FDA Briefing Document for a Meeting of the Nonprescription Drugs Advisory Committee

Healthcare Antiseptic Ingredients

Topic:
Pre-market safety testing framework for over-the-counter healthcare antiseptic drugs

Meeting Date: September 3, 2014

Disclaimer Statement

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I. Division Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
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M E M O R A N D U M

Date: August 7, 2014

From: Healthcare Antiseptic Team
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To: Members of the Nonprescription Drugs Advisory Committee (NDAC), Consultants and Guests

Subject: Overview of the September 3, 2014, NDAC meeting on healthcare antiseptics

1 Introduction

Thank you for your participation in the Nonprescription Drugs Advisory Committee (NDAC) meeting to be held on September 3, 2014. As members of the Advisory Committee you provide important expert scientific advice and recommendations to the US Food and Drug Administration (FDA or the Agency) on the decision making process related to safety testing of over-the-counter (OTC) healthcare antiseptic ingredients.

We are seeking advice on a framework for evaluating the safety of healthcare antiseptic active ingredients. In addition, in this document we provide a description of the data that are currently available for the commonly used healthcare antiseptic ingredients. We will describe how the existing data fit within our proposed framework and would like you to consider the existing data in your discussion of the appropriate safety standards for these products.

2 Background

Topical antiseptics are intended for use in helping to reduce the risk of infection by killing or inhibiting the growth of microorganisms on the skin. These products can be divided into three broad categories based on the intended use: healthcare antiseptics, consumer antiseptics, and food handler antiseptics. Healthcare antiseptics are products intended for use by healthcare professionals in places like hospitals, clinics, doctor's offices, outpatient settings, and nursing homes. In general, they are fast acting, broad

spectrum, and persistent preparations that significantly reduce the number of microorganisms on intact skin. Healthcare antiseptic products consist of healthcare personnel handwashes, surgical hand scrubs, and patient preoperative skin preparations, which are described in Table 1. Consumer antiseptics are largely marketed as antibacterial soaps (both liquid and solid topical dosage forms), which are intended for handwashing and general body cleansing, and first aid antiseptics for use on minor cuts, scrapes, and burns. Food handler antiseptics are marketed for handwashing in a variety of food processing and handling establishments. Each of these categories also includes antiseptic products intended for use without water (leave-on products) that are marketed for hand hygiene and are called hand rubs or hand sanitizers. For the purposes of this NDAC meeting, we will be discussing only healthcare antiseptics.

Table 1 – Healthcare Antiseptic Categories

Category	Indicated Use(s)
Healthcare Personnel Handwash, Healthcare Personnel Hand Rub	Handwash to help reduce bacteria that potentially can cause disease -or- For handwashing to decrease bacteria on the skin
Surgical Hand Scrub, Surgical Hand Rub	Significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
Patient Preoperative Skin Preparation, Preinjection Skin Preparation	For preparation of the skin prior to surgery -or- Helps reduce bacteria that potentially can cause skin infection -or- For preparation of the skin prior to an injection

Healthcare antiseptics are different from most OTC drugs for a couple of reasons. First, these products typically are not used by the general population. Healthcare antiseptics are intended to be used in healthcare facilities by professional staff, who have various degrees of medical training and experience. Second, unlike many OTC drugs, these products do not relieve identifiable symptoms. Their intended use is to prevent infection in the patient, who is often not the user of the product. Consequently, we must consider the risk to the user of the product even when the benefit may be for someone else.

3 Overview of Healthcare Antiseptic Regulation

All categories of antiseptics used on humans are regulated as drugs by FDA. Healthcare antiseptics may be marketed under one of two processes:

- The New Drug Application (NDA) process for new drugs or ANDA (abbreviated new drug application) process for generic drugs as described in 21 CFR Part 314
- The OTC drug monograph process as described in 21 CFR Part 330
    - OTC Drug Review (ingredients on the market prior to 1972)
    - Time and Extent Application ("new" ingredients after 1972)

Table 2 compares features of the NDA (ANDA for generic drugs) and the monograph processes. It is followed by details of each regulatory process. Because no healthcare

antiseptic active ingredients are currently under consideration under the Time and Extent (TEA) process, we will not discuss that process further in this document.

Table 2 – OTC Drug Regulatory Pathways	
NDA/ANDA Process	Monograph Process
Product-specific (including formulation)	Ingredient- and category-specific regulations (CFR 330-358)
Confidential filing	Public process - No data confidentiality
Application submitted for pre-marketing approval	No FDA product-specific pre-market application or pre-approval
Mandated timelines	No mandated timelines
Application fees (PDUFA)	No user fees
Potential for marketing exclusivity	No potential for marketing exclusivity
Reporting requirements	Limited reporting requirements (serious adverse events only)
Comply with good manufacturing practices	Comply with good manufacturing practices

In the sections that follow, the most important differences to note are that, compared to the NDA process, under the OTC monograph system: (1) individual final products do not undergo pre-market FDA review and approval, (2) individual products are not subject to FDA review of formulation or manufacturing changes prior to implementing those changes (and FDA notification of such changes is not required), and (3) changes to the monograph to accommodate new ingredients or other conditions of use, scientific advances, new safety information, etc., require a lengthy "rulemaking" process, which we will describe.

The NDA Process

The NDA process requires a demonstration that a specific final formulation of a drug product is safe and effective for use as directed in its approved labeling, based on safety and effectiveness data contained in the NDA. FDA must review the NDA and approve the drug for marketing before the product can be sold legally in the U.S., and after initial approval most changes to the product's formulation, manufacturing process, or other approved specifications must also be reviewed and approved before they are introduced. There are currently more than 30 healthcare antiseptic products approved in the U.S. under the NDA process.

The Monograph Process

An OTC drug monograph is an FDA regulation that serves as a kind of "rule book" for formulating OTC products by specifying "conditions of use" under which a given category of products (such as antiseptics) are considered to be "generally recognized as safe and effective" (GRASE) and not misbranded. In contrast to the NDA process, individual OTC drug products regulated under the monograph process are not reviewed and approved by FDA; instead they must conform to the conditions of use established in an applicable OTC drug monograph as well as the requirements enumerated in 21 CFR part 330, and in other regulations, such as 21 CFR part 201. In addition to identifying acceptable active ingredients (and their allowed concentrations), GRASE conditions of

use established in a monograph include labeling and can include other features such as dosages, route of administration, and in some cases such as antiseptics, final formulation efficacy testing.[1]

The development of regulations to address categories of OTC drug products began in 1972, when FDA initiated a scientific review of the active ingredients that were in marketed OTC drug products to evaluate their safety and effectiveness. This review, called the OTC Drug Review or OTC Drug Monograph process, resulted in the establishment of OTC drug monographs for each therapeutic category. The OTC Drug Review was prompted by the need to implement a statutory amendment requiring drugs to be effective, not just safe. There were a large number of OTC drugs already on the market at that time (~800 active ingredients and 1,400 uses of over 100,000 products), and thus, FDA decided that a product-by-product determination would not be feasible. FDA determined that it would be more efficient to focus its review on the active ingredients used in each OTC therapeutic category.

The OTC Drug Review, as established by regulation, is a three-phase rulemaking process. Each phase requires publication in the *Federal Register* and allows for a comment response from the public. The process culminates in the promulgation of regulations (sometimes referred to as final monographs), establishing standards for both the active ingredients and labeling in each OTC therapeutic drug category. The three phases are as follows:

1. Advisory Panel Review and Advance Notice of Public Rulemaking (ANPR)
2. Tentative Final Monograph (TFM)
3. Final Monograph (FM)

The first phase of the OTC Drug Review was accomplished by FDA-appointed advisory review panels. Panel members included scientifically qualified individuals and non-voting, technical liaison members representing consumer and industry interests. These panels were charged with reviewing the ingredients and labeling of marketed OTC drug products to determine whether each could be classified as generally recognized as safe and effective (GRASE) for use in self-treatment.

The panels recommended classification of OTC drugs accordingly to three categories:

- Category I: generally recognized as safe and effective and not misbranded for the claimed indication
- Category II: not generally recognized as safe and effective or misbranded
- Category III: insufficient data available to permit classification as either Category I or II

The panels also recommended labeling (including therapeutic indications), dosage instructions, and warnings about side effects and potential misuse and abuse. Reports

[1] In addition to complying with the terms of an applicable monograph, OTC drugs marketed under the monograph process must also comply with drug registration and listing requirements, current good manufacturing practices, and other applicable labeling requirements.

submitted by the panels to FDA and panel-recommended monographs were published in the *Federal Register* as advance notices of proposed rulemaking (ANPR). Each publication invited public comment.

The second phase of the OTC Drug Review is FDA's evaluation of the panels' findings, consideration of public comment, and evaluation of any new data that may have become available. The Agency then publishes its tentative conclusions as a proposed rule (tentative final monograph – TFM). This document establishes for public comment FDA's initial position on the related scientific issues, and the proposed provisions of the monographs. After the TFM is published, a period of time is allotted for submission of supporting statements, objections, requests for a public hearing, and new data.

In the third phase, after considering the public comments and submissions and processing requests for a hearing, the Agency issues a final rule, usually in the form of a final monograph (FM). Each FM is included in the Code of Federal Regulations (CFR). Other final regulations are developed when the existing data are insufficient to establish a monograph category or to support certain active ingredients within a category. These regulations define ingredients that cannot lawfully be marketed without an approved NDA, or claims that are unacceptable in labeling without an approved NDA.

Regulatory History of the Antiseptic Monograph

The OTC topical antiseptic rulemaking has had a broad scope, encompassing drug products that may contain certain active ingredients, which are labeled and marketed for different users. In 1974, FDA published the conclusions of the Antimicrobial I Panel as an ANPR for topical antiseptic products that encompassed products for both healthcare and consumer use (39 FR 33103, September 13, 1974). The ANPR covered seven different uses of these products: 3 for healthcare uses (healthcare personnel handwashes, surgical hand scrubs, and patient preoperative skin preparations) and 4 for consumer uses (antimicrobial soaps, skin antiseptics, skin wound cleansers, and skin wound protectants).

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." FDA published a separate TFM covering the first aid antiseptics in the *Federal Register* of July 22, 1991 (56 FR 33644). The use of antiseptics for first aid is not the subject of this meeting.

The four remaining categories of topical antiseptics were addressed in an amended TFM, published on June 17, 1994 (59 FR 31402).[2] This TFM covered: (1) antiseptic handwashes (i.e., consumer antiseptic handwashes); (2) healthcare personnel handwashes; (3) surgical hand scrubs; and (4) patient preoperative skin preparations. While leave-on healthcare antiseptics were discussed in the 1994 TFM, specific statements of identity were not defined for these products at that time. We now distinguish between the leave-on and rinse-off products. Leave-on healthcare personnel handwashes are called healthcare personnel hand rubs and leave-on surgical hand scrubs are called surgical hand rubs.

[2] FDA also identified a new category of antiseptics for use by the food industry and requested relevant data and information in this document.

On December 17, 2013, FDA published an amended TFM covering consumer antiseptic hand and body washes (but did not include consumer hand rubs) (78 FR 76444). In the 2013 TFM, FDA proposed standards for demonstrating the general recognition of safety and effectiveness for antiseptics for general consumer use. The proposed standards for demonstrating safety and effectiveness included assessing both hormonal effects and the potential for the development of antimicrobial resistance.

