PR (78 FR 76444 at 76463), FDA has reviewed studies on resistance data and antibiotic susceptibility of certain bacteria (Refs. 62, 68, 70, 71, 73, 154, 155, and 156), and determined that the available studies have examined few bacterial species, provide no information on exposure levels, and are not adequate to define the potential for the development of resistance or cross-resistance. Additional data are needed to more clearly define the potential for the development of resistance to benzalkonium chloride. Also, currently, no oral or dermal carcinogenicity data are publicly available. Thus, additional safety data are needed before benzalkonium chloride can be confirmed to be GRAS for use in health care antiseptic products.

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

- Human pharmacokinetic studies under maximal use conditions when applied topically (MUsT), including documentation of validation of the methods used to measure benzalkonium chloride and its metabolites;
- aata to help define the effect of formulation on dermal absorption;
- animal ADME;
- oral carcinogenicity;
- dermal carcinogenicity;
- DART studies;
- potential hormonal effects; and
- data from laboratory studies that assess the potential for the development of resistance to benzalkonium chloride and cross-resistance to antibiotics as discussed in section VII.C.4.

3. Benzethonium Chloride

In the 1994 TFM, FDA classified benzethonium chloride as lacking sufficient evidence of safety for use as a health care personnel hand wash and surgical hand scrub (59 FR 31402 at 31435). FDA is now proposing to classify benzethonium chloride as Category III for both safety and effectiveness. Since publication of the 1994 TFM, 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. 157, 158, and 159). These advisory bodies found benzethonium chloride to be safe for these uses. However, all these safety determinations have largely relied on the findings of

proprietary studies that are not publicly available. One of these evaluations, by the unidentified industry expert panel, was submitted to the rulemaking to support the safety of benzethonium chloride (Ref. 160).

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 for a complete evaluation. Furthermore, the submitted safety assessments with study summaries do not constitute an adequate record on which to base a GRAS classification (see generally § 330.10(a)(4)(i)). For FDA to include these studies in the administrative record for this rulemaking, the studies must be submitted to the rulemaking or otherwise made publicly available.

In addition to these summaries, as discussed in the 2013 Consumer Wash PR (78 FR 76444 at 76464-76465), FDA has reviewed the following: (1) ADME studies providing data from dermal and intravenous administration to rats and a rat in vitro dermal absorption study (Refs. 131 and 160 through 163). FDA determined that additional data from ADME studies in animals are necessary to support a GRAS determination 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; (2) A dermal carcinogenicity study (Ref. 131), which is adequate to show that benzethonium chloride does not pose a risk of cancer after repeated dermal administration; however, oral carcinogenicity data are still lacking; (3) DART data from teratology studies on

rats and rabbits, as well as an embryo-fetal rat study (Ref. 160) and determined that the DART data are not adequate to characterize all aspects of reproductive toxicity and that studies are needed to assess the effect of benzethonium chloride on male and female fertility and on prenatal and postnatal endpoints; and (4) Resistance data from studies on bacterial susceptibility for benzethonium chloride and antibiotics (Refs. 164 and 165) and determined that the available studies 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. In addition, we lack human pharmacokinetic studies under maximal use conditions, which are needed to define the level of systemic exposure following repeated use. Thus, additional safety data are needed before benzethonium chloride can be confirmed to be GRAS for use in health care antiseptic products.

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 (MUsT), including documentation of validation of the methods used to measure benzethonium chloride and its metabolites;
- data to help define the effect of formulation on dermal absorption;
- animal ADME;
- oral carcinogenicity;
- DART studies (fertility and embryo-fetal testing);
- potential hormonal effects; and

- data from laboratory studies that assess the potential for the development of resistance to benzethonium chloride and cross-resistance to antibiotics as discussed in section VII.C.4.

4. Chloroxylenol

In the 1994 TFM, FDA classified chloroxylenol as lacking sufficient evidence of safety for use as a health care personnel hand wash and surgical hand scrub for FDA to determine whether chloroxylenol is GRAS for use in health care antiseptic products (59 FR 31402 at 31435). FDA is now proposing to classify chloroxylenol as Category III for both safety and effectiveness. Additional safety data continue to be needed to support the long-term use of chloroxylenol in OTC health care antiseptic products. As discussed in the 2013 Consumer Wash PR, 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.

As discussed in the 2013 Consumer Wash PR (78 FR 76444 at 76465-76467), FDA reviewed the following:

- Human pharmacokinetic data from dermal and percutaneous absorption studies (Refs. 166 and 167) and determined that the human pharmacokinetic studies are inadequate and studies using dermal administration under maximal use conditions are needed to define the level of systemic exposure following repeated use and the effect of formulation on dermal absorption;

- dermal ADME studies (Refs. 168 and 169) that demonstrated that absorption of chloroxylenol occurs after dermal application in humans and animals, but that the administrative record for chloroxylenol still lacks data to fully 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;
- carcinogenicity data from a dermal toxicity study in mice (Ref. 170) and determined that a long-term dermal carcinogenicity study and an oral carcinogenicity study are needed to characterize the systemic effects from long-term exposure;
- DART data from a teratolotgy study in rats (Ref. 171) and determined that additional studies are necessary to assess the effect of chloroxylenol on fertility and early embryonic development and on prenatal and postnatal development; and
- resistance data from studies on antibiotic susceptibility in chloroxylenol-tolerant bacteria and antimicrobial susceptibilities of bacteria from industrial sources (Refs. 156, 164, 171, and 172) and determined that these studies 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.

Thus, additional safety data are needed before chloroxylenol can be confirmed to be GRAS for use in health care antiseptic products.

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 (MUsT), including documentation of validation of the methods used to measure chloroxylenol and its metabolites;
- data to help define the effect of formulation on dermal absorption;
- animal ADME at toxic exposure levels;
- dermal carcinogenicity;
- oral carcinogenicity;
- DART studies defining the effects of chloroxylenol on fertility and prenatal and postnatal development;
- potential hormonal effects; and
- data from laboratory studies that assess the potential for the development of resistance to chloroxylenol and cross-resistance to antibiotics as discussed in section VII.C.4.

5. Hexylresorcinol

In the 1994 TFM, FDA proposed to classify hexylresorcinol as GRAS for all antiseptic uses covered by that TFM, including health care antiseptic uses, based on the recommendations of the Panel, who concluded that the topical application of hexylresorcinol is safe (39 FR 33103 at 33134). FDA is now proposing to classify hexylresorcinol as Category III. In support of its GRAS 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. 173).

In light of the new safety information about systemic exposure to antiseptic active ingredients, the data relied on by the Panel should be supplemented 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. As discussed in the proposed rule covering consumer antiseptic washes (78 FR 76444 at 76458), FDA has reviewed an adequate oral carcinogenicity study with results it considers negative (Ref. 174), an ADME study providing data from oral administration to dogs (Ref. 175) and humans (Ref. 176), and other information, and determined that additional safety data are needed before hexylresorcinol can be considered GRAS for use in OTC antiseptic products. We conclude that these data gaps also exist for use as a health care antiseptic.

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 (i.e., MUsT), including documentation of validation of the methods used to measure hexylresorcinol and its metabolites;
- data to help define the effect of formulation on dermal absorption;
- animal ADME;
- dermal carcinogenicity;
- DART studies;
- potential hormonal effects; and
- data from laboratory studies that assess the potential for the development of resistance to hexylresorcinol and cross-resistance to antibiotics as discussed in section VII.C.4.

6. Iodine-Containing Ingredients

Elemental iodine, which is the active antimicrobial component of iodine-containing antiseptics, is only slightly soluble in water (Ref. 177). Consequently, iodine is frequently dissolved in an organic solvent (such as a tincture) or complexed with a carrier molecule. Both surfactant (e.g., poloxamer) and nonsurfactant (e.g., povidone) compounds have been complexed with iodine. The carrier molecules increase the solubility and stability of iodine by allowing the active form of iodine to be slowly released over time (Ref. 177). 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). In the 1994 TFM, all the iodine-containing active ingredients were proposed as GRAS for OTC health care antiseptic use (59 FR 31402 at 31435). FDA is now proposing to classify all iodine-containing active ingredients as Category III for both safety and effectiveness. Since the publication of the 1994 TFM, we have identified new safety data for the following active ingredients:

- Iodine tincture USP
- Iodine topical solution USP
- Povidone-iodine 5 to 10 percent

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 people are widely exposed to iodine, it has been the subject of comprehensive toxicological review by public health organizations (Refs. 178 and 179).

Much of the safety data we reviewed pertained to elemental iodine alone. Consequently, additional data on some of the carrier molecules are needed. In the 1994 TFM, FDA stated that neither the medium nor large molecular weight size povidone molecules (35,000 daltons or greater) presented a safety risk when limited to the topical uses described in the monograph and that larger size povidone-iodine molecules would not be absorbed under the 1994 TFM conditions of use (59 FR 31402 at 31424). We continue to think that data on the larger size molecules are not necessary to support a GRAS determination for iodine-containing ingredients. However, data are lacking on the absorption of smaller molecular weight povidone molecules and for other small molecular weight carriers (less than 500 daltons (Ref. 180)). Human absorption studies following maximal dermal exposure to these carriers can be used to determine the potential for systemic toxicity from the carrier molecule. For carrier molecules that are absorbed following dermal exposure, we propose that the following data are needed to support a GRAS determination: 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).

As discussed in the 2013 Consumer Wash PR (78 FR 76444 at 76459-76461), FDA has reviewed the following:

- Human pharmacokinetic data from absorption studies (Refs. 178, 181, 182, and 183) and determined that they do not provide sufficient information to estimate typical amounts of iodine that could be absorbed from health care antiseptic products containing iodine and iodine complexes;

- iodine ADME data (Refs. 178, 184, and 185), and determined that the distribution, metabolism, and excretion of iodine have been adequately assessed in humans and no further animal ADME data are needed to support a GRAS determination;
- oral carcinogenicity studies providing data from oral administration to rats and tumor promotion in rats (Refs. 186, 187, and 188) and determined that based upon the available data, oral doses of iodine do not significantly raise the risk of cancer in animals and no further oral carcinogenicity data are needed to make a GRAS determination;
- DART data from studies assessing the effects of iodine on reproduction, embryo-fetal development, lactation, and survival in animals (Refs. 178 and 189 through 195) and determined that the effect of iodine on development and reproductive toxicology are well characterized and additional DART studies are not needed to make a GRAS determination; and
- iodine data on hormonal effects, including studies of the effect of iodine on the thyroid gland (Refs. 178, 179, 181, 183, 190, 191, 192, and 196 through 206), and determined that, despite limitations in some of the studies, FDA believes there are adequate data regarding the potential of iodine to cause changes in thyroid hormone levels and additional studies are not necessary to make a GRAS determination.

In addition, based on the available data, more information is needed to support the frequent, topical use of iodine-containing health care antiseptics by pregnant and breastfeeding health care personnel. Iodine-containing health care antiseptics, particularly povidone-iodine, are used frequently as surgical hand scrubs. Although the daily exposure from surgical hand scrubs would be much lower than from health care personnel hand washes, because of the

potential for absorption of iodine and transient hypothyroidism in newborns (Refs. 191, 192, 199, and 203), chronic use of iodine-containing health care antiseptics by pregnant and breastfeeding health care personnel needs to be evaluated. Consequently, additional human pharmacokinetic data are needed to determine the level of iodine exposure following maximal health care antiseptic use (i.e., MUsT) to determine the potential effects from chronic use of these products.

Iodine safety data gaps. In summary, our administrative record for the safety of iodine-containing active ingredients is incomplete with respect to the following:

- Human pharmacokinetic studies of the absorption of iodine under maximal use conditions when applied topically (MUsT) for each of the iodine-containing active ingredients, including documentation of validation of the methods used to measure iodine and its metabolites;
- human absorption studies of the carrier molecule for small molecular weight povidone molecules (less than 35,000 daltons) and the other small molecular weight carriers (less than 500 daltons);
- dermal carcinogenicity studies for each of the iodine-containing active ingredients; and
- data from laboratory studies that assess the potential for the development of resistance to iodine and cross-resistance to antibiotics as discussed in section VII.C.4 .

7. Isopropyl Alcohol

In the 1994 TFM, FDA proposed to classify isopropyl alcohol (70 to 91.3 percent) as GRAS for all health care antiseptic uses (59 FR 31402 at 31436). FDA is now proposing to classify isopropyl alcohol as Category III. The GRAS determination in the 1994 TFM was based on the recommendations of the Miscellaneous External Panel, which based its recommendations

on human absorption data and blood isopropyl alcohol levels (47 FR 22324 at 22329). There was no comprehensive nonclinical review of the toxicity profile of isopropyl alcohol, nor was there a nonclinical safety evaluation of the topical use of isopropyl alcohol. We believe the existing evaluations need to be supplemented to fully evaluate the safety of isopropyl alcohol.

a. Summary of isopropyl alcohol safety data.

Isopropyl alcohol human pharmacokinetic data. Based on a review of published literature, there are some data to characterize the level of dermal absorption and expected systemic exposure in adults following topical use of isopropyl alcohol-containing products. However, these data do not cover maximal use in the health care setting. In a study by Brown, et al., the cutaneous absorption of isopropyl alcohol from a commonly used hand rub solution containing 70 percent isopropyl alcohol was assessed in 19 health care workers ranging in age from 22 to 67 years (Ref. 121). The hand rub solution was administered under "intensive clinical conditions" by application of 1.2 to 1.5 mL of the isopropyl alcohol-containing hand rub 30 times during a 1-hour period on 2 separate days separated by a 1-day washout. Serum isopropyl alcohol concentrations at 5 to 7 minutes post-exposure as assessed by gas chromatography (lower limit of quantitation of 2 mg/dL) were not detectable in these subjects following the simulated "intense clinical conditions."