As shown in Table 1, the following antiseptic uses are the subject of this meeting: healthcare personnel handwashes and rubs, surgical hand scrubs and rubs, and patient preoperative and preinjection skin preparations.

Status of Antiseptic Active Ingredients

As described above, prior to the publication of a final monograph, FDA uses the terms "Category I" (GRASE), "Category II" (not GRASE), and "Category III" (available data are insufficient to classify) to describe the status of active ingredients. By regulation, the results of any testing or other data necessary to resolve the safety or effectiveness issues that resulted in a Category III classification must be submitted to FDA during the OTC drug rulemaking process before the establishment of a final monograph.[3]

The healthcare antiseptic rulemaking covers 29 active ingredients and ingredient combinations (see **Appendix A**). The majority of these ingredients have been proposed as Category III – more data needed. In the 1994 TFM, seven of the active ingredients were proposed as Category II (not GRASE) and only five active ingredients were proposed as Category I (GRASE) for some or all healthcare antiseptic uses (see Table 3).

Table 3 – Healthcare Antiseptic Ingredients Proposed as Category I

Antiseptic Active Ingredient	Healthcare Personnel Hand Wash	Surgical Hand Scrub	Patient Preoperative Skin Preparation
Alcohol (ethanol), 60-95%	I	I	I
Isopropyl alcohol, 70-91.3%	IIIE*	IIIE*	I
Povidone-iodine, 5-10%	I	I	I
Iodine Tincture	NA**	NA**	I
Iodine Aqueous Solution	NA**	NA**	I

* IIIE indicates the ingredient is proposed as GRAS, but is lacking sufficient effectiveness data
** Not applicable because ingredient was not evaluated for this use

In addition to safety data that were already available for the Category I ingredients listed in Table 3, some safety data have been submitted to the healthcare antiseptic rulemaking for the following active ingredients:

- Benzalkonium chloride
- Benzethonium chloride
- Chloroxylenol
- Hexylresorcinol

[3] 21 CFR 330.10(a)(10)

- Triclocarban
- Triclosan

We would like you to consider the available data in your discussion of the appropriate safety standards for healthcare antiseptic products. A summary of the safety data in the administrative record for each of the ingredients listed in this section can be found in **Appendix B**. A full list of active ingredients covered by the healthcare antiseptic rulemaking can be found in **Appendix A**.

4. Overview of Safety Data Considerations for Healthcare Antiseptics

FDA is seeking general advice about the type and scope of safety data needed to determine that a healthcare antiseptic active ingredient is generally recognized as safe (GRAS) as part of the overall determination of GRASE status. The discussion that follows summarizes the applicable safety standard and describes FDA's current thinking, with regards to both general considerations for healthcare antiseptic safety evaluation and how the proposed standards would be applied to the existing available safety data for several common healthcare antiseptic ingredients.

a. General considerations

In evaluating the safety of a proposed monograph active ingredient, FDA applies the following regulatory standard:[4]

- Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability.
- Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing.
- General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

Many of the studies we propose are needed to support a GRAS determination for an OTC antiseptic active ingredient are similar to those recommended by the Antimicrobial I Panel (described in the ANPR (39 FR 33103 at 33135)). The Panel's recommendations for data to support the safety of an OTC topical antiseptic 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

[4] 21 CFR 330.10(a)(4)(i).

In the 1994 TFM, FDA continued to propose many ingredients as Category III due to a lack of data of the type requested by the Panel, such as chronic toxicity data, animal absorption, distribution, metabolism, and excretion (ADME) data, and dermal carcinogenicity data (e.g., 59 FR 31402 at 31413, 31415, and 31427). Since the publication of the 1994 TFM, however, there have been a number of important scientific developments affecting FDA's evaluation of the safety of healthcare antiseptic active ingredients and the data necessary to support a GRAS determination.

Since the 1994 TFM was published, new data have become available indicating that systemic exposure to topical antiseptic active ingredients may be more than previously thought. In addition, due to advances in technology, our ability to detect antiseptic active ingredients in body fluids such as serum and urine is greater. For example, studies have shown detectable blood alcohol levels after use of alcohol-containing healthcare personnel hand rubs or surgical hand rubs (Refs. 1-5). Other studies have shown that triclosan is absorbed through the skin and has been found in both human breast milk and urine (Refs. 6-7). While some systemic exposure data exist for these ingredients, many of the other healthcare 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.

Because healthcare antiseptics typically are chronic use products and often are used by pregnant women, FDA believes that an evaluation of the potential for chronic toxicity and effects on reproduction and development also should be included in the safety assessment. One potential effect of systemic exposure to antiseptic ingredients that has come to FDA's attention since publication of the 1994 TFM is data suggesting that some healthcare antiseptic active ingredients have hormonal effects. Triclosan and triclocarban can cause alterations in the thyroid and reproductive systems of neonatal and adolescent animals (see **Appendix B8** and **B9**). 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.

Also, since publication of the 1994 TFM, there is new information raising concerns about the impact of widespread antiseptic use on the development of antimicrobial resistance (Refs. 8-11). Bacteria use some of the same resistance mechanisms against both antiseptics and antibiotics. Thus, the use of antiseptic active ingredients with resistance mechanisms in common with antibiotics may have the potential to select for bacterial strains that are also resistant to clinically important antibiotics, adding to the problem of antibiotic resistance. Laboratory studies show that several of the antiseptic active ingredients 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) (see **Appendix B2**, **B3**, **B4**, and **B9**). These studies provide ample evidence of bacterial resistance mechanisms that could select for antiseptic or antibiotic resistance in the natural setting. The available data are not sufficient to support a finding that these mechanisms would not have meaningful clinical impact. Given the increasing evidence about the magnitude of the antibiotic resistance problem and the

speed with which new antibiotic resistant organisms are emerging, FDA believes it is important to assess this potential consequence of healthcare antiseptic use (Ref. 12).

In order to consider the issues related to promulgating a final monograph for healthcare antiseptic products, FDA needs to evaluate safety data made available in the administrative record (i.e., rulemaking docket). FDA has summarized the safety data that are currently available in the docket and in the published literature for each active ingredient in **Appendix B**.

b. FDA's current thinking on pre-market safety testing of healthcare antiseptics

The safety data requirements we are proposing are the minimum data FDA believes necessary to establish the safety of long-term, daily, repeated exposure to healthcare antiseptic active ingredients. The data we propose are needed to demonstrate safety for all healthcare antiseptic active ingredients fall into four broad categories: (1) human safety studies (e.g., human pharmacokinetic studies); (2) nonclinical studies described in current FDA guidance (e.g., animal ADME, developmental and reproductive toxicity studies, and carcinogenicity studies); (3) data to characterize potential hormonal effects; and, (4) data to evaluate the development of resistance.

1. Human safety studies

Because healthcare antiseptics are topically applied, FDA considers an important safety consideration to be whether dermal application results in skin penetration and systemic exposure to the active ingredient and, if so, to what extent. The available data indicate that some antiseptic active ingredients are absorbed after topical application in humans and animals; therefore, it is necessary to assess the effects of long-term dermal and systemic exposure to these ingredients. FDA also believes it is important that the human pharmacokinetic studies reflect maximal use conditions of healthcare antiseptics using different formulations to fully characterize the active ingredient's potential for dermal penetration. Once an active ingredient is included in a monograph it can be combined with a broad array of inactive ingredients and, in the case of combinations, with certain other active ingredients. The resulting final formulations are often not tested for safety. Furthermore, the addition of certain ingredients to a formulation may increase the absorption of the active ingredient above what it was when tested for inclusion in the monograph.

Many methods for the assessment of topical or dermal *in vivo* bioavailability have been proposed and presented at a number of scientific forums. Most of these methods, however, focus on either a small assessment area or a limited duration of exposure. Since the mid-1990s, FDA has required sponsors to conduct a Maximal Usage Trial (MUsT) as part of the clinical pharmacology/bioavailability assessment of a topical product NDA (Ref. 13). This study is conducted in subjects with the disease of interest applied at the upper limit of surface area involvement that is studied in the Phase 3 clinical trials and is proposed for labeling. That is to say, if an NDA sponsor desires labeling of up to 30% body surface area, then the MUsT is conducted in subjects with this same degree of body surface coverage. The study is thus designed to capture the effect of "maximal use" on

absorption into the blood with standard pharmacokinetic assessments (Cmax, Tmax, AUC, half-life, clearance, and volume of distribution).

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

2. Nonclinical (animal) studies

NDA products intended for chronic topical use generally undergo a comprehensive nonclinical testing program. NDA nonclinical safety studies that are described in the existing FDA guidances provide a framework for the types of studies that are recommended for FDA to assess the safety of each antiseptic active ingredient and make a GRAS determination. A description of each type of study and how FDA would use this information to determine safety is provided in Table 4.

Table 4 – Rationale for Animal Safety Studies

Type of Study	Proposed Study Conditions	What the Data Tell Us	How the Data Are Used
Animal pharmacokinetic absorption, distribution, metabolism, and excretion (ADME), including toxicokinetics (Refs. 14-16)	Both oral and dermal administration	Allows identification of the dose at which the toxic effects of an active ingredient are observed due to systemic exposure of the drug. ADME data provide: The rate and extent an active ingredient is absorbed into the body (e.g., AUC, 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	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.

Table 4 – Rationale for Animal Safety Studies			
Type of Study	Proposed Study Conditions	What the Data Tell Us	How the Data Are Used
		metabolites (e.g., T½)[2]	
Carcinogenicity (ICH S1A and S1B) (Refs. 17-18)	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 of toxicity, the level of exposure that produces this toxicity, and the highest level of exposure at which no adverse effects occur, referred to as the "no observed adverse effect level" (NOAEL). The NOAEL is used to determine a safety margin for human exposure.
Developmental toxicity (ICH S5) (Ref. 19)	Oral administration	Evaluates the effects of a drug on the developing offspring throughout gestation and postnatally until sexual maturation	
Reproductive toxicity (ICH S5) (Ref. 19)	Oral administration	Assesses the effects of a drug on the reproductive competence and fertility of sexually mature male and female animals	

[1] "AUC" denotes the area under the concentration-time curve, a measure of total exposure or the extent of absorption. "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%.

Animal ADME, including toxicokinetics

Animal pharmacokinetic absorption, distribution, metabolism, and excretion (ADME) data are used to identify toxic systemic exposure levels that can then be correlated to potential human exposure. The primary objective of toxicokinetics is to describe the systemic exposure achieved in animals and to relate the exposure achieved in toxicity studies to toxicological findings, thus contributing to the assessment of the relevance of these findings to clinical safety (Ref. 14). The toxicokinetic data obtained in animal studies are compared to clinical study data (such as from the MUsT) to obtain a safety margin of drug exposure which is used to project human safe levels. FDA currently recommends conducting animal toxicokinetic studies for antiseptic active ingredients because they provide an important bridge between toxic levels seen in animal studies (such as reproductive, genotoxicity, and carcinogenicity studies) and any potential human adverse events associated with dermal exposure. Toxicokinetic measurements are usually obtained during the course of ongoing nonclinical toxicity studies, such as carcinogenicity or developmental and reproductive toxicity studies.

Carcinogenicity studies: dermal and systemic
Consistent with the recommendations in ICH S1A[5], FDA generally requires carcinogenicity studies for any pharmaceutical whose expected clinical use is continuous for at least 6 months or when used for a minimum of six months in an intermittent manner. Healthcare antiseptics fall within these criteria. These studies assist in characterizing the potential dermal and systemic tumor risks associated with an active ingredient by identifying any observed tumors by type, the level of exposure at which tumors occur, and the highest level of exposure at which no adverse effects occur, referred to as the "no observed adverse effect level" (NOAEL). The NOAEL can then be used in the determination of the safety margin for human exposure to antiseptics containing the active ingredient. Systemic carcinogenicity studies in animals can also help to identify other systemic or organ toxicities that may be associated with the proposed ingredient.

For any chronically applied topical product, the NDA generally includes a dermal carcinogenicity evaluation that involves applying the drug to the skin of mice or rats for 2 years (i.e., lifetime exposure). If systemic absorption of the drug in the to-be-marketed product formulation occurs in humans, then a second carcinogenicity study by a route that produces systemic exposure generally is also required. This study may be a 2-year study or a shorter (usually 6 month) alternative model and is conducted in a species different from that used in the first topical exposure study. The alternative models are all mouse models.

Developmental and reproductive toxicity (DART) studies
FDA now recommends DART studies to evaluate the potential effects that exposure to the ingredient may have on developing offspring throughout gestation and postnatally until sexual maturation, as well as on the reproductive competence of sexually mature male and female animals (Ref. 19). Gestational and neonatal stages of development may also be particularly sensitive to active ingredients with hormonal activity (endocrine disruption). For this reason, we currently recommend that such studies include assessments of endpoints such as vaginal patency, preputial separation, anogenital distance, and nipple retention, which can be incorporated into traditional DART study designs to assess potential hormonal effects on the developing offspring. We also recommend performing behavioral assessments (e.g., mating behavior) of offspring, which may detect neuroendocrine effects.

3. Studies to characterize hormonal effects

The designs of general toxicity and DART studies can often be sufficient to identify developmental effects that can be caused by hormonally active compounds through the use of currently accepted endpoints and standard toxicology study designs. However, if a positive response is seen in any of the toxicity or DART studies and this response is not adequately understood, then additional studies may be needed to fully characterize the potential effects of drug exposure on the exposed individuals (Ref. 20). The additional studies could include juvenile animal, pubertal animal, or multigeneration studies, which

[5] International Conference on Harmonisation, "ICH Harmonised Tripartite Guideline: Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals S1A," 1995.

are designed to evaluate hormonal effects in developmental stages that supplement the information obtained from traditional DART studies.

Some antiseptic active ingredients, namely triclosan and triclocarban, have shown hormonal effects in animal models (see **Appendix B8** and **B9**), but most antiseptic active ingredients have not been evaluated for these effects despite the fact that several of the ingredients have evidence of systemic absorption. In those cases where adverse effects are noted on the developing offspring due to a disturbance of any of the organ systems, FDA believes that a risk-benefit analysis should be conducted based on the dose-response observed for the findings and the animal-to-human exposure comparison. If FDA's assessment indicates a potentially significant risk, then the antiseptic active ingredient with such findings would not be eligible to be considered for inclusion in the OTC monograph. Consequently, antiseptic active ingredients that may present a significant risk due to their use under the conditions of the monograph would require an NDA approval prior to marketing so that a risk-benefit assessment can be performed for the particular formulation.

4. Studies to evaluate the development of antimicrobial resistance

Since the 1994 TFM published, the issue of antiseptic resistance and the potential for antibiotic cross-resistance has been the subject of much study and scrutiny. In particular, triclosan has been shown to cause changes in bacterial efflux activity at nonlethal concentrations (see **Appendix B9**). Efflux pumps are an important nonspecific bacterial defense mechanism that can confer resistance to a number of substances toxic to the cell, including antibiotics.

Because of the frequent use of healthcare antiseptic products, it is necessary to assess this safety issue prior to classifying an antiseptic active ingredient as GRAS. Therefore, in addition to the clinical and nonclinical data requirements, FDA proposes that data are also needed to clarify the effect of antiseptic active ingredients on the emergence of bacterial resistance.

FDA considers laboratory studies to be a feasible first step in evaluating the impact of exposure to nonlethal amounts of antiseptic active ingredients on antiseptic and antibiotic bacterial susceptibilities. Several of the healthcare antiseptic active ingredients have laboratory data demonstrating the development of reduced susceptibility to antiseptics and antibiotics after exposure to nonlethal concentrations. However, the testing conducted thus far has been limited largely to human bacterial pathogens. Only limited data exist on the effects of antiseptic exposure on the bacteria that are predominant in the oral cavity, gut, skin flora, and the environment. These organisms represent pools of resistance determinants that are potentially transferable to human pathogens (Refs. 21-22). Broader laboratory testing would help to more clearly define the scope of the impact of antiseptic active ingredients on the development of resistance and provide a useful preliminary assessment of an antiseptic active ingredient's potential to foster the development of resistance.

In those cases where development of resistance data show that changes in bacterial susceptibilities are likely to occur in the healthcare setting, an analysis of the risk in relation to the effectiveness shown for the active ingredient would be conducted. Based

on this evaluation, a determination would be made as to whether the antiseptic active ingredient would be eligible to be considered for inclusion in an OTC monograph.

c. Considerations for special populations

Healthcare antiseptics are used by more than just patients. They are more frequently used by healthcare personnel, a group which includes women of childbearing potential. Some of the healthcare antiseptic active ingredients, such as alcohol and iodine, have been shown to have hormonal effects in humans (see **Appendix B1** and **B6**). Consequently, FDA has considered the impact of using healthcare antiseptics on pregnant and breastfeeding women and their babies. Based on current information, FDA is concerned about frequent, topical use of some healthcare antiseptic active ingredients by pregnant and breastfeeding healthcare personnel. Input from the panel is requested to help inform recommendations regarding repetitive use of healthcare antiseptics that contain alcohol or iodine in pregnant and breastfeeding women.

d. Summary of existing data using the proposed safety framework

Using the safety framework provided in this document and the data available in the administrative record for each healthcare antiseptic active ingredient, we have summarized our assessment of the ingredients in Table 5. The black boxes indicate areas where sufficient data exist based on our proposed standards. Boxes labeled "Some" indicate areas where some data exist, but the data are not adequate. Empty boxes indicate areas where safety data is lacking.

Table 5 – Summary of Data using Proposed Framework

	Human Absorption	Animal ADME	Oral Carc.	Dermal Carc.	DART	Hormonal Effects	Bacterial Resistance
Alcohol	Some	Some					
BKC*							Some
BZC*		Some			Some		Some
Chloro-xylenol**	Some	Some			Some		Some
Hexyl-resorcinol		Some					
Iodine, aqueous	Some						
Iodine, tincture	Some						
Povidone-iodine	Some						
Isopropyl alcohol	Some	Some		Some		Some	
Triclo-carban	Some	Some				Some	
Triclosan	Some	Some				Some	Some

*BKC, benzalkonium chloride; BZC, benzethonium chloride
** Also called PCMX

In summary, none of the healthcare antiseptic active ingredients meet all the safety standards proposed here. The types of data that are most frequently lacking include human maximal exposure data, dermal carcinogenicity, and data on hormonal effects.

5. Overview of Effectiveness Considerations for Healthcare Antiseptics

We will briefly describe the effectiveness considerations for healthcare antiseptics; however, the topic of using surrogate endpoints to demonstrate the effectiveness of healthcare antiseptic products was discussed at a NDAC meeting on March 23, 2005. Because this issue was already discussed by NDAC, we are not going to revisit the topic of effectiveness standards during the current NDAC meeting.

Despite the use of extensive infection control measures, nosocomial infections continue to be a significant cause of morbidity and mortality. OTC healthcare antiseptics are considered an integral part of hospital infection control strategies. While the benefit of these products is a basic tenet of infection control, data from clinical trials demonstrating the impact of these products on infection rates are lacking. Isolating the contribution of antiseptics to infection control is difficult because these products are part of a multifaceted approach to infection prevention and is further complicated by numerous factors beyond hospital infection control measures, such as patient health status. It remains unclear whether clinical efficacy trials can be conducted that adequately control for the myriad of confounding factors. While direct evidence of the clinical benefit of OTC healthcare antiseptics is limited, the use of these products remains a standard of care.

It is challenging to regulate the OTC healthcare antiseptics without methods to directly assess their clinical effect. Thus, FDA designated surrogate endpoints, as provided by current regulation. The experience with early NDAs for chlorhexidine gluconate was translated into a series of test methods and performance criteria, as described in the 1994 TFM.[6] These test methods and performance criteria are used in the final formulation testing of GRASE active ingredients so that effectiveness is demonstrated for each healthcare antiseptic formulation. The test methods are based on the premise that bacterial reductions translate to a reduced potential for infection and that bacterial reduction can be adequately demonstrated using tests that simulate conditions of actual use for each healthcare antiseptic product category. There are no corresponding clinical data that demonstrate that bacterial reductions of the required magnitude produce a reduction in clinical infection rates. Despite limited information about the correlation between the effectiveness criteria based on clinical simulation (e.g., bacterial log reduction) studies and clinical benefit, the 2005 NDAC did not feel that sufficient evidence was presented to justify a recommendation that FDA lower the effectiveness standards proposed in the TFM for healthcare antiseptic products.

[6] 59 FR 31402 at 31444

6 Summary

The safety and effectiveness of specific healthcare antiseptic active ingredients is determined by FDA on the basis of a scientific evidence review. The focus of the upcoming advisory committee meeting is the scope of safety testing that should be conducted in order for FDA to determine that a specific healthcare antiseptic active ingredient can be generally recognized as safe. FDA believes that establishing a workable framework that encompasses evolving science is a pivotal step toward the goal shared by all stakeholders: safe and effective healthcare antiseptics that address the serious health consequences of nosocomial and surgical site infections.

II. Draft Topics for Advisory Committee Discussion

1. Discuss the proposed standards for assessing the safety of OTC monograph healthcare antiseptic active ingredients (i.e., maximal dermal absorption data, animal ADME, oral and dermal carcinogenicity, reproductive toxicology, hormonal effects, and antimicrobial resistance).

2. Do you believe that the proposed safety standards are appropriate to demonstrate that a healthcare antiseptic active ingredient is generally recognized as safe (GRAS)?

    a. If not, how do you think the safety standards should be modified?

3. Based on the safety data currently available in the healthcare antiseptic rulemaking for alcohol, isopropyl alcohol, and iodine, discuss whether these active ingredients continue to be considered GRAS for chronic, topical antiseptic use?

    a. If not, what further data should be obtained?

    b. Should additional information or warnings be provided on products containing these ingredients for women who are pregnant or breastfeeding?

    c. If additional warnings are needed, what should they be?