Another study examined the pharmacokinetics of alcohol and isopropyl alcohol after separate and combined application in a double-blind, randomized, three-way crossover study (Ref. 120). Results show that all isopropyl alcohol concentrations measured in volunteers treated with 10 percent isopropyl alcohol in aqueous solution and the commercial combination product were below the detection limit of 0.5 mg/L. Another study by Turner and colleagues investigated the amount of isopropyl alcohol absorbed through the skin in 10 healthy male and

female adults following application of 3 mL of an isopropyl alcohol-containing hand rub (56 percent w/w isopropyl alcohol) applied to the hands every 10 minutes over a 4-hour period (Ref. 207). Nine of the 10 subjects exhibited measurable blood isopropyl alcohol concentrations at 5 minutes following final application of the hand rub (limit of detection, 0.5 mg/L). The range of isopropyl alcohol concentrations observed in this study was less than 0.5 mg/L to 1.8 mg/L.

A recent report assessed systemic absorption following the use of a hand rub containing 63.14 percent w/w isopropyl alcohol, using a surgical scrub method on 10 adults (Ref. 208). First, a hygienic hand rub was performed for 30 seconds. Ten minutes later, a 1.5-minute surgical hand rub procedure was performed before each of the three consecutive 90-minute surgical interventions. After application of the hand rub and air-drying, surgical gloves were donned. Samples were collected three times at 90-minute intervals after each surgical procedure and at 60 and 90 minutes after the third surgical procedure. The authors report that the highest median blood level was 2.56 mg/L for isopropyl alcohol.

In summary, dermal absorption of isopropyl alcohol following topical application of antiseptic hand rubs under simulated clinical conditions in adults suggests the systemic exposure to isopropyl alcohol when used as an active ingredient in health care antiseptic products is expected to be low. Clinical effects (mild intoxication) of elevated blood isopropyl alcohol levels occur at concentrations exceeding approximately 50 mg/dL (Ref. 209). The highest blood concentration of isopropyl alcohol observed across studies following various application scenarios with isopropyl alcohol-containing products was less than 2 mg/dL, or 4 percent of the systemic levels associated with acute clinical effects. However, the available studies did not assess the highest potential concentration of isopropyl alcohol (91.3 percent) that may be used in a health care antiseptic (59 FR 31402 at 31436), and these studies do not reflect the amount of

exposure that may occur during a regular 8- to 12-hour work shift in a health care facility. Consequently, human pharmacokinetic data under maximal use conditions as determined by a MUsT are still needed to support a GRAS determination for isopropyl alcohol for use in health care antiseptic products.

Isopropyl alcohol ADME data. There are few animal studies that examine the absorption of isopropyl alcohol following dermal exposure. The majority of studies used non-dermal routes of exposure (i.e., oral or inhalation) (Refs. 210 and 211). The available dermal exposure studies have demonstrated that there is some systemic exposure to isopropyl alcohol following dermal application. However, the extent of that exposure has not been fully characterized.

In a dermal exposure study in rats, 70 percent aqueous isopropyl alcohol solution was applied to a 4.5 square centimeter area of skin on the shaved backs of male and female Fischer F-344 rats and maintained under a sealed chamber for a period of 4 hours (Ref. 212). Most of the drug (approximately 85 percent of the dose) was recovered from the application site (i.e, was not absorbed). The remainder of the dose (approximately 15 percent) was detected in the blood within 1 hour after application, indicating that dermal exposure resulted in some systemic exposure. Maximum blood concentrations of isopropyl alcohol were attained at 4 hours and decreased steadily following removal of the test material. The half-life of elimination (T½) of isopropyl alcohol from blood was 0.77 and 0.94 hours for male and female rats, respectively. AUC was not determined.

Martinez, et al. compared isopropyl alcohol blood levels in rabbits after oral, dermal, and inhalation exposure (Ref. 213). Male rabbits (unidentified strain, three animals per group) were given 2 or 4 g/kg isopropyl alcohol via oral gavage, or unknown doses of isopropyl alcohol via inhalation exposure with or without concomitant dermal exposure. Isopropyl alcohol blood

levels were measured for up to 4 hours after the initiation of treatment. The highest blood isopropyl alcohol concentrations were observed from the oral route of administration (262 and 278 mg/dL in the 2 and 4 g/kg groups, respectively). The dermal and inhalation groups produced a mean blood isopropyl alcohol concentration of 112 mg/dL. The inhalation-only group had a mean blood concentration of 6 to 8 mg/dL. However, the study provides little information regarding the bioavailability of dermally applied isopropyl alcohol because of the unknown dosing for the group given isopropyl alcohol via the combination of inhalation and dermal exposures.

The available animal ADME data from non-dermal routes of exposure are sufficient to characterize the absorption, distribution, metabolism, and excretion of isopropyl alcohol. Isopropyl alcohol is rapidly absorbed following oral ingestion and inhalation (Ref. 214). Isopropyl alcohol is metabolized to acetone in both animals and man by the hepatic enzyme alcohol dehydrogenase and is then metabolized further to carbon dioxide through a variety of metabolic pathways (Refs. 215 and 216). In animals, the excretion of isopropyl alcohol is pulmonary with approximately 3 to 8 percent excreted in the urine (Ref. 214). In humans, isopropyl alcohol is predominantly eliminated in the urine with a small amount being excreted through expiration (Ref. 217).

Slauter, et al. characterized the disposition and pharmacokinetics of isopropyl alcohol following intravenous (IV), oral (single and multiple doses), and inhalation exposure in male and female F-344 rats and B6C3F1mice (Ref. 214). Animals were exposed to either an IV dose of 300 mg/kg, inhalation of 500 or 5,000 parts per million isopropyl alcohol for 6 hours, single oral doses of 300 mg/kg or 3,000 mg/kg, or multiple doses of 300 mg/kg for 8 days. AUC and T½ were calculated based on the study data. No major differences in the rate or route of elimination

between sexes or routes of exposure were demonstrated, and repeated exposure had no effect on excretion. However, the rate of elimination was shown to be dose-dependent, with higher doses increasing the T½. Isopropyl alcohol and its metabolites were distributed to all tissues without accumulation in any particular organ. While these data are adequate to define the ADME profile of isopropyl alcohol following non-dermal exposure, they are not sufficient to characterize what would occur following dermal exposure. Absorption data following dermal absorption in animals are still needed in order to determine the extent of systemic exposure following maximal dermal exposure to isopropanol-containing health care antiseptic products. Information on the distribution, metabolism, and excretion of isopropyl alcohol can be extrapolated from published data on the other routes of exposure.

Isopropyl alcohol carcinogenicity data. No data exist for the carcinogenicity potential of isopropyl alcohol following oral or dermal exposure in humans. The International Agency for Research on Cancer (IARC) monograph states that there is inadequate evidence of carcinogenicity of isopropyl alcohol in humans (Ref. 218). The IARC monograph indicates that an increased incidence of cancer of the paranasal sinuses was observed in workers at factories where isopropyl alcohol was manufactured by the strong-acid process. In this instance, the primary route of exposure was through inhalation, rather than topical. The risk for laryngeal cancer may also have been elevated in these workers. However, it is unclear whether the cancer risk was caused by the presence of isopropyl alcohol itself or one of its by-products (diisopropyl sulfate, which is an intermediate in the process; or isopropyl oils, which are formed as by-products; or to other chemicals, such as sulfuric acid).

Inhalation carcinogenicity studies have been performed in animals to assess the potential carcinogenicity of isopropyl alcohol for industrial workers under occupational exposure

conditions (Ref. 219). In a study in Fisher 344 rats and CD-1 mice by Burleigh-Flayer, et al., high-dose treated rats had higher mortality rates and shorter survival times compared to controls. However, lower exposure groups of rats and mice did not experience significant increases in any tumors following exposure to isopropyl alcohol via the inhalation route for up to 2 years (Ref. 219). Groups of animals were exposed via whole-body exposure chambers to 0 (control), 500 (low-dose), 2,500 (mid-dose) or 5,000 (high-dose) parts per million of isopropyl alcohol vapor 6 hours per day, 5 days per week for up to 78 weeks in CD-1 mice (55/sex/dose) and 104 weeks in Fischer 344 rats (65/sex/dose). These respective isopropyl alcohol exposure levels in the low-dose, mid-dose, and high-dose groups correspond to doses of approximately 570, 2,900, and 5,730 mg/kg/day in mice, and 350, 1,790, and 3,530 mg/kg/day in rats. At the end of treatment, a large panel of organs was collected from control and high-dose treated groups for histopathological examination. In the mid- and low-dose groups, only kidneys and testes were examined.

No increases in the incidence of neoplastic lesions were observed in either mice or rats. In mice, no differences in the mean survival time were noted for any of the exposure groups. No increases in the incidence of neoplastic lesions were noted from treatment groups in either sex. In rats, survival was poor in males but adequate in females; none of the high-dose males survived beyond 100 weeks of dosing. The mean survival time was 631 and 577 days ($\underline{p} < 0.01$) for the control and high-dose groups, respectively. No difference in mean survival time was noted for female rats. The main cause of death was chronic renal disease. Concentration-related increases in the incidence of interstitial cell adenoma of the testes were observed in male rats; however, this type of tumor is common among aged rats and was not considered to be treatment related.

No increased incidence of other neoplastic lesions was observed in male rats, and no increased incidence of neoplastic lesions was observed for female rats from any exposure group.

No dermal carcinogenicity studies of isopropyl alcohol have been completed in animals, and little dermal data from other sources are available. In a subchronic 1-year dermal toxicity study, Rockland mice (30 per group) were treated three times weekly for 1 year with isopropyl alcohol (Ref. 216). No skin tumors were observed, but the sex, dose, and observation period were not specified. Although no evidence of carcinogenic potential was seen in this study, it was not long enough to be considered adequate for the assessment of the carcinogenicity potential of isopropyl alcohol via the dermal route.

Isopropyl alcohol DART data. A number of fertility and multigenerational studies were conducted for isopropyl alcohol administered via the oral route of exposure (Refs. 220 through 225). Isopropyl alcohol was associated with maternal toxicity when pregnant animals were exposed to high doses during pregnancy, but no teratogenic effects were noted on the pups. Isopropyl alcohol was not found to be teratogenic in rats in a number of studies using the oral exposure route using a 2-generation study design. Adverse effects noted for postnatal pups treated at high doses of isopropyl alcohol were limited to decreased pup body weights and increased liver weights (Ref. 221). Based on the weight of evidence from several studies, Faber and colleagues calculated the no observed adverse effect level (NOAEL) for pup postnatal survivability as 700 mg/kg/day in rats (Ref. 221). However, using an alternative, quantitative approach that takes dose-response information into account (i.e., benchmark dose approach), other researchers have estimated a benchmark dose of 420 mg/kg/day (Ref. 226). In conclusion, additional DART data are not needed to support a GRAS determination for health care antiseptic products containing isopropyl alcohol.

Isopropyl alcohol data on hormonal effects. Studies evaluating hormonal effects of isopropyl alcohol are limited. We found only one study in the literature, which showed that exposure to high levels of isopropyl alcohol via the intraperitoneal route was associated with some perturbations in brain hormones (e.g., dopamine, noradrenaline, and serotonin) (Ref. 227). The significance of these changes in hormone levels on the long-term development of the treated pups has not been evaluated. Overall, this study is not adequate to characterize the potential for hormonal effects of isopropyl alcohol. The existing data come from a single study, using a route of exposure that is not relevant to health care antiseptics, and the study did not evaluate other important types of hormones (e.g., thyroid, sex hormones). Additional data to characterize the potential for hormonal effects of isopropyl alcohol are still needed to make a GRAS determination.

Isopropyl alcohol resistance data. We found no reports of bacterial resistance to isopropyl alcohol. Like alcohol, the antimicrobial mechanism of action of isopropyl alcohol is nonspecific, primarily caused by denaturation and coagulation of proteins (Refs. 146 through 149). High concentrations of isopropyl alcohol are toxic to most microorganisms due to its high oxygen demand and membrane-disruptive characteristics (Ref. 228). Because of isopropyl alcohol's speed of action and multiple, nonspecific toxic effects, microorganisms have a difficult time developing resistance to it.

Isopropyl alcohol is a common, cheap industrial solvent and researchers have been attempting to develop isopropyl alcohol-tolerant bacteria for use in biological treatment of isopropyl alcohol-containing industrial waste. A recent study identified an isopropyl alcohol-tolerant strain of Paracoccus denitrificans that could grow in isopropyl alcohol at a concentration of 1.6 percent (Ref. 229), and a strain of Bacillus pallidus has been shown to grow in isopropyl

alcohol up to 2.4 percent (Ref. 230). Thus, even isopropyl alcohol-tolerant strains could not survive in health care antiseptic products, which would contain at least 70 percent isopropyl alcohol (59 FR 31402 at 31442). Furthermore, isopropyl alcohol evaporates readily after topical application, so no antiseptic residue is left on the skin that could contribute to the development of resistance (Refs. 146 and 148). Consequently, the development of resistance as a result of health care antiseptic use is unlikely and additional data on the development of antimicrobial resistance to isopropyl alcohol are not needed to make a GRAS determination.

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

- Human pharmacokinetic studies under maximal use conditions when applied topically (MUsT), including documentation of validation of the methods used to measure isopropyl alcohol and its metabolites;
- animal ADME (dermal absorption);
- oral carcinogenicity;
- dermal carcinogenicity; and
- potential hormonal effects.

8. Triclocarban

In the 1994 TFM, FDA proposed to classify triclocarban as GRAS for all health care antiseptic uses. FDA is now proposing to classify triclocarban as Category III. The GRAS determination in the 1994 TFM was based on safety data and information that were submitted in response to the 1978 TFM on triclocarban formulated as bar soap (Ref. 231). 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, need to be

supplemented to fully evaluate the safety of triclocarban according to current scientific standards. New information regarding potential risks from systemic absorption and long-term exposure to antiseptic active ingredients is leading us to propose additional safety testing.

As discussed in the 2013 Consumer Wash PR (78 FR 76444 at 76461-76462), FDA has reviewed the following:

- Human absorption data (Refs. 231 through 235);
- animal ADME data (Refs. 231 and 236 through 240);
- a 2-year oral carcinogenicity study of triclocarban in rats (Refs. 241 and 242); and
- data on hormonal effects (Refs. 42 and 43).

Based on our evaluation of these data, additional safety data are needed before triclocarban can be considered GRAS for use in a health care antiseptic.

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 (MUsT), including documentation of validation of the methods used to measure triclocarban and its metabolites;
- data to help define the effect of formulation on dermal absorption;
- animal ADME;
- dermal carcinogenicity;
- DART studies;
- potential hormonal effects; and
- data from laboratory studies that assess the potential for the development of resistance to triclocarban and cross-resistance to antibiotics as discussed in section VII.C.4.

9. Triclosan

In the 1994 TFM, FDA classified triclosan as lacking sufficient evidence of safety for use as a health care personnel hand wash and surgical hand scrub (59 FR 31402 at 31436). FDA is now proposing to classify triclosan as Category III for all health care uses. Since the 1994 TFM, 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.

As discussed in the 2013 Consumer Wash PR (78 FR 76444 at 76467-76469), FDA has reviewed the following:

- Human absorption data (Refs. 243 through 248) in the consumer setting;
- animal ADME data (Refs. 243, 244, and 248 through 253) and determined that the 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;
- short-term dermal toxicity studies in animals (Refs. 254 through 257) and determined that a long-term dermal carcinogenicity study is needed to assess the relevance of the short-term dermal toxicity findings to a chronic use situation;
- a 2-year oral carcinogenicity study of triclosan in hamsters (Refs. 258 and 259) and determined the data are adequate to show that triclosan does not pose a risk of cancer after repeated oral administration under the experimental conditions used;

- DART data (Refs. 260 and 261) and determined that the triclosan DART data are adequate and additional traditional DART studies are not necessary to make a GRAS determination;
- data on hormonal effects (Refs. 42, 44 through 48, 51, and 262) and determined that the consequences of short-term thyroid and reproductive findings on the fertility, growth, and development of triclosan-exposed litters could be addressed by studies in juvenile animals; and
- data on the potential for development of antimicrobial resistance and cross-resistance between triclosan and antibiotics (Refs. 61, 62 through 66, 69, 72, 74 through 77, and 263) and determined that triclosan exposure can change efflux pump activity and alter antibiotic susceptibilities, but data are still needed that would clarify the potential public health impact of the currently available data.

In addition to the data already reviewed in the 2013 Consumer Wash PR (78 FR 76444 at 76467), new data for some of the safety categories has also become available.

a. Summary of new triclosan safety data

New triclosan human pharmacokinetics data. A recent biomonitoring study compared urine triclosan levels in a convenience sample of 76 health care workers in two hospitals (Ref. 264). One hospital used a 0.3 percent triclosan-containing soap in all patient care areas and restrooms. The second hospital used plain soap and water, having previously phased out triclosan-containing soaps. Both hospitals also had alcohol-based hand rub available. The use of triclosan-containing toothpaste and other personal care products was assessed through a questionnaire. Although the urinary concentrations of total (nonconjugated plus conjugated) triclosan were higher in health care workers that worked at the hospital using triclosan-

containing soap, the use of triclosan-containing toothpaste was correlated with the highest urinary triclosan levels.

This study provides some information about health care worker exposure to triclosan, but it does not attempt to measure triclosan exposure under maximal use conditions. In summary, although human absorption of triclosan has been adequately characterized for moderate daily use, such as in the consumer setting, studies to evaluate maximal use in the health care setting are not available and MUsT data are needed to make a GRAS determination.

New triclosan carcinogenesis data. A recent study examined the effect of triclosan treatment on the development of liver cancer in mice (Ref. 265). Oral exposure to triclosan at a daily dose of approximately 68.6 mg/kg for 8 months resulted in the proliferation of liver cells (hepatocytes); elevated accumulation of collagen in the liver, which is an indicator of fibrosis of the liver; and oxidative stress. Collectively, these findings suggest that long-term triclosan treatment in mice can lead to the type of liver injury that is a risk factor for the development of liver cancer (hepatocellular carcinoma).

The ability of triclosan to function as a tumor promoter (i.e., something that stimulates existing tumors to grow) also was evaluated. Male mice were pretreated with a single injection of a chemical that can initiate tumors (diethylnitrosamine (DEN)). Test mice then received triclosan at approximately 28.6 mg/kg in their drinking water while control mice received untreated water for 6 months. Triclosan-treated mice had a higher number of liver tumors, larger tumor size, and greater tumor incidence than mice given DEN alone, suggesting that triclosan may be a tumor promoter for other carcinogens in the liver. The authors conclude that long-term triclosan treatment substantially accelerates the development of hepatocellular carcinoma in mice. The relevance of this study to humans, however, is not clear. The concentrations of

triclosan used in this study are likely much higher than the concentrations that health care workers would be exposed to during antiseptic use. 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.

New triclosan findings on muscle function. In the 2013 Consumer Wash PR, we described a study on the physiological effects of triclosan treatment on muscle function in mice and fish (Ref. 266). A newer study further examined the physiological effects of triclosan treatment on muscle function in fish (Ref. 267). This study examined whether triclosan's effect on fish swimming performance correlates with altered messenger ribonucleic acid (mRNA) and protein expression of genes known to be critical for muscle function, and supports the negative effects on muscle function seen in the previous study. 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.

New triclosan data on hormonal effects. The studies reviewed in the 2013 Consumer Wash PR have demonstrated that triclosan has effects on the thyroid, estrogen, and testosterone systems in several animal species, including mammalian species (Refs. 42, 44 through 48, 51, and 262). A recent report describes two studies of the effect of triclosan exposure on thyroid hormone levels in pregnant and lactating rats, and in directly exposed offspring (Ref. 268). Pregnant rats (dams) were treated with 75, 150, or 300 mg triclosan per kilogram of body weight per day (mg/kg bw/day) throughout gestation and the lactation period by gavage. Total thyroxine (T_4) serum levels were measured in both the dams and offspring, which had indirect exposure to triclosan through the placenta and maternal milk. All doses of triclosan significantly lowered T_4 levels in dams, but no significant effects on T_4 levels were seen in the offspring at the

end of the lactation period. In the second study, pups were dosed directly (gavaged) with 50 or 150 mg triclosan/kg bw/day from postnatal day 3 to 16. Significant reductions in the T_4 levels of 16-day-old offspring in both dose groups were noted. This study corroborates the effects on the thyroid seen in previous animal studies, but does not provide long-term data on the hormonal effects of triclosan exposure. Another new study showed that when triclosan was administered directly into the stomach (i.e., intragastrically) of adult rats at doses of 10, 50, and 200 mg/kg for 8 weeks, it resulted in a significant decrease in daily sperm production, changes in sperm morphology, and epididymal histopathology in rats treated with the highest dose of triclosan (Ref. 269).

The information in these studies has not changed our assessment of the need for additional data on hormonal effects. 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.3) could address the consequences of short-term thyroid and reproductive findings on the fertility, growth, and development of triclosan-exposed litters.

New triclosan resistance data. The studies reviewed in the 2013 Consumer Wash PR showed that bacterial species with reduced susceptibility to triclosan were also resistant to one or more of the tested antibiotics (Refs. 61 through 66, 69, 72, 74 through 77, and 263). Several studies suggested that an efflux mechanism is responsible for the observed reduced triclosan susceptibility in some of the bacteria exhibiting resistance (Refs. 66, 69, 76, and 109). Newer studies have further characterized efflux pump activity in response to triclosan in a variety of

these bacterial species (Refs. 110 and 270 through 274). Although the clinical relevance of these studies is not clear, the possibility that triclosan contributes to changes in antibiotic susceptibility warrants further evaluation.

In addition to bacterial efflux activity, other mechanisms have been described that may also contribute to reduced triclosan susceptibility. At low concentrations, triclosan can inhibit an essential bacterial enzyme (enoyl-acyl carrier protein reductase) involved in fatty acid synthesis (Refs. 275 and 276). In bacteria, four enoyl-acyl carrier protein reductases have been identified: FabI, FabK, FabL, and FabV (Refs. 276 and 277). Several recent studies have further characterized the effect of triclosan on enoyl-acyl carrier protein reductases in different bacterial species, which confirmed that over-expression of the fabI gene results in reduced triclosan susceptibility in S. aureus (Ref. 278), demonstrated that FabV can confer resistance to triclosan in Pseudomonas aeruginosa (Ref. 279), and refuted the theory that FabK from Enterococcus faecalis is responsible for the inherent triclosan resistance of this organism (Ref. 280). Taken together, these studies suggest that some bacteria have multiple mechanisms that can be used to survive in the presence of triclosan.

A recent study analyzed 1,388 clinical isolates of S. aureus to determine their triclosan susceptibilities (Ref. 79). Sixty-eight strains that exhibited reduced susceptibility to triclosan, defined as a minimum bactericidal concentration greater than 4 mg/L, were chosen for further characterization, including sequencing of the fabI gene. Previous studies have shown that mutations in, or overexpression of, the fabI gene can result in reduced susceptibility to triclosan (Ref. 275). Among the 68 clinical isolates with reduced susceptibility to triclosan, only 30 had a mutation in the fabI gene, while 38 strains had a normal (wild-type) fabI gene. Further molecular analysis identified novel resistance mechanisms linked to the presence of an

additional, alternative fabI gene derived from another species of Staphylococcus in some of the strains, which was most likely acquired by horizontal transfer (the transmission of DNA between different organisms, rather than from parent to offspring). Clinical S. aureus strains with decreased susceptibility to triclosan had a strong association with the presence of a mutated fabI gene or the alternative fabI gene ($P < 0.001$). The authors suggest that this finding is the first clear evidence that utilization of antiseptics can drive development of antiseptic resistance in clinical isolates. The possibility that an antiseptic may drive the development of resistance and the possibility of horizontal transfer of resistance determinants to clinical isolates warrant further evaluation.

Other studies have evaluated the antiseptic and antibiotic susceptibility profiles of clinical isolates or isolates of bacteria associated with specific hospital outbreaks. In one study, the triclosan susceptibility of clinical isolates of S. epidermidis isolated from blood cultures of patients that were collected prior to the introduction of triclosan (during 1965-1966, "old" isolates) was compared to modern isolates, collected in 2010-2011 (Ref. 281). None of the isolates from 1965-1966 were tolerant to triclosan; however, 12.5 percent of the modern isolates had decreased triclosan susceptibility, with MIC values that were up to 32-fold higher than the highest value found in the old isolates. When triclosan-susceptible strains were grown in increasing concentrations of triclosan, both old and modern isolates could be adapted to the same triclosan MIC level as found in modern tolerant isolates. Although this study suggests that decreased susceptibility to triclosan can occur in relevant organisms as a result of triclosan exposure, the source(s) and extent of triclosan exposure for the modern isolates are unknown, which makes the relevance of these data to the clinical setting unclear.

In another recent study (Ref. 282), the antimicrobial activity of triclosan was evaluated for a multidrug-resistant strain of P. aeruginosa that had caused an outbreak in an oncohematology unit in Italy (Ref. 283). Experimental exposure to triclosan has been shown to lead to changes in bacterial efflux pump activity, which can result in antibiotics being removed from the bacterial cell and bacterial resistance (Ref. 66). The authors of this study examined whether triclosan exposure increased the level of antibiotic resistance in the outbreak strain. The outbreak strain was adapted to grow in the presence of triclosan by serial passage in gradually increasing triclosan concentrations, up to 3,400 mg/L triclosan. Then, the susceptibility of triclosan-adapted and unadapted P. aeruginosa to a panel of antibiotics that are typically exported by efflux pumps, namely tetracycline, ciprofloxacin, amikacin, levofloxacin, carbenicillin, and chloramphenicol, was determined. For all antibiotics examined, the MIC of the triclosan-adapted strain was 2-fold higher than the unadapted strain. The addition of efflux pump inhibitors reduced the MICs 2- to 4-fold for both strains and all antibiotics examined, suggesting that an efflux pump mechanism is involved in the reduced susceptibility. Despite the trend for the triclosan-adapted strain to be less susceptible to the tested antibiotics, the differences were very modest and the clinical relevance of these small changes in MIC, if any, are not known.

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. 61 through 66, 69, 72, 74 through 77, and 263).
- Data define triclosan's mechanisms of action and demonstrate that these mechanisms are dose dependent (Ref. 113).

- Data demonstrate that exposure to triclosan changes efflux pump activity, a common nonspecific bacterial resistance mechanism (Refs. 66, 69, 76, and 109).
- Data show that low levels of triclosan may persist in the environment (Refs. 91, 116, 117, and 284 through 289).