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IV. Appendices

A. List of active ingredients covered by the healthcare antiseptic rulemaking

B. Summary of safety data in the administrative record for individual active ingredients
   - B1 Alcohol (ethanol)
   - B2 Benzalkonium chloride
   - B3 Benzethonium chloride
   - B4 Chloroxylenol (PCMX)
   - B5 Hexylresorcinol
   - B6 Iodine and Iodophors
   - B7 Isopropyl alcohol
   - B8 Triclocarban
   - B9 Triclosan

APPENDIX A

Listing of Healthcare Antiseptic Active Ingredients and Classifications from the 1994 TFM

Active Ingredient	Healthcare personnel handwash	Surgical hand scrub	Patient preoperative skin preparation
Alcohol 60 to 95 percent	I[1]	I	I
Benzalkonium chloride	IIISE	IIISE	IIIE
Benzethonium chloride	IIISE	IIISE	IIIE
Chloroxylenol	IIISE	IIISE	IIIE
Cloflucarban	IIISE	II	II
Fluorosalan	II	II	II
Hexachlorophene	II	II	II
Hexylresorcinol	IIIE	IIIE	IIIE
Iodine Active Ingredients			
Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)	IIIE	IIIE	NA
Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)	IIIE	IIIE	IIIE
Iodine tincture U.S.P.	NA	NA	I
Iodine topical solution USP	NA	NA	I
Nonylphenoxypoly (ethyleneoxy) ethanoliodine	IIIE	IIIE	IIIE
Poloxamer-iodine complex	IIIE	IIIE	IIIE
Povidone-iodine 5 to 10 percent	I	I	I
Undecoylium chloride iodine complex	IIIE	IIIE	IIIE
Isopropyl alcohol 70-91.3 percent	IIIE	IIIE	I
Mercufenol chloride	NA	NA	IIIE
Methylbenzethonium chloride	IIISE	IIISE	IIIE
Phenol (less than 1.5 percent)	IIISE	IIISE	IIIE
Phenol (greater than 1.5 percent)	II	II	II
Secondary amyltricresols	IIIE	IIIE	IIISE
Sodium oxychlorosene	IIISE	IIISE	IIISE
Tribromsalan	II	II	II
Triclocarban	IIIE	IIIE	IIIE
Triclosan	IIISE	IIISE	IIIE
Combinations			
Calomel, oxyquinoline benzoate, triethanolamine, and phenol derivative	NA	NA	II
Mercufenol chloride and secondary amyltricresols in 50 percent alcohol	NA	NA	IIISE
Triple dye	NA	NA	II

[1] I = Category I (GRASE); II = Category II (not GRASE); III = Category III (insufficient data to classify as Category I or II); E=effectiveness; S=safety; NA=Not Applicable because not evaluated for this use

APPENDIX B1 – Safety Assessment of Alcohol (Ethanol)

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 alcohol absorption through human skin is much lower than absorption via the oral route.

Summary of alcohol safety data

Alcohol human pharmacokinetics 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 healthcare antiseptics. As described in this subsection, a variety of alcohol-based hand rub product formulations have been used in these studies, concluding that the dermal absorption of alcohol is relatively low. The available data are based on moderate hand rub use (7.5 to 40 hand rub applications per hour, studied for 30 to 240 minutes); maximal use data are not available. From available data on moderate use, the highest observed exposure was 1.5 g, the equivalent of 10% of an alcohol-containing drink (equivalent to approximately 14 g of alcohol (Ref. 33)).

The systemic exposure to alcohol-based hand rubs was investigated in a study where 5 male volunteers applied 5 milliliters (mL) of a 62% alcohol-containing hand rub to both hands and rubbed until dry (Ref. 1). The hand rub process was repeated 50 times over a period of 4 hours. For all participants, the blood alcohol concentrations immediately following the last hand rub application were less than 5 milligrams per deciliter (mg/dL), with 5 mg/dL being the alcohol detection limit of the assay. This study was prompted by a case report of a physician who tested the tolerability of a 62% alcohol-based hand rub (Ref. 2). That case report describes the result that after 25 product applications over the course of two hours, the blood alcohol level immediately following the final application was less than the detection limit of 5 mg/dL.

In another study, twenty healthcare workers rubbed their hands with a 70% alcohol-containing hand rub under “intensive clinical conditions” (Ref. 3). Subjects applied 1.2 to 1.5 mL of hand rub solution 30 times during a one-hour period on two separate days, which were separated by a one day wash-out period. Serum alcohol levels were assessed at 5 to 7 minutes post-exposure. Serum alcohol levels were detectable in only two subjects and the levels were very low (0.6 and 1.2 mg/dL).

The pharmacokinetics of alcohol was studied in a double-blind, randomized, three-way crossover study (Ref. 4). Fourteen healthy male volunteers applied 20 mL of 74.1% alcohol in aqueous solution, 10% isopropyl alcohol in aqueous solution, or a commercial product containing a combination of these two ingredients continuously for 10 minutes. Each solution was tested in crossover fashion separated by a 48-hour washout period. No significant differences in serum alcohol concentrations following the application of 74.1% alcohol solution or the combination product versus baseline were observed. The mean alcohol concentrations measured at 15 and 60 minutes following application of all three treatments ranged between the detection limit of the assay (0.5 mg/L) and 1.5 mg/L.

Alcohol absorption following healthcare personnel and surgical hand disinfection using three different alcohol-based hand rubs was also investigated (Ref. 5). Twelve volunteers applied three commercial hand rubs containing 95%, 85%, or 55% alcohol using either a healthcare personnel hand rub or surgical hand rub procedure. Each product use was separated from the others by a 7-day washout period. In the healthcare personnel hand rub experiment, subjects rubbed both hands for 30 seconds using 4 mL of product and performed a total of 20 rubs over a 30-minute period. Mean blood alcohol concentration-time profiles were calculated. Following hand rubbing, median blood alcohol concentrations increased gradually and peaked after 30 minutes for all three hand rub concentrations. The total doses of alcohol applied during the healthcare personnel hand rub procedure were 60 grams (g), 56.2 g, and 39.6 g for the 95%, 85%, and 55% alcohol-containing products, respectively. The highest median alcohol concentration observed was 20.95 mg/L, following application of the 95% alcohol product. The highest amount of alcohol absorbed during the healthcare personnel hand rub procedure was 1,365 milligrams (mg) (2.3% of the administered dose with the 95% alcohol product).

In the surgical hand rub experiment, 4 mL of product was applied to the hands and forearms with the aim of keeping hands and forearms covered for an application time of 3 minutes. This procedure was repeated every 5 minutes for a total of 10 times. Following surgical hand rubbing, the total doses of alcohol applied were 149.9 g, 140 g, and 99 g for the 95%, 85%, and 55% alcohol-based products, respectively. The highest median alcohol concentration observed was 30.10 mg/L, following application of the 85% product. The amount of alcohol absorbed was 1,542 mg, which corresponds to 1.1% of the administered dose of the 85% alcohol product. The limit of detection of the assay utilized in this study was 0.14 mg/mL and the LLOQ was 0.34 mg/mL.

Another study assessed the level of transdermal and pulmonary alcohol absorption among 86 healthcare workers under actual use conditions in a hospital (Ref. 6). Participants were given a bottle of 70% alcohol hand rub product of known weight and applied 3 mL to the hands and rubbed until dry (approximately 30 seconds) several times during a 4-hour work shift. The amount of hand rub used varied with profession and workplace. On average, the healthcare workers used 27.5 g of product over the 4-hour shift (range 1.23 to 59.84 g), which corresponds to approximately 9 hand rubs per shift.

Blood and urine samples were collected before the beginning of the shift and within 10 minutes of the last hand rub application, and the amount of alcohol in expired air was measured using a Breathalyzer. Alcohol was not detected in any urine samples, and in only one of 86 blood samples. A low level of alcohol (0.22 mg/L) was detected in the blood of a nurse who had used 7.9 g of alcohol-based hand rub during the shift. Approximately 2 minutes after the last hand rub application at the end of the shift, no alcohol could be detected in 67 percent (58 of 86) of the participants using a Breathalyzer. In the remaining 28 participants, the mean level of alcohol in the expired air was 0.076 mg/L; however, this value returned to zero in all participants within 15 minutes. Although the number of hand rub applications varied markedly among participants, overall the amount of alcohol detected after alcohol hand rub use was relatively low.

Alcohol ADME data. Some animal ADME data are available, but additional information regarding the distribution, metabolism, and excretion of alcohol in animals is still needed.

In mice, intraperitoneal injection of 4 g/kg alcohol on gestation day 7 produced a peak blood alcohol concentration of 5.46 ± 0.31 mg/ml (Ref. 7). Pregnant Hartley guinea pigs dosed orally with two doses of 1 g/kg alcohol with a 2-hour interval between the daily doses (2 g alcohol/kg/day) showed a mean blood alcohol concentration of 27.6 ± 3.0 millimolar (mM) one hour after the second alcohol dose on day 55 (Ref. 8). Four- to 25-month old female Fischer 344 rats dosed intraperitoneally with 4.0 g/kg alcohol had mean blood alcohol concentrations of 0.42-0.52%, 0.39-0.40%, and less than 0.0005% at 2.5, 6 and 16 hours after dosing, respectively (Ref. 9).

After absorption, alcohol is metabolized primarily in the liver by alcohol dehydrogenase to acetaldehyde, which is a possible human carcinogen (Ref. 10). Acetaldehyde, in turn, is rapidly metabolized to acetic acid by aldehyde dehydrogenase. Only one of the hand rub absorption studies determined acetaldehyde concentrations after intensive hand rub use. The highest median blood acetaldehyde concentrations were 0.5 mg/L, 0.5 mg/L, and 0.6 mg/L for 95%, 85%, and 55% alcohol hand rubs, respectively (Ref. 5).

Alcohol carcinogenicity data. The available evidence indicates that when orally administered, alcohol is a carcinogen in both humans and animals. The carcinogenicity of alcohol has been studied by the dermal and oral routes of administration in animals. In humans, carcinogenicity data on alcohol are available from the oral route of administration. Chronic dermal application of alcohol does not appear to be carcinogenic in animals.

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. 11). 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% alcohol for 5 days per week for 103 weeks. The amount of alcohol administered corresponds to a daily dose of 442 mg/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 due to background incidence or to 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. 12). Each species had a vehicle control group that was treated with 95% 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. 13). Application of 0.02 mL alcohol alone on the skin of NMRI mice 3 times per week for 20 weeks did not cause any tumors. This study has several deficiencies, such as lack of daily dosing and short study duration; nevertheless, it provides additional support that alcohol is not tumorigenic to skin after dermal administration.

Chronic administration of orally ingested alcohol has been associated with carcinogenicity in both animals and humans (Ref. 10). In animals, alcohol treatment increased tumor incidences in multiple organs (Refs. 14-16). The International Agency for Research on Cancer (IARC) has classified alcohol as a human carcinogen when used as a beverage (Ref. 10). In humans, drinking around 50 grams 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. 17-18). No significant increases in cancer risk for any of the cancer types listed above appear to be associated with less than one alcoholic drink (about 10 g of alcohol) per day.

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, alcohol consumption in pregnant women may result in fetal alcohol syndrome and other major structural malformations (Ref. 19). Fetal alcohol syndrome has been documented in infants of mothers who consumed large amounts of alcohol throughout pregnancy (80 mL daily), and there is no known level of safe alcohol consumption during pregnancy (Ref. 20).