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 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:

- Human pharmacokinetic studies under maximal use conditions when applied topically (MUsT), including documentation of validation of the methods used to measure triclosan and its metabolites;
- animal ADME;
- dermal carcinogenicity;

- potential hormonal effects; and
- data to clarify the relevance of antimicrobial resistance laboratory findings to the health care setting

VIII. Proposed Effective Date

Based on the currently available data, this proposed rule finds that additional data are necessary to establish the safety and effectiveness of health care antiseptic active ingredients for use in OTC health care antiseptic drug products. Accordingly, health care antiseptic active ingredients would be nonmonograph in any final rule based on this proposed rule. We recognize, based on the scope of products subject to this monograph, that manufacturers will need time to comply with a final rule based on this proposed rule. However, because of the potential effectiveness and safety considerations raised by the data for some antiseptic active ingredients evaluated, we believe that an effective date later than 1 year after publication of the final rule would not be appropriate or necessary. Consequently, any final rule that results from this proposed rule will be effective 1 year after the date of the final rule's publication in the Federal Register. On or after that date, any OTC health care antiseptic drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not GRAS/GRAE or to be misbranded, could not be introduced or delivered for introduction into interstate commerce unless it is the subject of an approved new drug application or abbreviated new drug application. Any OTC health care antiseptic 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-2015-N-0101 (formerly Docket No. FDA-1975-N-0012).

A. Introduction

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

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The proposed rule could impose significant economic burdens 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 (2013) Implicit Price

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

B. Summary of Costs and Benefits

The proposed rule's costs and benefits are summarized in table 12 entitled "Economic Data: Costs and Benefits Statement." Benefits are attributed to reducing the potential adverse health effects associated with exposure to antiseptic active ingredients in the event that any active ingredient is shown to be unsafe or ineffective for chronic use. Annual benefits are estimated to range between $0 and $0.16 million. We estimate the present value associated with $0.16 million of annual benefits, over a 10-year period, to approximately equal $1.4 million at a 3 percent discount rate and $1.1 million at a 7 percent discount rate.

Costs include the one-time costs associated with reformulating products, relabeling reformulated products, and conducting both safety and efficacy tests. We estimate one-time upfront costs to approximately range between $64.0 million and $90.8 million. Annualizing these costs over a 10-year period, we estimate total annualized costs to range from $7.3 and $10.4 million at a 3 percent discount rate to $8.5 and $12.1 million at a 7 percent discount rate.

FDA also examined the economic implications of the rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires Agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. The rule could impose a significant economic impact on a substantial number of small entities. For small entities, we estimate the rule's costs to roughly range between 0.01 and 82.18 percent of average annual revenues. In the Initial Regulatory Analysis, we assess several regulatory options that would reduce the proposed rule's burden on small entities. These options include extending testing

compliance time to 24 months (rather than 12 months), and extending relabeling compliance times to 18 months (rather than 12 months).

The full discussion of economic impacts is available in Docket No. FDA-2015-N-0101 http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.

Table 12.--Economic Data: Costs and Benefits Statement

Category		Low Estimate	Median Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year	0.0	$0.08	$0.16	2013	7%	10 years	Value of reduced number of adverse events associated with using non-GRAS/GRAE antiseptic active ingredients. Range of estimates captures uncertainty.
	Annualized Monetized $millions/year	0.0	$0.08	$0.16	2013	3%	10 years	
	Annualized Quantified billion/year	0	10.3	20.6		7%	10 years	Reduced antiseptic active ingredient exposure (in milliliters). Range of estimates captures uncertainty.
	Annualized Quantified billion/year	0	10.3	20.6		3%	10 years	
	Qualitative	Value of infection avoidance associated with switching from non-GRAS/GRAE antiseptic active ingredients to NDA or ANDA antiseptics.						
Costs	Annualized Monetized $millions/year	$8.5	$10.3	$12.1	2013	7%	10 years	Annualized costs of reformulating and testing antiseptic products. Range of estimates capture uncertainty.
	Annualized Monetized $millions/year	$7.3	$8.9	$10.4	2013	3%	10 years	
	Annualized Quantified billion/year					7%		
	Annualized Quantified					3%		

	billion/year							
	Qualitative	Where the products affected by this proposed rule are currently chosen over NDA and ANDA alternatives (such as chlorhexidine products), a switch brought on by the rule may lead to search costs or other types of transactions costs. In this scenario, there are also the potential costs associated with adverse reactions if patients are allergic to substitute products.						
Transfers	Federal Annualized					7%		
	Monetized $millions/year					3%		
	From/To							
	Other Annualized					7%		
	Monetized $millions/year					3%		
	From/To							
Effects	State, Local, or Tribal Government: Not applicable Small Business: The costs associated with potentially affected small entities range between 0.01 and 82.18 percent of their average annual revenues. 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 FD&C Act (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the FD&C Act provides that no State or political subdivision of a State may establish or continue in effect any requirement that: (1) relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A) of the FD&C Act and (2) is different from or in addition to, or that is otherwise not identical with, a requirement under the FD&C 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 remove from the health care antiseptic monograph any active ingredient for which the additional safety and effectiveness data required to show that a health care antiseptic product containing that ingredient would be GRAS/GRAE have not become available. Any final rule would have a preemptive effect in that it would preclude States from issuing requirements related to OTC health care 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 have been placed on display in the Division of Dockets Management (see ADDRESSES) 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.)

1. Brown, T. L., et al., "Can Alcohol-Based Hand-Rub Solutions Cause You to Lose Your Driver's License? Comparative Cutaneous Absorption of Various Alcohols," Antimicrobial Agents and Chemotherapy, 51:1107-1108, 2007.

2. Calafat, A. M., et al., "Urinary Concentrations of Triclosan in the U.S. Population: 2003-2004," Environmental Health Perspectives, 116:303-307, 2008.

3. Centers for Disease Control and Prevention, "Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, July 2010," 2010.

4. Kramer, A., et al., "Quantity of Ethanol Absorption After Excessive Hand Disinfection Using Three Commercially Available Hand Rubs Is Minimal and Below Toxic Levels for Humans," BMC Infectious Diseases, 7:117, 2007.

5. Miller, M. A., et al., "Does the Clinical Use of Ethanol-Based Hand Sanitizer Elevate Blood Alcohol Levels? A Prospective Study," American Journal of Emergency Medicine, 24:815-817, 2006.

6. Transcript of the January 22, 1997, Meeting of the Joint Nonprescription Drugs and Anti-Infective Drugs Advisory Committees in OTC Vol. 230002.

7. Comment No. FDA-1975-N-0012-0081.

8. Transcript of the March 23, 2005, Meeting of the Nonprescription Drugs Advisory Committee, 2005, available at http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4184T1.pdf.

9. Summary Minutes of the November 14, 2008, Feedback Meeting with Personal Care Products Council and Soap and Detergent Association in OTC Vol. 230002.

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

11. Comment Nos. FDA-1975-N-0012-0004, -0062, -0064, -0068, -0073, -0069, -0079, -0071, -0075, -0081, -0082, -0085, -0087, -0132, -0088, -0089, -0090,-0091, -0092, -0093, -0094,-0095, -0096, -0097, -0098, -0100, -0102, -0105, -0107, -0111, -0108, -0109, -0110, -0134, -0112, -0113, -0115, -0116, -0117, -0119, -0123, -0128, -0127, -0135, -0148, -0153, -0154, -0155, -0158, -0157, -0159, -0163, -0176, -0177, -0199, -0200, -0201, -0202, -0215, -0216, -0217, -0218, -0219, -0005, -0223, -0284, -0281, -0282, -0283, -0224, -0275, -0285, -0286, -0276, -0275, -0288, -0277, -0287, -0266, -0268, -0065, -0130, -0164, -0166, -0184, -0227, -0187, -0192, -0194, -0196, -0237, -0238, -0037, -0038, -0245, -0258, -0273, -0204, -0206, -

0207, -0208, -0209, -0212, -0213, -0214, -0269, -0053, -0122, -0124, -0160, -0172, -0180, -0181, -0229, -0230, -0231, -0232, -0234, -0247, -0249, -0250, -253, -0255, -0264, -0010, -0129, -0138, -0066, -0126, -0140, -0178, -0191,-0118,-0121, -0161, -0179, -0198, -0241,-0243, -0010, -0015, -0016, -0017, and -0018.

12. Comment Nos. FDA-1975-N-0012-0003, -0063, -0062, -0069, -0070, -0071, -0075, -0085, -0088, -0089, -0090, -0091, -0092, -0094, -0095, -0096,-0102, -0105, -0107, -0111, -0108, -0109, -0134, -0112, -0115, -0116, -0119, -0127, -0148, -0149, -0151, -0159, -0176, -0177, -0200, -0201, -0202, -0219, -0220, -0223, -0281,-0282, -0283, -0224, -0286, -0276, -0275, -0288, -0266, -0289, -0065, -0130, -0164, -0166, -0184, -0227, -0187, -0189, -0196, -0015, -0237, -0238, -0274, -0238, -0214, -0053, -0122, -0137, -0143, -0146, -0160, -0162, -0186, -0180, -0181, -0183, -0229, -0230, -0231, -0232, -0235, -0248, -0255, -0256, -02643, -0010, -0139, -0150, -0106, -0136, -0141, -0142, -0152, -0168, -0169, -0170, -0242, -0066, -0171, -0161, -0179, -0241, -0243, -0221, -0265, -0271, -0010, -0050, -0052, -0077, -0078, -0083, -0084, -0050, -0051, and -0052.

13. Product labels in OTC Vol. 03HCATFM.

14. Comment No. FDA-1975-N-0012-0062.

15. Comment No. FDA-1975-N-0012-0115.

16. Comment No. FDA-1975-N-0012-0091.

17. Comment No. FDA-1975-N-0012-0187.

18. Comment No. FDA-1975-N-0012-0065.

19. Comment No. FDA-1975-N-0012-0102.

20. Comment No. FDA-1975-N-0012-0229.

21. Centers for Disease Control and Prevention, "Guideline for Hand Hygiene in Health-Care Settings: Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force," Morbidity and Mortality Weekly Report, 51:1-45, 2002.

22. Mangram, A. J., et al., "Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee," American Journal of Infection Control, 27:97-132, 1999.

23. WHO, "WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care Is Safer Care," WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care Is Safer Care, Geneva, 2009.

24. van Kleef, E., et al., "Excess Length of Stay and Mortality Due to Clostridium difficile Infection: A Multi-State Modelling Approach," Journal of Hospital Infection, available at http://dx.doi.org/10.1016/j.jhin.2014.08.008, 2014.

25. Scott, R. D., "The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention," 2009, available at http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf.

26. Goudie, A., et al., "Attributable Cost and Length of Stay for Central Line-Associated Bloodstream Infections," Pediatrics, 133:e1525-e1532, 2014.

27. Zimlichman, E., et al., "Health Care-Associated Infections: A Meta-Analysis of Costs and Financial Impact on the US Health Care System," JAMA Internal Medicine, 173:2039-2046, 2013.

28. Larson, E., "Innovations in Health Care: Antisepsis as a Case Study," American Journal of Public Health, 79:92-99, 1989.

29. Malik, V. K. and A. Dey, "Surgical Site Infection: Preventive Strategies," Principles and Practice of Wound Care, Jaypee Brothers Medical Publishers Ltd., New Delhi, 98-101, 2012.

30. The Joint Commission, "2015 National Patient Safety Goals: Hospital," 2015, available at http://www.jointcommission.org/assets/1/6/2015_NPSG_HAP.pdf.

31. Fierer, N., et al., "The Influence of Sex, Handedness, and Washing on the Diversity of Hand Surface Bacteria," Proceedings of the National Academy of Sciences of the USA, 105:17994-17999, 2008.

32. Aiello, A. E., et al., "A Comparison of the Bacteria Found on the Hands of 'Homemakers' and Neonatal Intensive Care Unit Nurses," Journal of Hospital Infection, 54:310-315, 2003.

33. Briefing Material for the March 23, 2005, Meeting of the Nonprescription Drugs Advisory Committee, available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4098B1_02_01-FDA-TOC.htm.

34. FDA Review of Health Care Personnel Hand Wash Effectiveness Data in OTC Vol. 03HCATFM.

35. FDA Review of Surgical Hand Scrub Effectiveness Data in OTC Vol. 03HCATFM.

36. FDA Review of Patient Preoperative Skin Preparation Effectiveness Data in OTC Vol. 03HCATFM.

37. FDA Review of Health Care Antiseptic Clinical Outcome Effectiveness Data in OTC Vol. 03HCATFM.

38. Comment Nos. FDA-1975-N-0012-0064, -0071, 0081, -0082, -0087, -0088, and -0096.

39. Comment Nos. FDA-1975-N-0012-0073, -0071, -0075, -0081, -0085, -0089, -0093, -0096, -0105, -0111, -0108, -0109, -0113, -0116, -0117, -0119, -0128, -0127, -0153, -0154, -0155, -0158, -0157, -0176, -0177, -0200, -0201, -0282, -0275, -0285, -0286, -0276, -0288, -0266, -0164, -0166, -0184, -0227, -0194, -0238, -0037, -0258, -0124, -0143, -0160, -0172, -0264, -0178, -0191, -0118, -0121, -0161, -0198, -0241, and -0243.

40. ICH guideline, "Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals S1A," November 1995, available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1A/Step4/S1A_Guideline.pdf.

41. American Diabetes Association, "Standards of Medical Care in Diabetes--2013," Diabetes Care, 36:S11-S66, 2013.

42. Ahn, K. C., et al., "In Vitro Biologic Activities of the Antimicrobials Triclocarban, Its Analogs, and Triclosan in Bioassay Screens: Receptor-Based Bioassay Screens," Environmental Health Perspectives, 116:1203-1210, 2008.

43. Chen, J., et al., "Triclocarban Enhances Testosterone Action: A New Type of Endocrine Disruptor?," Endocrinology, 149:1173-1179, 2008.

44. Crofton, K. M., et al., "Short-Term In Vivo Exposure to the Water Contaminant Triclosan: Evidence for Disruption of Thyroxine," Environmental Toxicology and Pharmacology, 24:194-197, 2007.

45. Gee, R. H., et al., "Oestrogenic and Androgenic Activity of Triclosan in Breast Cancer Cells," Journal of Applied Toxicology, 28:78-91, 2008.

46. Jacobs, M. N., G. T. Nolan, and S. R. Hood, "Lignans, Bacteriocides and Organochlorine Compounds Activate the Human Pregnane X Receptor (PXR)," Toxicology and Applied Pharmacology, 209:123-133, 2005.

47. Kumar, V., C. Balomajumder, and P. Roy, "Disruption of LH-Induced Testosterone Biosynthesis in Testicular Leydig Cells by Triclosan: Probable Mechanism of Action," Toxicology, 250:124-131, 2008.

48. Kumar, V., et al., "Alteration of Testicular Steroidogenesis and Histopathology of Reproductive System in Male Rats Treated With Triclosan," Reproductive Toxicology, 27:177-185, 2009.

49. Paul, K. B., et al., "Short-Term Exposure to Triclosan Decreases Thyroxine In Vivo via Upregulation of Hepatic Catabolism in Young Long-Evans Rats," Toxicological Sciences, 113:367-379, 2010.

50. Stoker, T. E., E. K. Gibson, and L. M. Zorrilla, "Triclosan Exposure Modulates Estrogen-Dependent Responses in the Female Wistar Rat," Toxicological Sciences, 117:45-53, 2010.

51. Zorrilla, L. M., et al., "The Effects of Triclosan on Puberty and Thyroid Hormones in Male Wistar Rats," Toxicological Sciences, 107:56-64, 2009.

52. Anway, M. D. and M. K. Skinner, "Epigenetic Transgenerational Actions of Endocrine Disruptors," Endocrinology, 147:S43-49, 2006.

53. Bernal, A. J. and R. L. Jirtle, "Epigenomic Disruption: The Effects of Early Developmental Exposures," Birth Defects Research (Part A), 88:938-944, 2010.

54. Alexander, E. K., et al., "Timing and Magnitude of Increases in Levothyroxine Requirements During Pregnancy in Women With Hypothyroidism," New England Journal of Medicine, 351:241-249, 2004.

55. Mitchell, M. L. and R. Z. Klein, "The Sequelae of Untreated Maternal Hypothyroidism," European Journal of Endocrinology, 151 U45-48, 2004.

56. Pop, V. J., et al., "Low Maternal Free Thyroxine Concentrations During Early Pregnancy Are Associated With Impaired Psychomotor Development in Infancy," Clinical Endocrinology, 50:149-155, 1999.

57. Fraise, A. P., "Biocide Abuse and Antimicrobial Resistance--A Cause for Concern?," Journal of Antimicrobial Chemotherapy, 49:11-12, 2002.

58. Gilbert, P. and A. J. McBain, "Potential Impact of Increased Use of Biocides in Consumer Products on Prevalence of Antibiotic Resistance," Clinical Microbiology Reviews, 16:189-208, 2003.

59. Levy, S. B., "Antimicrobial Consumer Products: Where's the Benefit? What's the Risk?," Archives of Dermatology, 138:1087-1088, 2002.

60. Russell, A. D., "Biocides and Pharmacologically Active Drugs as Residues and in the Environment: Is There a Correlation With Antibiotic Resistance?," American Journal of Infection Control, 30:495-498, 2002.

61. Birosova, L. and M. Mikulasova, "Development of Triclosan and Antibiotic Resistance in Salmonella enterica serovar Typhimurium," Journal of Medical Microbiology, 58:436-441, 2009.

62. Braoudaki, M. and A. C. Hilton, "Adaptive Resistance to Biocides in Salmonella enterica and Escherichia coli O157 and Cross-Resistance to Antimicrobial Agents," Journal of Clinical Microbiology, 42:73-78, 2004.

63. Braoudaki, M. and A. C. Hilton, "Low Level of Cross-Resistance Between Triclosan and Antibiotics in Escherichia coli K-12 and E. coli O55 Compared to E. coli O157," FEMS Microbiology Letters, 235:305-309, 2004.

64. Brenwald, N. P. and A. P. Fraise, "Triclosan Resistance in Methicillin-Resistant Staphylococcus aureus (MRSA)," Journal of Hospital Infection, 55:141-144, 2003.

65. Chen, Y., et al., "Triclosan Resistance in Clinical Isolates of Acinetobacter baumannii," Journal of Medical Microbiology, 58:1086-1091, 2009.

66. Chuanchuen, R., et al., "Cross-Resistance Between Triclosan and Antibiotics in Pseudomonas aeruginosa Is Mediated by Multidrug Efflux Pumps: Exposure of a Susceptible Mutant Strain to Triclosan Selects nfxB Mutants Overexpressing MexCD-OprJ," Antimicrobial Agents and Chemotherapy, 45:428-432, 2001.

67. Cookson, B. D., et al., "Transferable Resistance to Triclosan in MRSA," Lancet, 337:1548-1549, 1991.

68. Joynson, J. A., B. Forbes, and R. J. Lambert, "Adaptive Resistance to Benzalkonium Chloride, Amikacin and Tobramycin: The Effect on Susceptibility to Other Antimicrobials," Journal of Applied Microbiology, 93:96-107, 2002.

69. Karatzas, K. A., et al., "Prolonged Treatment of Salmonella enterica serovar Typhimurium With Commercial Disinfectants Selects for Multiple Antibiotic Resistance, Increased Efflux and Reduced Invasiveness," Journal of Antimicrobial Chemotherapy, 60:947-955, 2007.

70. Lambert, R. J., J. Joynson, and B. Forbes, "The Relationships and Susceptibilities of Some Industrial, Laboratory and Clinical Isolates of Pseudomonas aeruginosa to Some Antibiotics and Biocides," Journal of Applied Microbiology, 91:972-984, 2001.

71. Langsrud, S., G. Sundheim, and A. L. Holck, "Cross-Resistance to Antibiotics of Escherichia coli Adapted to Benzalkonium Chloride or Exposed to Stress-Inducers," Journal of Applied Microbiology, 96:201-208, 2004.

72. Ledder, R. G., et al., "Effects of Chronic Triclosan Exposure Upon the Antimicrobial Susceptibility of 40 Ex-Situ Environmental and Human Isolates," Journal of Applied Microbiology, 100:1132-1140, 2006.

73. Loughlin, M. F., M. V. Jones, and P. A. Lambert, "Pseudomonas aeruginosa Cells Adapted to Benzalkonium Chloride Show Resistance to Other Membrane-Active Agents But Not to Clinically Relevant Antibiotics," Journal of Antimicrobial Chemotherapy, 49:631-639, 2002.

74. Randall, L. P., et al., "Effect of Triclosan or a Phenolic Farm Disinfectant on the Selection of Antibiotic-Resistant Salmonella enterica," Journal of Antimicrobial Chemotherapy, 54:621-627, 2004.

75. Randall, L. P., et al., "Prevalence of Multiple Antibiotic Resistance in 443 Campylobacter spp. Isolated From Humans and Animals," Journal of Antimicrobial Chemotherapy, 52:507-510, 2003.

76. Sanchez, P., E. Moreno, and J. L. Martinez, "The Biocide Triclosan Selects Stenotrophomonas maltophilia Mutants That Overproduce the SmeDEF Multidrug Efflux Pump," Antimicrobial Agents and Chemotherapy, 49:781-782, 2005.

77. Seaman, P. F., D. Ochs, and M. J. Day, "Small-Colony Variants: A Novel Mechanism for Triclosan Resistance in Methicillin-Resistant Staphylococcus aureus," Journal of Antimicrobial Chemotherapy, 59:43-50, 2007.

78. Tkachenko, O., et al., "A Triclosan-Ciprofloxacin Cross-Resistant Mutant Strain of Staphylococcus aureus Displays an Alteration in the Expression of Several Cell Membrane Structural and Functional Genes," Research in Microbiology, 158:651-658, 2007.

79. Ciusa, M. L., et al., "A Novel Resistance Mechanism to Triclosan That Suggests Horizontal Gene Transfer and Demonstrates a Potential Selective Pressure for Reduced Biocide Susceptibility in Clinical Strains of Staphylococcus aureus," International Journal of Antimicrobial Agents, 40:210-220, 2012.

80. Tandukar, M., et al., "Long-Term Exposure to Benzalkonium Chloride Disinfectants Results in Change of Microbial Community Structure and Increased Antimicrobial Resistance," Environmental Science and Technology, 47:9730-9738, 2013.

81. Zmantar, T., et al., "Detection of Macrolide and Disinfectant Resistance Genes in Clinical Staphylococcus aureus and Coagulase-Negative staphylococci," BMC Research Notes, 4:453, 2011.

82. Ho, J. and J. Branley, "Prevalence of Antiseptic Resistance Genes qacA/B and Specific Sequence Types of Methicillin-Resistant Staphylococcus aureus in the Era of Hand Hygiene," Journal of Antimicrobial Chemotherapy, 67:1549-1550, 2012.

83. Johnson, J. G., et al., "Frequency of Disinfectant Resistance Genes in Pediatric Strains of Methicillin-Resistant Staphylococcus aureus," Infection Control and Hospital Epidemiology, 34:1326-1327, 2013.

84. Batra, R., et al., "Efficacy and Limitation of a Chlorhexidine-Based Decolonization Strategy in Preventing Transmission of Methicillin-Resistant Staphylococcus aureus in an Intensive Care Unit," Clinical Infectious Diseases, 50:210-217, 2010.

85. Buffet-Bataillon, S., et al., "Effect of Higher Minimum Inhibitory Concentrations of Quaternary Ammonium Compounds in Clinical E. coli Isolates on Antibiotic Susceptibilities and Clinical Outcomes," Journal of Hospital Infection, 79:141-146, 2011.

86. Otter, J. A., et al., "Selection for qacA Carriage in CC22, But Not CC30, Methicillin-Resistant Staphylococcus aureus Bloodstream Infection Isolates During a Successful Institutional Infection Control Programme," Journal of Antimicrobial Chemotherapy, 68:992-999, 2013.

87. Sangal, V., et al., "Impacts of a Long-Term Programme of Active Surveillance and Chlorhexidine Baths on the Clinical and Molecular Epidemiology of Methicillin-Resistant Staphylococcus aureus (MRSA) in an Intensive Care Unit in Scotland," International Journal of Antimicrobial Agents, 40:323-331, 2012.

88. Interagency Task Force on Antimicrobial Resistance, "A Public Health Action Plan to Combat Antimicrobial Resistance. 2012 Update," 2012, available at http://www.cdc.gov/drugresistance/itfar/introduction_overview.html.

89. Ferrer, I. and E. T. Furlong, "Identification of Alkyl Dimethylbenzylammonium Surfactants in Water Samples by Solid-Phase Extraction Followed by Ion Trap LC/MS and LC/MS/MS," Environmental Science and Technology, 35:2583-2588, 2001.

90. Ferrer, I. and E. T. Furlong, "Accelerated Solvent Extraction Followed by On-Line Solid-Phase Extraction Coupled to Ion Trap LC/MS/MS for Analysis of Benzalkonium Chlorides in Sediment Samples," Analytical Chemistry, 74:1275-1280, 2002.

91. Miller, T. R., et al., "Fate of Triclosan and Evidence for Reductive Dechlorination of Triclocarban in Estuarine Sediments," Environmental Science and Technology, 42:4570-4576, 2008.

92. ICH guidance for industry, "S1B Testing for Carcinogenicity of Pharmaceuticals," July 1997, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

93. ICH guidance for industry, "S7A Safety Pharmacology Studies for Human Pharmaceuticals," July 2001, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

94. ICH guideline, "Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2)," November 2005, available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S5_R2/Step4/S5_R2__Guideline.pdf.

95. ICH guidance for industry, "S1C(R2) Dose Selection for Carcinogenicity Studies," (Revision 1), September 2008, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

96. ICH guidance for industry, "M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," (Revision 1), January 2010, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

97. FDA draft guidance for industry, "Acne Vulgaris: Developing Drugs for Treatment," September 2005, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

98. FDA draft guidance for industry, "Endocrine Disruption Potential of Drugs: Nonclinical Evaluation," September 2013, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

99. FDA, "Guideline for the Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application," 1987, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072112.pdf.

100. Bashaw, E. D., et al., "Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products," Therapeutic Innovation and Regulatory Science, 2014.

101. Evans, V. A. and P. Orris, "The Use of Alcohol-Based Hand Sanitizers by Pregnant Health Care Workers," Journal of Occupational and Environmental Medicine, 54:3, 2012.

102. Diamanti-Kandarakis, E., et al., "Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement," Endocrine Reviews, 30:293-342, 2009.

103. Sweetnam, P. M., et al., "The Role of Receptor Binding in Drug Discovery," Journal of Natural Products, 56:441-455, 1993.

104. "Redbook 2000: IV.C.9.a: Guidelines for Reproduction Studies," 2000, available at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm.