Alcoholic women are known to have a variety of menstrual and reproductive disorders and alcohol abuse has also been associated with early menopause (Ref. 21). Ingestion of alcohol, even in amounts insufficient to cause major damage to the liver or other organs, may lead to menstrual irregularities in women and temporal infertility (Refs. 22-23). Additionally, epidemiologic data from a representative national sample of 917 women showed increased rates of menstrual disturbances and infertility associated with increasing self–reported alcohol consumption (Ref. 24). In a study conducted in two Australian twin cohorts, alcoholic women in both cohorts show overall delayed reproduction (Ref. 25). Thus, although further studies are needed, the above results suggest a direct connection between alcohol consumption and alterations of reproductive system function.

Alcohol animal data on hormonal effects. Alcohol appears to affect the level of a number of hormones in animals. Esquifino et al. recently reviewed the effect of alcohol on the circadian rhythm of several hormones in rats (Ref. 26). The authors concluded that alcohol exposures are associated with suppression of the HPA-axis in male rats; decreases in hypothalamic gonadotropin-releasing hormone and luteinizing hormone in adult and peripubertal rats; and increases in prolactin, follicle stimulating hormone, testosterone, and thyroid stimulating hormone in peripubertal rats. Karl and Fisher reported that alcohol at a concentration of 280 to 300 mg/dL increased production of human chorionic gonadotropin and progesterone by cultured trophoblasts in vitro (Ref. 27).

Male rat pups delivered by dams receiving alcohol (35% of dietary calorie intake) in the last week of pregnancy showed decreases in serum testosterone levels (Ref. 28). Alcohol at concentrations of at least 25 mg/mL decreased the ability of rat Leydig cells to secrete testosterone by up to 44% (Ref. 29). Juvenile female rats fed an alcohol-containing liquid diet for 2 months (dosing commencing at 21 to 28 days of age) showed decreases in serum estradiol and progesterone levels (Ref. 30). Emanuele et al. reported that

alcohol (2 to 3 g/kg, dosed intraperitoneally) decreased serum prolactin levels in prepubertal and adult rats (Ref. 31).

Alcohol human data on hormonal effects. Pregnant healthcare workers are a particularly vulnerable population given that alcohol is a teratogen, and alcohol-containing antiseptic hand rubs are used frequently in healthcare settings. Alcohol in the maternal bloodstream crosses readily into the placenta and the fetal compartment. This results in similar blood alcohol concentrations in the mother, the fetus, and the amniotic fluid. The fetus has very limited metabolic capacity for alcohol primarily because of low to absent hepatic activity for the metabolism of alcohol (Ref. 32). 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.

Maternal alcohol use (by ingestion) is the leading known cause of developmental and cognitive disabilities, and is a preventable cause of birth defects. Children exposed to alcohol in utero are at risk for growth deficiencies, facial deformities, central nervous system impairment, behavioral disorders, and impaired intellectual development. Consuming alcohol during pregnancy also increases the risk of miscarriage, low birth weight, and stillbirth.

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 pharmacokinetics subsection above). As noted previously, the available data suggest that with moderate use, the highest expected exposure would be approximately 10% of an alcohol-containing drink. However, healthcare workers who use these products chronically and repetitively may be required to use alcohol-containing hand rubs prior to and following contact with patients, body fluids, etc., and therefore may be exposed to these products a hundred times or more per day (Ref. 34). Consequently, alcohol-containing healthcare antiseptics must be considered in the context of the impact of exposure to approximately 10%, and possibly more, of an alcohol-containing drink every day, for the duration of pregnancy.

Although pharmacokinetic data of alcohol-containing hand rubs show that systemic exposure is very low, there are no safety data on use during pregnancy. Because a safe threshold level of alcohol exposure in pregnancy is not known, the American College of Obstetricians and Gynecologists (ACOG), the Centers for Disease Control and Prevention (CDC), and the Surgeon General recommend that pregnant women abstain from alcohol consumption (Refs. 35-37). FDA agrees with the recommendations of the ACOG, CDC, and Surgeon General regarding abstention from alcohol exposure during pregnancy. As a result, we recommend that a warning be added to alcohol-containing healthcare antiseptics to avoid repetitive, chronic use in pregnancy, or for healthcare workers or others who need repetitive and chronic hand rubbing during pregnancy to consider alternative methods for hand hygiene in order to avoid any systemic exposure to alcohol. Addition of a warning to the label would not be based on a known safety signal, but rather, on a cautionary approach based on the fact that there is no known safe level of alcohol exposure in pregnancy.

Alcohol resistance data. The antimicrobial mechanism of action of alcohol is described as non-specific, usually by denaturation and coagulation of proteins (Refs. 38-40). Alcohol evaporates readily after topical application, so no antiseptic residue is left on the skin. Consequently, the development of resistance as a result of healthcare antiseptic use is unlikely.

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, including documentation of validation of the methods used to measure alcohol and its metabolites
- Animal ADME following dermal application
- Data to help define the effect of formulation on dermal absorption

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APPENDIX B2 – Safety Assessment of 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 a healthcare personnel handwash or surgical hand scrub (59 FR 31402 at 31435). Because of its widespread use as an antimicrobial agent in cosmetics and as a disinfectant for hard surfaces in agriculture and medical settings, the safety of benzalkonium chloride has also been reviewed by the Environmental Protection Agency and an industry review panel (Cosmetic Ingredient Review (CIR)) (Refs. 1and 2) 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 healthcare antiseptic active ingredient (Ref. 3).

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. For FDA to evaluate the safety of benzalkonium chloride for this rulemaking, these studies must be submitted to the rulemaking or otherwise be publicly available.

Summary of benzalkonium chloride safety data

Benzalkonium chloride carcinogenicity data. Currently, no oral or dermal carcinogenicity data are publicly available. We found one short term dermal toxicity study (Ref. 4). Mice were treated with a single topical application of 0.8, 3, 13, or 50% benzalkonium chloride aqueous solution and monitored for 1 month. Treatment with either the 13% or 50% solution (concentrations well above the actual use concentrations of 0.1-5%) caused death in 9 of 48 and 20 of 48 mice in each group, respectively. The surviving mice developed skin lesions at the application site. The low-dose groups (0.8% and 3% solutions) showed slightly lower body weights and rates of growth than the control group, suggesting a slight detrimental effect from dermal exposure to these low concentrations. The available data are not adequate to assess the carcinogenic potential of benzalkonium chloride.

Benzalkonium chloride resistance data. Several gram-negative (*Escherichia coli*, *Salmonella*, *Pseudomonas*, *Acinetobacter*, *Enterobacter*, *Klebsiella*, and *Campylobacter*) and gram-positive (*Staphylococcus* and *Listeria monocytogenes*) bacteria have been shown to readily adapt when grown in the presence of subinhibitory levels of benzalkonium chloride in laboratory studies (Refs. 5-34). These bacteria also displayed reduced susceptibility to antibiotics compared to the nonadapted parental strain (Refs. 6-12, 22, 23, 25, 26, 30, 31, 36, and 37). Six studies showed an association between reduced susceptibility to benzalkonium chloride and the antibiotic chloramphenicol (Refs. 6, 8, 9, 26, 30, and 36). This association was shown in four different bacteria; however, no common mechanism has been identified to explain this finding. There are data available suggesting that efflux pumps may not play a major role in the reduced susceptibility of *Salmonella* (Ref. 11) and *Listeria* (Refs. 32 and 34) to benzalkonium chloride.

In a study by Lambert and colleagues (Ref. 38), human clinical and industrial isolates and standard culture collection strains of *P. aeruginosa* were examined for reduced susceptibility to benzalkonium chloride, chlorhexidine, and eight antibiotics. No statistically significant association between benzalkonium chloride and antibiotic susceptibility (i.e., cross-resistance) was found in the industrial isolates. In contrast, there was a highly significant correlation between benzalkonium chloride and gentamycin resistance in the clinical isolates. In other words, strains that were resistant to gentamycin also tended to have reduced benzalkonium chloride susceptibility. Although the authors suggest that the clinical environment is responsible for cross-resistance, this study is not large enough to provide sufficient support for this theory.

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

Similar to what has been observed with triclosan, exposure to benzalkonium chloride in the laboratory has resulted in changes to the antibiotic susceptibility profiles of some bacteria (Refs. 6-12, 22, 23, 25, 26, 30, 31, 36, and 37). However, the data are limited in scope. The available studies have examined few bacterial species, provide no information on exposure levels, and are not adequate to define the potential for the development of resistance or cross-resistance. Additional laboratory studies are necessary to more clearly define the potential for the development of resistance to benzalkonium chloride. Depending on the results of the laboratory studies, additional data may also be needed to assess the level of risk posed by benzalkonium chloride.

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

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

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APPENDIX B3 – Safety Assessment of Benzethonium Chloride

In the 1994 TFM, FDA classified benzethonium chloride as lacking sufficient evidence of safety for use as a healthcare personnel handwash and surgical hand scrub (59 FR 31402 at 31435). Since FDA's proposed classification, two industry review panels (CIR and a second industry panel identified in a comment only as an "industry expert panel") and a European regulatory advisory board (Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers) have evaluated the safety of benzethonium chloride when used as a preservative in cosmetic preparations and as an active ingredient in consumer hand soaps (Refs. 1, 2, and 3). These advisory bodies found benzethonium chloride to be safe for these uses. However, all of these safety determinations have largely relied on the findings of proprietary studies that are not publicly available. One of these evaluations, the findings of the unidentified industry expert panel, was submitted to the rulemaking to support the safety of benzethonium chloride.

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 healthcare antiseptic products, e.g., ADME, DART, and oral carcinogenicity studies. The safety assessments used to support the unidentified industry expert panel's finding of safety, however, are publicly available only in the form of summaries. Consequently, these studies are not available to FDA and are precluded from a complete evaluation by FDA. Further, the submitted safety assessments with study summaries do not constitute an adequate record on which to base a GRAS classification. For FDA to include these studies in the administrative record for this rulemaking, they must be submitted to the rulemaking or otherwise publicly available.

Summary of benzethonium chloride safety data

Benzethonium chloride ADME data. In 1988, the National Toxicology Program (NTP) studied the extent of absorption following single and repeated once-daily dermal doses of benzethonium chloride and determined the pattern of tissue distribution and route of elimination of ^{14}C-labeled benzethonium chloride in rats (Ref. 4). They also determined the kinetics of distribution and excretion following intravenous administration. Under the conditions of the dermal studies, benzethonium chloride was readily absorbed following single or repeated dermal applications.

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

More recent data submitted to support the safety of benzethonium chloride have shown a much lower level of absorption. In response to the 1994 TFM, a manufacturer provided data from a preliminary rat dermal absorption study and an *in vitro* dermal absorption

study. In the rat study, an aqueous 1% solution of ^{14}C-benzethonium chloride was applied to the shaved back of rats and covered with a nonocclusive patch. Blood, urine, and feces were collected for 48 hours after dosing. Little or no radioactivity was detected in blood or urine samples. Approximately 7% of the administered radioactivity was detected in the fecal samples. The remaining radioactivity was not accounted for.

The in vitro dermal absorption study compared the absorption of benzethonium chloride through rat and human skin. Pieces of skin were obtained from rats and human plastic surgery patients. Total absorption was higher in rat compared to human skin. Under the conditions of this study, the total amount of benzethonium chloride maximally absorbed by human skin during 24 hours was 4.14%. Accumulation of benzethonium chloride in the skin was less than 1% in human skin but was about 5% in rat skin.