105. EPA, "Guidelines for Reproductive Toxicity Risk Assessment," October 1996, available at http://www2.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf.

106. FDA guidance for industry, "Nonclinical Safety Evaluation of Pediatric Drug Products," available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079247.pdf.

107. Stoker, T. E., et al., "Endocrine-Disrupting Chemicals: Prepubertal Exposures and Effects on Sexual Maturation and Thyroid Function in the Male Rat. A Focus on the EDSTAC Recommendations," Critical Reviews in Toxicology, 30:197-252, 2000.

108. McMurry, L. M., M. Oethinger, and S. B. Levy, "Overexpression of marA, soxS, or acrAB Produces Resistance to Triclosan in Laboratory and Clinical Strains of Escherichia coli," FEMS Microbiology Letters, 166:305-309, 1998.

109. Tabak, M., et al., "Effect of Triclosan on Salmonella typhimurium at Different Growth Stages and in Biofilms," FEMS Microbiology Letters, 267:200-206, 2007.

110. Srinivasan, V. B., et al., "Role of Novel Multidrug Efflux Pump Involved in Drug Resistance in Klebsiella pneumoniae," PLoS One, 9:e96288, 2014.

111. Levy, S. B., "Active Efflux, A Common Mechanism for Biocide and Antibiotic Resistance," Journal of Applied Microbiology Symposium Supplement, 92:65S-71S, 2002.

112. Russell, A. D., "Do Biocides Select for Antibiotic Resistance?," Journal of Pharmacy and Pharmacology, 52:227-233, 2000.

113. Yazdankhah, S. P., et al., "Triclosan and Antimicrobial Resistance in Bacteria: An Overview," Microbial Drug Resistance, 12:83-90, 2006.

114. Martinez, J. L., "The Role of Natural Environments in the Evolution of Resistance Traits in Pathogenic Bacteria," Proceedings in Biological Science, 276:2521-2530, 2009.

115. Nguyen, M. and G. Vedantam, "Mobile Genetic Elements in the Genus Bacteroides, and Their Mechanism(s) of Dissemination," Mobile Genetic Elements, 1:187-196, 2011.

116. Cha, J. and A. M. Cupples, "Detection of the Antimicrobials Triclocarban and Triclosan in Agricultural Soils Following Land Application of Municipal Biosolids," Water Research, 43:2522-2530, 2009.

117. Kolpin, D. W., et al., "Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance," Environmental Science and Technology, 36:1202-1211, 2002.

118. Russell, A. D. and G. McDonnell, "Concentration: A Major Factor in Studying Biocidal Action," Journal of Hospital Infection, 44:1-3, 2000.

119. Bevan, R. J., et al., "An Assessment of Potential Cancer Risk Following Occupational Exposure to Ethanol," Journal of Toxicology and Environmental Health, Part B, 12:188-205, 2009.

120. Kirschner, M. H., et al., "Transdermal Resorption of an Ethanol- and 2-Propanol-Containing Skin Disinfectant," Langenbecks Archives of Surgery, 394:151-157, 2009.

121. Brown, T. L., et al., "Can Alcohol-Based Hand-Rub Solutions Cause You to Lose Your Driver's License? Comparative Cutaneous Absorption of Various Alcohols," Antimicrobial Agents and Chemotherapy, 51:1107-1108, 2007.

122. Ahmed-Lecheheb, D., et al., "Dermal and Pulmonary Absorption of Ethanol From Alcohol-Based Hand Rub," Journal of Hospital Infection, 81:31-35, 2012.

123. Miller, M. A., A. Rosin, and C. S. Crystal, "Alcohol-Based Hand Sanitizer: Can Frequent Use Cause an Elevated Blood Alcohol Level?," American Journal of Infection Control, 34:150-151, 2006.

124. Bessonneau, V. and O. Thomas, "Assessment of Exposure to Alcohol Vapor From Alcohol-Based Hand Rubs," International Journal of Environmental Research and Public Health, 9:868-879, 2012.

125. Beskitt, J. L. and J. D. Sun, "In Vitro Skin Penetration Characteristics of Ethanol in the Rabbit, Mouse, Rat, and Human," Journal of Toxicology--Cutaneous and Ocular Toxicology, 16:61-75, 1997.

126. Behl, C. R., et al., "Hydration and Percutaneous Absorption: I. Influence of Hydration on Alkanol Permeation Through Hairless Mouse Skin," Journal of Investigative Dermatology, 75:346-352, 1980.

127. Durrheim, H., et al., "Permeation of Hairless Mouse Skin I: Experimental Methods and Comparison With Human Epidermal Permeation by Alkanols," Journal of Pharmaceutical Sciences, 69:781-786, 1980.

128. Behl, C. R., et al., "Hydration and Percutaneous Absorption III: Influences of Stripping and Scalding on Hydration Alteration of the Permeability of Hairless Mouse Skin to Water and n-Alkanols," Journal of Pharmaceutical Sciences, 71:229-234, 1982.

129. Flynn, G. L., H. Durrheim, and W. I. Higuchi, "Permeation of Hairless Mouse Skin II: Membrane Sectioning Techniques and Influence on Alkanol Permeabilities," Journal of Pharmaceutical Sciences, 70:52-56, 1981.

130. National Toxicology Program, "TR 478: Toxicology and Carcinogenesis Studies of Diethanolamine in F344/N Rats and B6C3F1 Mice," 1999.

131. National Toxicology Program, "NTP Toxicology and Carcinogenesis Studies of Benzethonium Chloride (CAS No. 121-54-0) in F344/N Rats and B6C3F1 Mice (Dermal Studies)," National Toxicology Program Technical Report Series, 438:1-220, 1995.

132. Stenback, F., "The Tumorigenic Effect of Ethanol," Acta Pathologica, Microbiologica, et Immunologica Scandinavica, 77:325-326, 1969.

133. International Agency for Research on Cancer, "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 96, Alcohol Consumption and Ethyl Carbamate," 2010, available at http://monographs.iarc.fr/ENG/Monographs/vol96/mono96.pdf.

134. National Toxicology Program, "TR 510: Toxicology and Carcinogenesis Studies of Urethane, Ethanol, and Urethane/Ethanol in B6C3F1 Mice," 2004.

135. Watabiki, T., et al., "Long-Term Ethanol Consumption in ICR Mice Causes Mammary Tumor in Females and Liver Fibrosis in Males," Alcoholism, Clinical and Experimental Research, 24:117S-122S, 2000.

136. Soffritti, M. F., et al., "Results of Long-Term Experimental Studies on the Carcinogenicity of Methyl Alcohol and Ethyl Alcohol in Rats," Annals of the New York Academy of Science, 982:46-69, 2003.

137. Baan, R., et al., "Carcinogenicity of Alcoholic Beverages," Lancet, 8:292-293, 2007.

138. Centers for Disease Control and Prevention, "Alcohol Use in Pregnancy," Updated April 17, 2014, available at http://www.cdc.gov/ncbddd/fasd/alcohol-use.html.

139. Karl, P. I. and S. E. Fisher, "Ethanol Alters Hormone Production in Cultured Human Placental Trophoblasts," Alcoholism, Clinical and Experimental Research, 17:816-821, 1993.

140. Santucci, L., T. J. Graham, and D. H. Van Thiel, "Inhibition of Testosterone Production by Rat Leydig Cells With Ethanol and Acetaldehyde: Prevention of Ethanol Toxicity With 4-methylpyrazole," Alcoholism, Clinical and Experimental Research, 7:135-139, 1983.

141. Salonen, I., P. Pakarinen, and I. Huhtaniemi, "Effect of Chronic Ethanol Diet on Expression of Gonadotropin Genes in the Male Rat," Journal of Pharmacology and Experimental Therapeutics, 260:463-467, 1992.

142. Emanuele, N. and M. A. Emanuele, "The Endocrine System: Alcohol Alters Critical Hormonal Balance," Alcohol Health and Research World, 21:53-64, 1997.

143. Heller, M. and L. Burd, "Review of Ethanol Dispersion, Distribution, and Elimination From the Fetal Compartment," Birth Defects Research (Part A), 100:277-283, 2014.

144. Paintner, A., A. D. Williams, and L. Burd, "Fetal Alcohol Spectrum Disorders--Implications for Child Neurology, Part 1: Prenatal Exposure and Dosimetry," Journal of Child Neurology, 27:258-263, 2012.

145. American College of Obstetricians and Gynecologists, "Alcohol and Pregnancy: Know the Facts," 2008, available at http://www.acog.org/About_ACOG/News_Room/News_Releases/2008/Alcohol_and_Pregnancy_Know_the_Facts.

146. Ali, Y., et al., "Alcohols," Disinfection, Sterilization, and Preservation, 5th ed., Philadelphia, PA: Lippincott Williams and Wilkins, 229-254, 2001.

147. Kampf, G. and A. Kramer, "Epidemiologic Background of Hand Hygiene and Evaluation of the Most Important Agents for Scrubs and Rubs," Clinical Microbiology Reviews, 17:863-893, 2004.

148. McDonnell, G. E., "Alcohols," Antisepsis, Disinfection, and Sterilization--Types, Action, and Resistance, ASM Press, Washington DC, 90-92, 2007.

149. Rutala, W. A., D. J. Weber, and Healthcare Infection Control Practices Advisory Committee (HICPAC), "Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008," 2008, available at http://www.cdc.gov/hicpac/pdf/guidelines/disinfection_nov_2008.pdf.

150. G-Alegria, E., et al., "High Tolerance of Wild Lactobacillus plantarum and Oenococcus oeni Strains to Lyophilisation and Stress Environmental Conditions of Acid pH and Ethanol," FEMS Microbiology Letters, 230:53-61, 2004.

151. Cosmetic Ingredient Review, "Final Report on the Safety Assessment of Benzalkonium Chloride," Journal of the American College of Toxicology, 8:589-625, 1989.

152. U.S. Environmental Protection Agency, "Reregistration Eligibility Decision for Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC)," 2006.

153. Comment No. FDA-1975-N-0012-0166.

154. Bore, E., et al., "Adapted Tolerance to Benzalkonium Chloride in Escherichia coli K-12 Studied by Transcriptome and Proteome Analyses," Microbiology, 153:935-946, 2007.

155. Chuanchuen, R., et al., "Susceptibilities to Antimicrobials and Disinfectants in Salmonella Isolates Obtained From Poultry and Swine in Thailand," Journal of Veterinary Medical Science, 70:595-601, 2008.

156. Lear, J. C., et al., "Chloroxylenol- and Triclosan-Tolerant Bacteria From Industrial Sources--Susceptibility to Antibiotics and Other Biocides," International Biodeterioration and Biodegradation, 57:51-56, 2006.

157. "Annual Review of Cosmetic Ingredient Safety Assessments-2004/2005," International Journal of Toxicology, 25 Suppl 2:1-89, 2006.

158. Scientific Committee on Cosmetic Products and Non-Food Products, "Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) Intended for Consumers Concerning Benzethonium Chloride," 2002.

159. Scientific Committee on Cosmetic Products and Non-Food Products, "Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) Intended for Consumers Concerning Benzethonium Chloride," 2003.

160. Comment No. FDA-1975-N-0012-0134.

161. Comment No. FDA-1975-N-0012-0171.

162. Comment No. FDA-1975-N-0012-0150.

163. Comment No. FDA-1975-N-0012-0186.

164. Lambert, R. J., "Comparative Analysis of Antibiotic and Antimicrobial Biocide Susceptibility Data in Clinical Isolates of Methicillin-Sensitive Staphylococcus aureus, Methicillin-Resistant Staphylococcus aureus and Pseudomonas aeruginosa Between 1989 and 2000," Journal of Applied Microbiology, 97:699-711, 2004.

165. Nakahara, H., et al., "Benzethonium Chloride Resistance in Pseudomonas aeruginosa Isolated From Clinical Lesions," Zentralblatt fur Bakteriologie, Mikrobiologie und Hygiene A, 257:409-413, 1984.

166. Jordan, B. J., et al., "Human Volunteer Studies on Dettol Bathing Product," Docket No. 1975N-0183H, 1973.

167. Jordan, B. J., J. D. Nichols, and M. J. Rance, "Dettol Bathing Product-Preliminary Volunteer Study," Docket No. 1975N-0183H, 1973.

168. Havler, M. E. and M. J. Rance, "The Metabolism of p-Chloro-m-xylenol (PCMX) in Sprague Dawley and Gunn Wistar Rats," Docket No. 1975N-0183H.

169. Sved, D. W., "A Dermal Absorption Study With [14C]-Labeled PCMX in Mice," Docket No. 1975N-0183H.

170. "A 13-Week Dermal Toxicity Study in Mice," Comment No. FDA-1975-N-0012-0242.

171. "Teratology Study in Rats," Docket No. 1975N-0183.

172. Lear, J. C., et al., "Chloroxylenol- and Triclosan-Tolerant Bacteria From Industrial Sources," Journal of Industrial Microbiology and Biotechnology, 29:238-242, 2002.

173. OTC Volume No. 020080.

174. National Toxicology Program, "NTP: Toxicology and Carcinogenesis Studies of 4-Hexylresorcinol in F3441N Rats and B6C3F1 Mice, Technical Report Series, No. 330," 1988.

175. Robbin, B. H., "Quantitative Studies on the Absorption and Excretion of Hexylresorcinol and Heptylresorcinol Under Different Conditions," Journal of Pharmacology and Experimental Therapy, 43:325-333, 1931.

176. Robbin, B. H., "Quantitative Studies on the Absorption and Excretion of Certain Resorcinols and Cresols in Dogs and Man," Journal of Pharmacology, 52:54-60, 1934.