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

Benzethonium chloride carcinogenicity data. In 1995, the NTP conducted dermal carcinogenicity studies of benzethonium chloride in an ethanol vehicle in rats and mice (Ref. 4). There were no treatment-related differences from control animals in survival, clinical signs (e.g., reddening or crusting of the skin), body weights, organ weights, or neoplastic lesions in either rats or mice. Histological evaluation revealed dose-related (minimal in low dose, moderate in high dose) epithelial hyperplasia in both rats and mice at doses greater than 0.15 mg/kg/day. In rats, epidermal ulceration was frequent in high dose females and in one high dose male.

There was no systemic toxicity or carcinogenicity at any dose level in either species. The no observed effect level (NOEL) for systemic toxicity was 1.5 mg/kg/day based on systemic toxicity and carcinogenicity. While we agree with NTP's analysis of the systemic toxicity, we disagree with the NOEL for dermal toxicity because epithelial hyperplasia and reddening of the skin were noted at all doses greater than 0.15 mg/kg/day. Therefore, we consider the NOEL for dermal toxicity to be 0.15 mg/kg/day. The submitted dermal carcinogenicity data are adequate and show that benzethonium chloride does not pose a risk of cancer after repeated dermal administration under the experimental conditions used; however, data from an oral carcinogenicity study are lacking.

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

An embryo-fetal rat study with sufficient detail for evaluation was submitted to the docket. In this study, pregnant female rats were administered benzethonium chloride on gestational days 6 through 15. Maternal toxicity was noted among the high dose-treated females. In the other dose groups, toxicity findings were sporadic and not dose-related. There were no treatment related gross necropsy findings or reproductive endpoint changes caused by the treatment. The incidence of delayed sternal ossification and/or nonossified sternal centrae was noted in all treatment groups and was statistically significant. However, this finding is not considered biologically significant as the incidence was not dose-related, the litter incidence values did not differ significantly, and the values were within the range of historical values. The maternal NOAEL is 100 mg/kg/day based on body weight changes and deaths at the dose of 170 mg/kg/day.

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

Benzethonium chloride resistance data. We found two studies that examined bacterial susceptibility profiles for both benzethonium chloride and antibiotics. One study (Ref. 5) provided the data collectively, so no associations between reduced susceptibility to benzethonium chloride and specific antibiotics could be determined. The second study (Ref. 6) found a positive correlation between reduced susceptibility to benzethonium chloride and ciprofloxacin or oxacillin in clinical isolates of MRSA. There were no associations between benzethonium chloride and antibiotic resistance in the other tested organisms (methicillin sensitive *S. aureus* or *P. aeruginosa*).

Overall, the available studies are limited in scope. They examine few bacterial species, provide no information on the level of benzethonium chloride exposure, and are not adequate to define the potential for the development of resistance and cross-resistance to antibiotics. Additional laboratory studies are necessary to more clearly define the potential for the development of resistance to benzethonium chloride. Depending on the results of the laboratory studies, additional data may also be needed to assess the level of risk posed by benzethonium chloride.

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

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

- Animal ADME
- Data to help define the effect of formulation on dermal absorption
- Oral carcinogenicity
- DART studies (fertility and embryo fetal testing)
- Potential hormonal effects
- Data from laboratory studies that assess the potential for the development of resistance to benzethonium chloride and cross resistance to antibiotics

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APPENDIX B4 – Safety Assessment of Chloroxylenol (PCMX)

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

Summary of chloroxylenol safety data

Chloroxylenol human pharmacokinetic data. The dermal absorption of chloroxylenol has been studied in humans following single and repeated bathing (10 minutes daily for 1 to 10 days) and following a single 30-minute percutaneous application to the back of one subject (Refs. 1 and 2). The studies were conducted with few subjects and a single formulation, and as shown in Table A, produced inconsistent results.

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

Study	No. of Subjects	Bath	Absorption[1]	
			Milligrams	Percent
Jordan, Nichols, and Rance, Preliminary Bathing Study (Ref. 1)	1	1st	5.74	0.5
Jordan, B. J., et. al., Repeat Bathing Study (Ref. 2)	4	1st	2.4 to 4.4	0.2 to 0.37
		10th	2.4 to 6.4	0.2 to 0.5
Jordan, B. J., et. al., Dermal ADME under Occlusion Study (Ref. 2)	1	N/A	7.2	15.7

[1] Based on amounts in urine.

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

The percutaneous absorption study (Ref. 2) also provides some limited information on the elimination of chloroxylenol in humans. Assays of urine samples revealed that all chloroxylenol was excreted as conjugated metabolites. No unchanged chloroxylenol was found in the urine at any time point, and most of the drug was excreted in the first 8 hours after application.

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

Chloroxylenol ADME data. Dermal ADME studies in rats and mice are available (Refs. 3 and 4). In a study conducted by Sved (Ref. 4), increasing doses of ^{14}C-labeled chloroxylenol were applied to the shaved backs of mice as a single or repeated dose (once daily for 14 or 28 days). Absorption was apparent at all time points and increased with increasing length of exposure. Approximately 50% of the applied dose was absorbed at 24 hours after a single dose and approximately 65% at 24 hours after 14 and 28 days of daily dosing. The amount of chloroxylenol absorbed was proportional to the administered dose. The plasma half-life for chloroxylenol was 18, 22, and 12 hours for low, mid, and high dose males, respectively, and 70, 9, and 12 hours for low to high dose females, respectively. The half-life in skin was longer at lower doses of chloroxylenol.

After dermal application chloroxylenol has been found in the following tissues: Kidney, lung, liver, adrenal glands, skin, heart, ovary, ovarian fat, skeletal muscle, skull, spinal cord, spleen, eyes, femur, and brain (Refs. 3 and 4). Tissue concentrations increased with repeated dosing, up to 1.8-fold in the kidney, up to 3.8-fold in the liver, and up to 8.9-fold in the brain (Ref. 3). Concentrations in tissue also increased with dose. Unlike the concentrations in the liver and kidney, chloroxylenol levels in the brain did not appear to reach steady-state concentrations after 28 days of dosing, particularly at the lower chloroxylenol concentrations (Ref. 3). The relevance of these findings from a chronic use perspective cannot be evaluated without long-term animal studies.

The majority of chloroxylenol is excreted in the urine, and this is largely as polar conjugated metabolites. Only traces of unchanged chloroxylenol are present in urine. Havler identified a minor metabolite of chloroxylenol, hydroxylated chloroxylenol, which represents 10-15% of the metabolites found in urine (Ref. 3). Both chloroxylenol and the minor metabolite are excreted as a mixture of glucuronide and sulfate conjugates (Ref. 3). Excretion is largely complete 24 hours after a single dermal application.

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

Chloroxylenol carcinogenicity data. In the 1994 TFM, FDA stated that a lifetime dermal carcinogenicity study (up to 2 years) in mice was needed to assess the dermal toxicity of chloroxylenol (59 FR 31402 at 31415). In response to this request, data from a 13-week dose ranging dermal toxicity study in mice were submitted (Ref. 5). The study results show dose-related dermal adverse effects that may be indicative of dermal toxicity, such

as erythema (skin redness), edema (swelling), and exfoliation (skin peeling). Microscopic changes consistent with a mild dermal irritant were also noted. These changes included hyperplasia (abnormal multiplication of skin cells) and hyperkeratosis of the epidermis (overgrowth of outermost layer of the skin) in all dosed animals, inflammation of the superficial dermis (a deeper layer of the skin) in most treated animals, crust formation, and necrosis (degradation) of epidermal cells. There were also dose-dependent lesions that increased in significance with dose. Hyperplasia of bone marrow and increased extramedullary hematopoiesis (formation of red blood cells outside the bone barrow) in the spleen consistent with an increasing inflammatory reaction were observed in the high dose group. The no observed effect level (NOEL) was 15% chloroxylenol and the no observed adverse effect level (NOAEL) was less than 30%.

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

Chloroxylenol DART data. Data are available from a teratology study in rats that adequately characterizes chloroxylenol's potential effects on embryo and fetal development (Ref. 6). The maternal NOEL in this study was 100 mg/kg/day. The maternal lowest observed effect level was 500 mg/kg/day based on decreased food consumption and decreased body weight gain. The NOEL for developmental toxicity was 1,000 mg/kg/day. However, this study is not sufficient to characterize effects on other aspects of reproduction. Additional studies are necessary to assess the effect of chloroxylenol on fertility and early embryonic development and on pre and postnatal development.

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

In a pair of studies (Refs. 8 and 9), Lear and colleagues collected, identified, and measured antimicrobial susceptibilities of bacteria from industrial sources. The authors saw no difference in the antibiotic susceptibility patterns of the industrial and standard strains of *P. aeruginosa.* Overall, there were few changes in antibiotic resistance patterns between the standard and industrial strains.

While these studies provide little evidence of cross-resistance to antibiotics, they are limited in scope. They examine few bacterial species, provide no information on the level of chloroxylenol exposure, and are not adequate to define the potential for the

development of resistance to chloroxylenol and cross-resistance to antibiotics. If the data from initial laboratory studies indicate a potential for the development of chloroxylenol resistance and antibiotic cross-resistance, additional data will be necessary to assess the level of risk posed by chloroxylenol.

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

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

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APPENDIX B5 – Safety Assessment of Hexylresorcinol

In the 1994 TFM, FDA proposed to classify hexylresorcinol as GRAS for all healthcare antiseptic uses based on the recommendations of the Panel, who concluded that the topical application of hexylresorcinol is safe (39 FR 33103 at 33134). In support of its conclusion, the Panel cited hexylresorcinol's long history of use as an oral antihelmintic (a drug used in the treatment of parasitic intestinal worms) in humans and the lack of allergic reactions or dermatitis associated with topical use. The Panel noted that no information was provided regarding dermal or ophthalmic toxicity or absorption and blood levels attained after application to intact or abraded skin or mucous membranes, but concluded that the few animal toxicity studies submitted as summaries indicated a "low order" of toxicity.

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

Summary of available hexylresorcinol safety data

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

In the only study in humans (Ref. 2), two men received oral doses of 1 g of 4-hexylresorcinol. An average of 18% of the dose was recovered in urine within the first 12 hours; thereafter, the compound was not detected in urine samples. Fecal excretion accounted for 64% of the dose. It has been reported that hexylresorcinol is excreted via the urine mainly in the form of an ethereal sulfate conjugate (Ref. 3).

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

Hexylresorcinol carcinogenicity data. An adequate oral carcinogenicity study was conducted by the National Toxicology Program (NTP) in which hexylresorcinol was administered orally to groups of rats and mice of each sex 5 days per week for 2 years (Ref. 4). No evidence of carcinogenicity was found in rats. However, precancerous cells of the adrenal gland were observed at increased incidences in dosed male mice. A marginal upward trend in tumors of the adrenal gland was also observed in male mice. The increase of these two types of cancers was not statistically significant and was considered equivocal by the NTP.