177. McDonnell, G. E., "Halogens and Halogen-Releasing Agents" in Antisepsis, Disinfection, and Sterilization--Types, Action, and Resistance, ASM Press, Washington DC, 102-111, 2007.

178. Agency for Toxic Substances and Disease Registry, "Toxicological Profile for Iodine," April 2004, available at http://www.atsdr.cdc.gov/toxprofiles/tp158.pdf.

179. International Programme on Chemical Safety, "Iodine and Inorganic Iodides: Human Health Aspects," Concise International Chemical Assessment Document 72, 2009.

180. Bos, J. D. and M. M. H. M. Meinardi, "The 500 Dalton Rule for the Skin Penetration of Chemical Compounds and Drugs," Experimental Dermatology, 9:165-169, 2000.

181. Brown, R. S., et al., "Routine Skin Cleansing With Povidone-Iodine Is Not a Common Cause of Transient Neonatal Hypothyroidism in North America: A Prospective Controlled Study," Thyroid, 7:395-400, 1997.

182. Connolly, R. J. and J. J. Shepherd, "The Effect of Preoperative Surgical Scrubbing With Povidone Iodine on Urinary Iodine Levels," Australian and New Zealand Journal of Surgery, 42:94-95, 1972.

183. Nobukuni, K., et al., "The Influence of Long-Term Treatment With Povidone-Iodine on Thyroid Function," Dermatology, 195 Suppl 2:69-72, 1997.

184. Hays, M. T., "Estimation of Total Body Iodine Content in Normal Young Men," Thyroid, 11:671-675, 2001.

185. Vandilla, M. A. and M. J. Fulwyler, "Thyroid Metabolism in Children and Adults Using Very Small (Nanocurie) Doses of Iodine and Iodine-131," Health Physics, 9:1325-1331, 1963.

186. Kanno, J., et al., "Tumor-Promoting Effects of Both Iodine Deficiency and Iodine Excess in the Rat Thyroid," Toxicologic Pathology, 20:226-235, 1992.

187. Takegawa, K., et al., "Induction of Squamous Cell Carcinomas in the Salivary Glands of Rats by Potassium Iodide," Japanese Journal of Cancer Research, 89:105-109, 1998.

188. Takegawa, K., et al., "Large Amount of Vitamin A Has No Major Effects on Thyroidal Hormone Synthesis in Two-Stage Rat Thyroid Carcinogenesis Model Using N-bis(2-hydroxypropyl)nitrosamine and Thiourea," Journal of Toxicological Sciences, 25:67-75, 2000.

189. Arrington, L. R., et al., "Effects of Excess Dietary Iodine Upon Rabbits, Hamsters, Rats and Swine," Journal of Nutrition, 87:394-398, 1965.

190. Coakley, J. C., et al., "Transient Primary Hypothyroidism in the Newborn: Experience of the Victorian Neonatal Thyroid Screening Programme," Australian Paediatric Journal, 25:25-30, 1989.

191. Danziger, Y., A. Pertzelan, and M. Mimouni, "Transient Congenital Hypothyroidism After Topical Iodine in Pregnancy and Lactation," Archives of Disease in Childhood, 62:295-296, 1987.

192. Delange, F., et al., "Topical Iodine, Breastfeeding, and Neonatal Hypothyroidism," Archives of Disease in Childhood, 63:106-107, 1988.

193. Linder, N., et al., "Topical Iodine-Containing Antiseptics and Subclinical Hypothyroidism in Preterm Infants," Journal of Pediatrics, 131:434-439, 1997.

194. Shoyinka, S. V., I. R. Obidike, and C. O. Ndumnego, "Effect of Iodine Supplementation on Thyroid and Testicular Morphology and Function in Euthyroid Rats," Veterinary Research Communications, 32:635-645, 2008.

195. Smerdely, P., et al., "Topical Iodine-Containing Antiseptics and Neonatal Hypothyroidism in Very-Low-Birthweight Infants," Lancet, 2:661-664, 1989.

196. Bongers-Schokking, J. J., et al., "Influence of Timing and Dose of Thyroid Hormone Replacement on Development in Infants With Congenital Hypothyroidism," Journal of Pediatrics, 136:292-297, 2000.

197. Calaciura, F., et al., "Childhood IQ Measurements in Infants With Transient Congenital Hypothyroidism," Clinical Endocrinology, 43:473-477, 1995.

198. Casteels, K., S. Punt, and J. Bramswig, "Transient Neonatal Hypothyroidism During Breastfeeding After Post-Natal Maternal Topical Iodine Treatment," European Journal of Pediatrics, 159:716-717, 2000.

199. Chanoine, J. P., et al., "Increased Recall Rate at Screening for Congenital Hypothyroidism in Breast Fed Infants Born to Iodine Overloaded Mothers," Archives of Disease in Childhood, 63:1207-1210, 1988.

200. Fisher, D. A., "The Importance of Early Management in Optimizing IQ in Infants With Congenital Hypothyroidism," Journal of Pediatrics, 136:273-274, 2000.

201. Jackson, H. J. and R. M. Sutherland, "Effect of Povidone-Iodine on Neonatal Thyroid Function," Lancet, 2:992, 1981.

202. Jeng, M. J., et al., "The Effect of Povidone-Iodine on Thyroid Function of Neonates With Different Birth Sizes," Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi, 39:371-375, 1998.

203. Koga, Y., et al., "Effect on Neonatal Thyroid Function of Povidone-Iodine Used on Mothers During Perinatal Period," Journal of Obstetrics and Gynaecology (Tokyo, Japan), 21:581-585, 1995.

204. Lyen, K. R., et al., "Transient Thyroid Suppression Associated With Topically Applied Povidone-Iodine," American Journal of Diseases of Children, 136:369-370, 1982.

205. Nobukuni, K. and S. Kawahara, "Thyroid Function in Nurses: The Influence of Povidone-Iodine Hand Washing and Gargling," Dermatology, 204 Suppl 1:99-102, 2002.

206. Perez-Lopez, F. R., "Iodine and Thyroid Hormones During Pregnancy and Postpartum," Gynecological Endocrinology, 23:414-428, 2007.

207. Turner, P., B. Saeed, and M. C. Kelsey, "Dermal Absorption of Isopropyl Alcohol From a Commercial Hand Rub: Implications for Its Use in Hand Decontamination," Journal of Hospital Infection, 56:287-290, 2004.

208. Below, H., et al., "Dermal and Pulmonary Absorption of Propan-1-ol and Propan-2-ol From Hand Rubs," American Journal of Infection Control, 40:250-257, 2012.

209. Puschel, K., "Percutaneous Alcohol Intoxication," European Journal of Pediatrics, 136:317-318, 1981.

210. Dhillon, S., "Toxicology Updates-Isopropanol," Journal of Applied Toxicology, 15:501-506, 1995.

211. International Programme on Chemical Safety, "2-Propanol," 1990, available at http://www.inchem.org/documents/ehc/ehc/ehc103.htm.

212. Boatman, R. J., et al., "Dermal Absorption and Pharmacokinetics of Isopropanol in the Male and Female F-344 Rat," Drug Metabolism and Disposition, 26:197-202, 1998.

213. Martinez, T. T., et al., "A Comparison of the Absorption and Metabolism of Isopropyl Alcohol by Oral, Dermal and Inhalation Routes," Veterinary and Human Toxicology, 28:233-236, 1986.

214. Slauter, R. W., et al., "Disposition and Pharmacokinetics of Isopropanol in F-344 Rats and B6C3F1 Mice," Fundamental and Applied Toxicology, 23:407-420, 1994.

215. Kapp, R. W., Jr., et al., "Isopropanol: Summary of TSCA Test Rule Studies and Relevance to Hazard Identification," Regulatory Toxicology and Pharmacology, 23:183-192, 1996.

216. WHO International Program on Chemical Safety Working Group, "2-Propanol," Environmental Health Criteria, 103:132, 1990.

217. Slaughter, R. J., et al., "Isopropanol Poisoning," Clinical Toxicology, 52:470-478, 2014.

218. WHO International Agency for Research on Cancer, "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Re-Evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide," 71 (part 3):1027-1036, 1999, available at http://monographs.iarc.fr/ENG/Monographs/vol71/mono71.pdf.

219. Burleigh-Flayer, H., et al., "Isopropanol Vapor Inhalation Oncogenicity Study in Fischer 344 Rats and CD-1 Mice," Fundamental and Applied Toxicology, 36:95-111, 1997.

220. Bates, H. K., et al., "Developmental Neurotoxicity Evaluation of Orally Administered Isopropanol in Rats," Fundamental and Applied Toxicology, 22:152-158, 1994.

221. Faber, W. D., K. L. Pavkov, and R. Gingell, "Review of Reproductive and Developmental Toxicity Studies With Isopropanol," Birth Defects Research Part B Developmental and Reproductive Toxicology, 83:459-476, 2008.

222. Lehman, A. J., H. Schwerma, and E. Rickards, "Isopropyl Alcohol: Acquired Tolerance in Dogs, Rate of Disappearance From the Blood Stream in Various Species, and Effects on Successive Generation of Rats," Journal of Pharmacology and Experimental Therapeutics, 85:61-69, 1945.

223. Nelson, B. K., et al., "Teratogenicity of n-Propanol and Isopropanol Administered at High Inhalation Concentrations to Rats," Food and Chemical Toxicology, 26:247-254, 1988.

224. Tyl, R. W., et al., "Developmental Toxicity Evaluation of Isopropanol by Gavage in Rats and Rabbits," Fundamental and Applied Toxicology, 22:139-151, 1994.

225. Bevan, C., et al., "Two Generation Reproductive Toxicity Study With Isopropanol in Rats," Journal of Applied Toxicology, 15:117-123, 1995.

226. Allen, B., et al., "Calculation of Benchmark Doses for Reproductive and Developmental Toxicity Observed After Exposure to Isopropanol," Regulatory Toxicology and Pharmacology, 28:38-44, 1998.

227. Gorkal, A. R. and A. Namasivayam, "Effect of Isopropanol on Rat Brain Monoamine Levels," Pharmacology and Toxicology, 65:390-392, 1989.

228. McEvoy, E. M., P. C. Wright, and M. T. Bustard, "The Effect of High Concentration Isopropanol on the Growth of a Solvent-Tolerant Strain of Chlorella vulgaris," Enzyme and Microbial Technology, 35:140-146, 2004.

229. Geng, Y., et al., "Biodegradation of Isopropanol by a Solvent-Tolerant Paracoccus denitrificans Strain," Preparative Biochemistry and Biotechnology, 45:491-499, 2015.

230. Bustard, M. T., et al., "Biodegradation of High-Concentration Isopropanol by a Solvent-Tolerant Thermophile, Bacillus pallidus," Extremophiles, 6:319-323, 2002.

231. Hiles, R. A. and C. G. Birch, "The Absorption, Excretion, and Biotransformation of 3,4,4'-Trichlorocarbanilide in Humans," Drug Metabolism and Disposition, 6:177-183, 1978.

232. Howes, D. and J. G. Black, "Percutaneous Absorption of Triclocarban in Rat and Man," Toxicology, 6:67-76, 1976.

233. Scharpf, L. G., Jr., I. D. Hill, and H. I. Maibach, "Percutaneous Penetration and Disposition of Triclocarban in Man. Body Showering," Archives of Environmental Health, 30:7-14, 1975.

234. Schebb, N. H., et al., "Whole Blood Is the Sample Matrix of Choice for Monitoring Systemic Triclocarban Levels," Chemosphere, 2012.

235. Schebb, N. H., et al., "Investigation of Human Exposure to Triclocarban After Showering and Preliminary Evaluation of Its Biological Effects," Environmental Science and Technology, 45:3109-3115, 2011.

236. Birch, C. G., et al., "Biotransformation Products of 3,4,4'-Trichlorocarbanilide in Rat, Monkey, and Man," Drug Metabolism and Disposition, 6:169-176, 1978.

237. Gruenke, L. D., et al., "A Selected Ion Monitoring GC/MS Assay for 3,4,4'-Trichlorocarbanilide and Its Metabolites in Biological Fluids," Journal of Analytical Toxicology, 11:75-80, 1987.

238. Hiles, R. A. and C. G. Birch, "Nonlinear Metabolism and Disposition of 3,4,4'-Trichlorocarbanilide in the Rat," Toxicology and Applied Pharmacology, 46:323-337, 1978.

239. Hiles, R. A., et al., "The Metabolism and Disposition of 3,4,4'-Trichlorocarbanilide in the Intact and Bile Duct-Cannulated Adult and in the Newborn Rhesus Monkey (M. mulatta)," Toxicology and Applied Pharmacology, 46:593-608, 1978.

240. Warren, J. T., R. Allen, and D. E. Carter, "Identification of the Metabolites of Trichlorocarbanilide in the Rat," Drug Metabolism and Disposition, 6:38-44, 1978.

241. Comment No. SUP41, Docket No. 1975N-0183.

242. Comment No. CP4, Docket No. 1975N-0183.

243. Beiswanger, B. B. and M. A. Tuohy, "Analysis of Blood Plasma Samples for Free Triclosan, Triclosan-Glucuronide, Triclosan Sulfate and Total Triclosan From Subjects Using a Triclosan Dentrifice or a Dentrifice, Bar Soap and Deodorant," Comment No. FDA-1975-N-0012-0288.

244. Plezia, P., "A Pilot Study for In Vivo Evaluation of the Percutaneous Absorption of Triclosan," Comment No. FDA-1975-N-0012-0196.