FDA agrees that the findings in male mice should not be considered a positive carcinogenic signal. No changes were noted in the adrenal glands in 16- and 30-day subgroups included in the study. Also, the fact that the marginal increase in changes that occurred in male mice were not corroborated in earlier repeat dose toxicity studies in female mice, or in rats of either sex, makes the weight of the evidence for the male-only findings weak. In an 18-month intravaginal study (Ref. 5), injection of 1% hexylresorcinol dissolved in carbowax 1000 twice weekly in 20 female mice did not cause any genital tract tumors.

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

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

- Human pharmacokinetic studies under maximal use conditions when applied topically, including documentation of validation of the methods used to measure hexylresorcinol and its metabolites
- Animal ADME
- Data to help define the effect of formulation on dermal absorption
- Dermal carcinogenicity
- DART studies
- Potential hormonal effects
- Data from laboratory studies that assess the potential for the development of resistance to hexylresorcinol and cross-resistance to antibiotics

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APPENDIX B6 – Safety Assessment of Iodine and Iodophors

Iodophor complexes are complexes formed between iodine, which is the active antimicrobial component, and a carrier molecule. Both surfactant and nonsurfactant compounds have been complexed with iodine. The rate of the release of "free" elemental iodine from the complex is a function of the equilibrium constant of the complexing formulation (39 FR 33103 at 33129). The following iodine solutions and iodophor complexes were proposed as GRAS in the 1994 TFM for OTC healthcare antiseptic use, but only three of these (iodine tincture USP, iodine topical solution USP, and povidone-iodine) were also proposed as GRAE (i.e., Category I) (59 FR 31402 at 31435):

- Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
- Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
- Iodine tincture USP
- Iodine topical solution USP
- Nonylphenoxypoly (ethyleneoxy) ethanoliodine
- Poloxamer-iodine complex
- Povidone-iodine 5 to 10 percent
- Undecoylium chloride iodine complex

Iodine is found naturally in the human body and is essential for normal human body function. In the body, iodine accumulates in the thyroid gland and is a critical component of thyroid hormones. People obtain iodine through their food and water, which are often supplemented with iodine to prevent iodine deficiency. Because people are widely exposed to iodine, it has been the subject of comprehensive toxicological review by public health organizations (Refs. 1 and 2).

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

Summary of iodophor safety data

Iodophor human pharmacokinetics data. Several studies demonstrated that iodine applied to human skin was systemically absorbed to some extent (Ref. 1). The studies consistently found raised blood concentrations of both organic (protein-bound) and

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

Most of the absorption studies evaluated povidone-iodine. Significant iodine absorption was seen as a result of topical application of povidone-iodine either as a surgical scrub (Ref. 3) or as an antiseptic treatment of premature babies in a neonatal intensive care nursery (Ref. 4). Nobukuni et al. (Ref. 5) evaluated the effect of long-term topical povidone-iodine treatment on serum iodine levels and thyroid function in bedridden inpatients. Inpatients treated with povidone-iodine had higher blood concentrations of organic iodine compared to the control group, suggesting absorption of topically applied iodine. It is possible that steady-state levels may have been achieved in this study; however, this was not directly demonstrated.

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

Iodophor ADME data. In addition to human absorption data, the distribution, metabolism, and excretion of iodine have been characterized in humans for oral exposures (Ref. 1). Because the distribution of absorbed iodine has been shown to be similar regardless of the route of exposure, we can use data from oral exposures in assessing distribution, metabolism, and excretion of iodine from topical exposure. Most of the iodine from orally ingested sodium iodide accumulates in the thyroid (approximately 20 to 30%) as iodide or is excreted in the urine (30 to 60%) within 10 hours (Refs. 1 and 6). The elimination half-life of absorbed iodine is approximately 31 days in healthy adult males (Ref. 6), but has considerable variability (Ref. 7). Overall, the distribution, metabolism, and excretion of iodine have been adequately assessed in humans and no further animal ADME data is needed.

Iodophor carcinogenicity data. We found no dermal carcinogenicity data for iodine; however, oral carcinogenicity data are available. The oral carcinogenicity data indicate that iodine does not pose a risk of cancer in rats after repeated oral administration to rats under the experimental conditions used (Ref. 8). Overall, there was no significant increase in the incidence of tumors from iodine exposure. Although there was an increased incidence of squamous cell carcinomas in the submandibular salivary gland in the high dose group, this increase was not significant.

The ability of iodine to function as a tumor promoter (i.e., something that stimulates existing tumors to grow) also has been evaluated in rats. In a study by Takegawa et al. (Ref. 9), rats were pretreated with a chemical that can initiate tumors (DHPN). One group then received a high dose of potassium iodide (1,000 parts per million (ppm)) in their water while a control group received untreated water over 82 weeks. The iodine-

treated group had a significantly higher incidence of follicular thyroid cancer compared to the control group, suggesting that iodine may be a tumor promoter for other carcinogens in the thyroid gland.

In another study (Ref. 10), rats were injected with either DHPN or saline and then received doses of potassium iodide in their drinking water to simulate conditions of iodine deficiency to iodine excess. For the two highest-dose groups, 5 of 20 rats and 2 of 20 rats developed thyroid tumors, respectively. Although the authors concluded that excess iodine can promote thyroid tumor formation, these results were barely significant, and higher dosing did not correlate with increased tumor promotion activity. Therefore, some evidence suggests that very high oral doses of iodine may have tumor promoter activity. However, based upon the available data, oral doses of iodine do not significantly raise the risk of cancer in animals.

Iodophor DART data. The effects of iodine on embryo-fetal development and on fertility were studied in animals (Ref. 11). No fetal malformations were reported when the fetuses were exposed to iodine prenatally, nor were there any effects on fertility in adult animals that were exposed to iodine. The design of these studies, however, does not fit into current testing paradigms for an adequate evaluation of the reproductive and developmental toxicity of a drug.

One series of studies (Ref. 11) evaluated the effects of diets supplemented with high levels of iodine on reproduction, lactation, and survival in rats, hamsters, rabbits, and pigs. For the rats, excess iodine in the diet (2,500 ppm) was associated with an increase in the incidence of death in newborns and an increase in the time to give birth. In rabbits, a dose-dependent decrease in newborn survival was observed. There were no observed effects in hamsters or pigs. The results suggest a species difference in response to similar levels of excess iodine; however, the daily iodine intake per kilogram (kg) of body weight varied among species. Further, these studies do not evaluate all the necessary endpoints regarding fertility and embryo-fetal development.

Shoyinka, Obidike, and Ndumnego (Ref. 12) evaluated the effect of iodine on the male reproductive system of rats. A statistically significant ($p<0.05$) increase in the average weights of the testes and epididymides, and approximately 12 percent decrease in epididymal sperm counts were observed in the high dose-treated group. The authors suggest that excess iodine may reduce fertility by lowering epididymal sperm counts.

We found no information on reproductive effects in humans due to dermal iodine exposure. However, transient hypothyroidism (diminished production of thyroid hormones) in infants has been reported as a result of topical exposure to povidone-iodine (Refs. 13-17). Thyroid hormone deficiency from any cause at critical times of development may result in adverse effects, including abnormal pubertal development (Ref. 1). Although excess iodine may result in hypothyroidism, iodine deficiency is more likely to cause prenatal and postnatal hypothyroidism (Ref. 1).

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

Iodophor data on hormonal effects. We found no nonclinical studies that examine the effect of excess iodine on endocrine systems in animal models. However, clinical data indicate that at high doses iodine ingestion exerts a direct effect on the thyroid gland and on the regulation of thyroid hormone production and secretion (Ref. 1). The effects of iodine on the thyroid gland have been shown to include hypothyroidism, hyperthyroidism (excessive production or secretion of thyroid hormones), and inflammation of the thyroid. These conditions can adversely affect reproduction, growth, and developmental systems in humans.

The data demonstrating the thyroid effects of iodine are primarily from oral administration (Ref. 1). There is much less information on thyroid effects after topical administration of iodine. The majority of cases of thyroid hormone changes resulting from topical administration of iodine involve mothers and newborn infants. Studies have shown that topical povidone-iodine applied to pregnant and breast-feeding women causes transient hypothyroidism in their newborns (Refs. 14, 15, 18, and 19). Iodine-induced hypothyroidism has been reported in nursing infants whose mothers used topical or vaginal iodine-containing antiseptics during pregnancy or after delivery (Refs. 14, 15, and 20). Other studies have shown hypothyroidism in infants after topical iodine exposure (Refs. 4, 13, 17, and 21). Elevated thyroid stimulating hormone (TSH) levels have been reported in full-term newborns after repeated topical application of povidone-iodine (Refs. 22 and 23).

Iodine readily crosses the placenta and is concentrated in the mammary gland and secreted in breast milk (Ref. 24). Although iodine-induced hypothyroidism is transient in newborns, even transient hypothyroidism should be avoided during this critical phase of brain development to prevent loss of intellectual capacity (Refs. 25-27).

For adults, the association between topically applied iodine and hypothyroidism is unclear. One study in 27 bedridden inpatients treated continuously with povidone-iodine for 3 to 133 months showed changes in TSH levels (Ref. 5). Another study in 16 nurses who used povidone-iodine regularly for handwashing and gargling (Ref. 28) found that thyroid hormone levels were not significantly different from control subjects who rarely used povidone-iodine, which suggests topical povidone-iodine does not significantly affect thyroid function.

Oral exposure to iodine has been demonstrated to cause significant thyroid effects (Refs. 1 and 2). Several clinical studies demonstrated that high oral doses of iodine can affect blood levels of thyroid hormones, but rarely did these effects seriously impair thyroid function. Oral iodine exposure exceeding 200 mg/day (2.8 mg/kg/day) during pregnancy can result in congenital hypothyroidism (Ref. 1). Generally, however, adverse effects were only observed following very high oral doses that caused very high serum iodine concentrations.

Drawing conclusions from these studies is difficult because the studies have several limitations. Many of these studies lacked control groups, used small subject numbers, and/or did not record subjects' iodine status at baseline (iodine-deficient subjects may be more susceptible to thyroid effects caused by iodine exposure). The study results are also difficult to compare because the studies used different subject age groups, subject types,

iodine formulations and amounts, durations and frequency of iodine treatment, and methods for measuring absorbed iodine levels or thyroid effects. Despite these deficiencies, we believe there are adequate data regarding the potential of iodine to cause changes in thyroid hormone levels and additional studies are not necessary.

Based on the available data, however, we are concerned about frequent, topical use of iodine-containing healthcare antiseptics by pregnant and breastfeeding healthcare personnel. Iodine-containing healthcare antiseptics, particularly povidone-iodine, are used frequently as patient preoperative skin preparations and surgical hand scrubs. Due to the potential for absorption of iodine and transient hypothyroidism in newborns, chronic use of iodine-containing healthcare antiseptics by pregnant and breastfeeding healthcare personnel could lead to adverse effects. Consequently, we recommend that pregnant and breastfeeding women avoid repetitive use of iodine-containing healthcare antiseptics. In addition, thyroid function tests (T4 and TSH) should be monitored in the event that repeat applications of iodine-containing healthcare antiseptics are necessary for a pregnant or breastfeeding healthcare worker.