245. Queckenberg, C., et al., "Absorption, Pharmacokinetics, and Safety of Triclosan After Dermal Administration," Antimicrobial Agents and Chemotherapy, 54:570-572, 2010.

246. Allmyr, M., et al., "Human Exposure to Triclosan Via Toothpaste Does Not Change CYP3A4 Activity or Plasma Concentrations of Thyroid Hormones," Basic and Clinical Pharmacology and Toxicology, 2009.

247. Lin, Y. J., "Buccal Absorption of Triclosan Following Topical Mouthrinse Application," American Journal of Dentistry, 13:215-217, 2000.

248. Moss, T., D. Howes, and F. M. Williams, "Percutaneous Penetration and Dermal Metabolism of Triclosan (2,4, 4'-trichloro-2'-hydroxydiphenyl ether)," Food and Chemical Toxicology, 38:361-370, 2000.

249. Sandborgh-Englund, G., et al., "Pharmacokinetics of Triclosan Following Oral Ingestion in Humans," Journal of Toxicology and Environmental Health, Part A, 69:1861-1873, 2006.

250. Tulp, M. T., et al., "Metabolism of Chlorodiphenyl Ethers and Irgasan DP 300," Xenobiotica, 9:65-77, 1979.

251. Van Dijk, A., "14C-Triclosan: Absorption, Distribution, Metabolism, and Elimination After Single/Repeated Oral and Intravenous Administration to Hamsters," Comment No. FDA-1975-N-0012-0288.

252. Van Dijk, A., "14C-Triclosan: Absorption, Distribution, Metabolism, and Elimination After Single/Repeated Oral and Intravenous Administration to Mice," Comment No. FDA-1975-N-0012-0288.

253. Wu, J. L., J. Liu, and Z. Cai, "Determination of Triclosan Metabolites by Using In-Source Fragmentation From High-Performance Liquid Chromatography/Negative Atmospheric

Pressure Chemical Ionization Ion Trap Mass Spectrometry," Rapid Communications in Mass Spectrometry, 24:1828-1834, 2010.

254. Burns, J. M., et al., "14-Day Repeated Dose Dermal Study of Triclosan in Rats (CHV 6718-102)," Comment No. CP9, Docket No. 1975N-0183H, 1997.

255. Burns, J. M., et al., "14-Day Repeated Dose Dermal Study of Triclosan in Mice (CHV 6718-101)," Comment No. CP9, Docket No. 1975N-0183H, 1997.

256. Burns, J. M., et al., "14-Day Repeated Dose Dermal Study of Triclosan in CD-1 Mice (CHV 2763-100)," Comment No. CP9, Docket No. 1975N-0183H, 1997.

257. Trimmer, G. W., "90-Day Subchronic Dermal Toxicity Study in the Rat With Satellite Group With Irgasan DP 300 (MRD-92-399)," Comment No. C1, Docket No. 1975N-0183H, 1994.

258. Chambers, P. R., "FAT 80'023/S Potential Tumorigenic and Chronic Toxicity Effects in Prolonged Dietary Administration to Hamsters," Comment No. PR5, Docket No. 1975N-0183H, 1999.

259. Chasseaud, L. F., et al., "Toxicokinetics of FAT 80'023/S After Prolonged Dietary Administration to Hamsters," Comment No. PR5, Docket No. 1975N-0183H, 1999.

260. Comment No. FDA-1975-N-0012-0288.

261. Morseth, S. L., "Two-Generation Reproduction Study in Rats FAT 80'023 (HLA Study No. 2386-100)," Comment No. RPT7, Docket No. 1975N-0183, 1988.

262. James, M. O., et al., "Triclosan Is a Potent Inhibitor of Estradiol and Estrone Sulfonation in Sheep Placenta," Environment International, 2009.

263. Cookson, B., "Clinical Significance of Emergence of Bacterial Antimicrobial Resistance in the Hospital Environment," Journal of Applied Microbiology, 99:989-996, 2005.

264. MacIsaac, J. K., et al., "Health Care Worker Exposures to the Antibacterial Agent Triclosan," Journal of Occupational and Environmental Medicine, 56:834-839, 2014.

265. Yueh, M. F., et al., "The Commonly Used Antimicrobial Additive Triclosan Is a Liver Tumor Promoter," Proceedings of the National Academy of Sciences of the USA, 111:17200-17205, 2014.

266. Cherednichenko, G., et al., "Triclosan Impairs Excitation-Contraction Coupling and Ca2+ Dynamics in Striated Muscle," Proceedings of the National Academy of Sciences of the USA, 109:14158-14163, 2012.

267. Fritsch, E. B., et al., "Triclosan Impairs Swimming Behavior and Alters Expression of Excitation-Contraction Coupling Proteins in Fathead Minnow (Pimephales promelas)," Environmental Science and Technology, 47:2008-2017, 2013.

268. Axelstad, M., et al., "Triclosan Exposure Reduces Thyroxine Levels in Pregnant and Lactating Rat Dams and in Directly Exposed Offspring," Food and Chemical Toxicology, 59:534-540, 2013.

269. Lan, Z., et al., "Triclosan Exhibits a Tendency to Accumulate in the Epididymis and Shows Sperm Toxicity in Male Sprague-Dawley Rats," Environmental Toxicology, 2013.

270. Fernando, D. M., et al., "Triclosan Can Select for an AdeIJK-Overexpressing Mutant of Acinetobacter baumannii ATCC 17978 That Displays Reduced Susceptibility to Multiple Antibiotics," Antimicrobial Agents and Chemotherapy, 58:6424-6431, 2014.

271. Hernandez, A., et al., "The Binding of Triclosan to SmeT, the Repressor of the Multidrug Efflux Pump SmeDEF, Induces Antibiotic Resistance in Stenotrophomonas maltophilia," PLoS Pathogens, 7:e1002103, 2011.

272. Mavri, A. and S. S. Mozina, "Involvement of Efflux Mechanisms in Biocide Resistance of Campylobacter jejuni and Campylobacter coli," Journal of Medical Microbiology, 61:800-808, 2012.

273. Mavri, A. and S. Smole Mozina, "Development of Antimicrobial Resistance in Campylobacter jejuni and Campylobacter coli Adapted to Biocides," International Journal of Food Microbiology, 160:304-312, 2013.

274. Srinivasan, V. B. and G. Rajamohan, "KpnEF, A New Member of the Klebsiella pneumoniae Cell Envelope Stress Response Regulon, Is an SMR-Type Efflux Pump Involved in Broad-Spectrum Antimicrobial Resistance," Antimicrobial Agents and Chemotherapy, 57:4449-4462, 2013.

275. McMurry, L. M., M. Oethinger, and S. B. Levy, "Triclosan Targets Lipid Synthesis," Nature, 394:531-532, 1998.

276. Zhang, Y. M., Y. J. Lu, and C. O. Rock, "The Reductase Steps of the Type II Fatty Acid Synthase as Antimicrobial Targets," Lipids, 39:1055-1060, 2004.

277. Saleh, S., et al., "Triclosan--An Update," Letters in Applied Microbiology, 52:87-95, 2011.

278. Nielsen, L. N., et al., "Staphylococcus aureus But Not Listeria monocytogenes Adapt to Triclosan and Adaptation Correlates With Increased fabI Expression and agr Deficiency," BMC Microbiology, 13:177, 2013.

279. Zhu, L., et al., "Triclosan Resistance of Pseudomonas aeruginosa PAO1 Is Due to FabV, a Triclosan-Resistant Enoyl-acyl Carrier Protein Reductase," Antimicrobial Agents and Chemotherapy, 54:689-698, 2010.

280. Zhu, L., et al., "The Two Functional Enoyl-acyl Carrier Protein Reductases of Enterococcus faecalis Do Not Mediate Triclosan Resistance," MBio, 4:e00613-13, 2013.

281. Skovgaard, S., et al., "Staphylococcus epidermidis Isolated in 1965 Are More Susceptible to Triclosan Than Current Isolates," PLoS One, 8:e62197, 2013.

282. D'Arezzo, S., et al., "High-level Tolerance to Triclosan May Play a Role in Pseudomonas aeruginosa Antibiotic Resistance in Immunocompromised Hosts: Evidence From Outbreak Investigation," BMC Research Notes, 5:43, 2012.

283. Lanini, S., et al., "Molecular Epidemiology of a Pseudomonas aeruginosa Hospital Outbreak Driven by a Contaminated Disinfectant-Soap Dispenser," PLoS One, 6:e17064, 2011.

284. Boyd, G. R., et al., "Pharmaceuticals and Personal Care Products (PPCPs) in Surface and Treated Waters of Louisiana, USA and Ontario, Canada," Science and the Total Environment, 311:135-149, 2003.

285. Halden, R. U. and D. H. Paull, "Co-Occurrence of Triclocarban and Triclosan in U.S. Water Resources," Environmental Science and Technology, 39:1420-1426, 2005.

286. Kinney, C. A., et al., "Bioaccumulation of Pharmaceuticals and Other Anthropogenic Waste Indicators in Earthworms From Agricultural Soil Amended With Biosolid or Swine Manure," Environmental Science and Technology, 42:1863-1870, 2008.

287. Singer, H., et al., "Triclosan: Occurrence and Fate of a Widely Used Biocide in the Aquatic Environment: Field Measurements in Wastewater Treatment Plants, Surface Waters, and Lake Sediments," Environmental Science and Technology, 36:4998-5004, 2002.

288. Ying, G. G., X. Y. Yu, and R. S. Kookana, "Biological Degradation of Triclocarban and Triclosan in a Soil Under Aerobic and Anaerobic Conditions and Comparison With Environmental Fate Modelling," Environmental Pollution, 150:300-305, 2007.

289. Pycke, B. F. G., et al., "Transformation Products and Human Metabolites of Triclocarban and Triclosan in Sewage Sludge Across the United States," Environmental Science and Technology, 48:7881-7890, 2014.

290. Centers for Disease Control and Prevention, "Alcohol and Public Health. Frequently Asked Questions," 2014, available at http://www.cdc.gov/alcohol/faqs.htm#standDrink.

291. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), "Research Strategy to Address the Knowledge Gaps on the Antimicrobial Resistance Effects of Biocides," 2010, available at http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_028.pdf.

292. National Institute on Alcohol Abuse and Alcoholism, "Fetal Alcohol Exposure," July 2013, available at http://pubs.niaaa.nih.gov/publications/FASDFactsheet/FASDfact.htm.

293. Little, P. J., M. L. Adams, and T. J. Cicero, "Effects of Alcohol on the Hypothalamic-Pituitary-Gonadal Axis in the Developing Male Rat," Journal of Pharmacology and Experimental Therapeutics, 263:1056-1061, 1992.

List of Subjects in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310, as proposed to be amended December 17, 2013, at 78 FR 76444, is proposed to be further 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, 379k-1; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.

2. Amend § 310.545 as follows:

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

b. Add paragraphs (a)(27)(vi) through (x);

c. In paragraph (d) introductory text, remove"(d)(39)" and in its place add "(d)(42)"; and

d. Add paragraph (d)(42).

The additions read as follows:

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

(a) * * *

(27) * * *

(v) [Reserved]

(vi) Health care personnel hand 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

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) ethanoliodine

Phenol

Poloxamer iodine complex

Povidone-iodine

Secondary amyltricresols

Sodium oxychlorosene

Tribromsalan

Triclocarban

Triclosan

Undecoylium chloride iodine complex

(vii) Health care personnel hand rub drug products. Approved as of [DATE 1 YEAR AFTER DATE OF PUBLICATION OF THE FINAL RULE IN THE FEDERAL REGISTER].

Alcohol (ethanol and ethyl alcohol)

Benzalkonium chloride

Isopropyl alcohol

(viii) Surgical hand scrub 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) ethanoliodine

Phenol

Poloxamer iodine complex

Povidone-iodine

Secondary amyltricresols

Sodium oxychlorosene

Tribromsalan

Triclocarban

Triclosan

Undecoylium chloride iodine complex

(ix) Surgical hand rub drug products. Approved as of [DATE 1 YEAR AFTER DATE OF PUBLICATION OF THE FINAL RULE IN THE FEDERAL REGISTER].

Alcohol (ethanol and ethyl alcohol)

Isopropyl alcohol

(x) Patient preoperative skin preparation drug products. Approved as of [DATE 1 YEAR AFTER DATE OF PUBLICATION OF THE FINAL RULE IN THE FEDERAL REGISTER].

Alcohol (ethanol and ethyl alcohol)

Benzalkonium chloride

Benzethonium chloride

Chloroxylenol

Cloflucarban

Fluorosalan

Hexachlorophene

Hexylresorcinol

Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)

Iodine tincture

Iodine topical solution

Isopropyl alcohol

Mercufenol chloride

Methylbenzethonium chloride

Nonylphenoxypoly (ethyleneoxy) ethanoliodine

Phenol

Poloxamer iodine complex

Povidone-iodine

Secondary amyltricresols

Sodium oxychlorosene

Tribromsalan

Triclocarban

Triclosan

Triple dye

Undecoylium chloride iodine complex

Combination of calomel, oxyquinoline benzoate, triethanolamine, and phenol derivative

Combination of mercufenol chloride and secondary amyltricresols in 50 percent alcohol

* * * * *

(d) * * *

(42) [DATE 1 YEAR AFTER DATE OF PUBLICATION OF THE FINAL RULE IN THE FEDERAL REGISTER], for products subject to paragraphs (a)(27)(vi) through (a)(27)(x) of this section.

Dated: April 27, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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