Iodophor safety data gaps. In summary, our administrative record for the safety of iodine and iodophor complexes is incomplete with respect to the following:

- Human studies of the absorption of iodine following maximal dermal exposure
- Human absorption studies of the carrier molecule for small molecular weight povidone molecules and the other carrier molecules
- Dermal carcinogenicity studies for iodine and each of the iodophor complexes
- Data from laboratory studies that assess the potential for the development of resistance to iodine and cross-resistance to antibiotics

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APPENDIX B7 – Safety Assessment of Isopropyl Alcohol

In the 1994 TFM, FDA proposed to classify isopropyl alcohol (70 to 91.3%) as GRAS for all healthcare antiseptic uses (59 FR 32402). This determination was based on the recommendations of the Miscellaneous External Panel (the Panel). The Panel based its recommendations solely on human absorption data and blood isopropyl alcohol levels (47 FR 22324 at 22329). In other words, 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 are no longer sufficient to fully evaluate the safety of isopropyl alcohol. New information regarding potential risks from systemic absorption and long-term exposure to antiseptic active ingredients is leading us to reevaluate the safety of topical use of isopropyl alcohol in healthcare antiseptics.

Summary of isopropyl alcohol safety data

Isopropyl alcohol human pharmacokinetics data. Based on a review of published literature, there is 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 healthcare setting. In a study by Brown et al., the cutaneous absorption of isopropyl alcohol from a commonly used hand rub solution containing 70% isopropyl alcohol was assessed in 19 healthcare workers ranging in age from 22 to 67 years (Ref.1). 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 one-hour period on two separate days separated by a one-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."

Kirschner, et al., examined the pharmacokinetics of alcohol and isopropyl alcohol after separate and combined application in a double-blind, randomized, three-way crossover study (Ref. 2). Results show that all isopropyl alcohol concentrations measured in volunteers treated with 10% 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 ten healthy male and female adults following application of 3 mL of an isopropyl alcohol-containing hand rub (56% w/w isopropyl alcohol) applied to the hands every 10 minutes over a four-hour period (Ref. 3). Nine of the ten 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 < 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% w/w isopropyl alcohol using a surgical scrub method on ten adults (Ref. 4). 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 3 consecutive 90 minute surgical interventions. After application of the hand rub and air-drying, surgical gloves

were donned. Samples were collected 3 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 under these conditions is expected to be low. Clinical effects (mild intoxication) of elevated blood isopropyl alcohol levels occur at concentrations exceeding approximately 50 mg/dL (Ref. 9). 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% of systemic levels associated with acute clinical effects.

Isopropyl alcohol ADME data. Absorption of isopropyl alcohol has been examined in rats, dogs, and rabbits (Ref. 10). Although different routes of administration were used, isopropyl alcohol was detected in the blood within 30 minutes of exposure. Boatman et al. studied the dermal absorption of isopropyl alcohol in rats (Ref. 11). Seventy percent aqueous isopropyl alcohol solution was applied to the shaved backs of male and female Fischer F-344 rats under occluded conditions for a period of 4 hours. Isopropyl alcohol was detected in the blood within one hour after application. Maximum blood concentrations of isopropyl alcohol were attained at 4 hours and decreased steadily following removal of the test material. Dermal absorption rates were approximately 0.77 $mg/cm^2/hr$. Skin permeability coefficients were approximately 1.37×10^{-3} cm/hr. Most of the drug (i.e., approximately 85% of the dose) was recovered from the application site. The results indicate that 15% of the isopropyl alcohol applied to the skin could be absorbed and bioavailable in rats.

The distribution of isopropyl alcohol was studied in dogs. Thirty minutes after injection into gastrointestinal loops, isopropyl alcohol was detected in blood, spinal fluid, liver, kidney, and brain (Refs. 10 and 12).

Martinez et al. compared isopropyl alcohol blood levels in rabbits after oral, dermal, and inhalation exposure (Ref. 13). Male rabbits (unidentified species, 3 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 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. The study provided little information regarding the bioavailability of dermally applied isopropyl alcohol due to the lack of a dermal application group alone and the unknown dosing for the group given combination inhalation and dermal isopropyl alcohol.

Isopropyl alcohol is metabolized via oxidation by aldehyde dehydrogenase (ADH) to acetone (Ref. 14). Metabolism of isopropyl alcohol to acetone in the rat, dog, and rabbit has been reported in several studies (Refs. 10, 15, and 16). Kapp et al. reviewed the pharmacokinetics and metabolism of isopropyl alcohol after non-dermal routes of

administration (Ref. 15). Table B summarizes plasma drug concentrations and elimination half-lives of isopropyl alcohol after oral, intravenous, and inhalation routes of administration. About 80% of an orally administered dose is absorbed within 30 minutes (Ref. 16). The volume of distribution of isopropyl alcohol is 0.6–0.7 L/kg, similar to total body water.

Table B: Pharmacokinetic Data after Administration of [^{14}C]-Isopropyl alcohol [a]

Species	Route	Dose	Peak blood level (μg eq/g)	Elimination rate constant (hr)	Half-life (hr)
Rat	Intravenous	300 mg/kg	309	0.574	1.3
Rat	Oral	300 mg/kg	276	0.552	1.3
Rat	Oral	3000 mg/kg	1341	0.159	5.4
Rat	Oral × 8 days	300 mg/kg	238	0.423	1.7
Rat	Inhalation	500 ppm	32	0.862	0.9
Rat	Inhalation	5000 ppm	876	0.366	2.0
Mouse	Intravenous	300 mg/kg	203	0.848	0.9
Mouse	Inhalation	500 ppm	65	1.075	0.7
Mouse	Inhalation	5000 ppm	1885	0.414	1.7

[a] Taken from Kapp et al. (Ref.15).

Isopropyl alcohol carcinogenicity data. The International Agency for Research on Cancer (IARC) monograph states that there is inadequate evidence of carcinogenicity of isopropyl alcohol in humans (Ref. 17). 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. The risk for laryngeal cancer may also have been elevated in these workers. However, it is unclear whether the cancer risk was due to the presence of isopropyl alcohol itself or one of its byproducts (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).

No oral carcinogenicity studies of isopropyl alcohol have been completed in animals. Inhalation carcinogenicity studies have been performed to assess the potential carcinogenicity for industrial workers under occupational exposure conditions. Burleigh-Flayer et al. reported that inhalation of isopropyl alcohol for up to 2 years did not result in significant increases in any tumors in rats or mice; however, some groups of treated rats had higher mortality rates and shorter survival times compared to controls (Ref. 18). 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 (ppm) 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 nominal 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 ($p < 0.01$) 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 neoplastic lesions was observed in male rats; however, this type of tumor is prevalent in aged rats, and is not considered to be treatment related. No increased incidence of neoplastic lesions was observed for female rats from any exposure group.

Dermal carcinogenicity bioassays of isopropyl alcohol in animals have not been described in the public literature. In a study where mice were dosed once weekly via subcutaneous injection with 20 mg undiluted isopropyl alcohol for 20-40 weeks, no evidence of tumors were seen at the injection sites. In a 1-year dermal toxicity study, Rockland mice (30 per group) were treated three times weekly for 1 year with isopropyl alcohol (Ref. 10). No skin tumors were observed, but the sex, dose, and observation period were not specified. Neither of these studies can 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 multi-generation studies were conducted for isopropyl alcohol administered via the oral route of exposure (Refs. 19-23). Isopropyl alcohol was associated with maternal toxicity when pregnant animals are exposed to high doses during pregnancy but no teratogenic effects were noted on the pups treated through their mothers. 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. 20).

Isopropyl alcohol data on hormonal effects. Studies evaluating hormonal effects of isopropyl alcohol were 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. 25). The significance of these changes in hormone levels on the long-term development of the treated pups has not been evaluated.

Isopropyl alcohol resistance data. We found no reported bacterial resistance to isopropyl alcohol. Like alcohol, the antimicrobial mechanism of action of isopropyl alcohol is described as non-specific, usually by denaturation and coagulation of proteins (Refs. 26-28). Isopropyl alcohol evaporates readily after topical application, so no antiseptic residue is left on the skin. Consequently, the development of resistance as a result of healthcare antiseptic use is unlikely.

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, including documentation of validation of the methods used to measure isopropyl alcohol and its metabolites
- Animal ADME
- Oral carcinogenicity
- Dermal carcinogenicity
- Potential hormonal effects

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APPENDIX B8 – Safety Assessment of Triclocarban

In the 1994 TFM, FDA proposed to classify triclocarban as GRAS for all healthcare antiseptic uses. This determination was based on safety data and information that were submitted in response to the 1978 TFM on triclocarban formulated as bar soap (Ref. 1). These data included blood levels, target organs for toxicity, and no effect levels and were discussed in the 1991 First Aid TFM (56 FR 33644 at 33664). The existing data, however, are no longer sufficient to fully evaluate the safety of triclocarban. New information regarding potential risks from systemic absorption and long-term exposure to antiseptic active ingredients is leading us to propose additional safety testing.

Summary of triclocarban safety data

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

We found several studies in humans that examine the absorption of triclocarban after topical application (Refs. 2-5). Most of these studies evaluated absorption after a single topical exposure and used a small number of subjects. After a single exposure, blood levels of triclocarban ranged from below the limit of detection (10 ng/mL) to a Cmax of 530 nanomolar (nM) (167 ng/mL) (Refs. 2-4). Small amounts of triclocarban were also detectable in the urine and feces of subjects. The estimated total average recovery ranged between 0.39 and 0.6% of the applied dose. Although small, these studies suggest that very little triclocarban is absorbed after a single topical exposure; however, steady-state levels were not evaluated.

Howes and Black (Ref. 5) examined absorption of triclocarban after repeated daily application in a 28-day bathing study. Twelve subjects bathed once daily using bar soap that contained 2% triclocarban. Each subject was exposed to approximately 260 mg of triclocarban per day. Triclocarban was below the limit of detection (25 ng/mL) in all samples at all time points. A manufacturer of triclocarban has suggested that steady-state levels were achieved in this study, but this was not directly demonstrated.

In addition to systemic exposure as a result of dermal absorption, users may have prolonged exposure to those antiseptic active ingredients that remain bound to the skin after use (that is, substantive). Triclocarban has been shown to be substantive. North-Root et al. (Ref. 6) measured the amount of triclocarban that remained on the skin after a single application of bar soap in 12 human subjects. An average of 1.4% of the applied triclocarban remained on the skin. Substantive product remaining on the skin after rinsing may lead to additional absorption and systemic exposure.

Overall, the human pharmacokinetic studies are not adequate, and we propose that human pharmacokinetic studies using dermal administration under maximal use conditions are

still needed to define the level of systemic exposure following repeated use. In addition, data are needed to help define the effect of formulation on dermal absorption.

Triclocarban ADME data. Triclocarban is readily metabolized in both humans and animals (Refs. 7-10). Birch et al. identified the metabolites of triclocarban in plasma and urine after oral exposure in rats, rhesus monkeys, and humans (Ref. 7). The principal metabolites common to all species were the sulfate and glucuronide conjugates of 2′-, 3′-, and 6-hydroxy-triclocarban. However, there were differences in triclocarban metabolism between rats and higher primates, and the monkey appears to be the more appropriate model for studying triclocarban pharmacokinetics in humans (Ref. 7).

Elimination of triclocarban metabolites from the plasma appears to be biphasic. In adult rhesus monkeys, elimination from the plasma occurs in two distinct phases: Rapid elimination of parent triclocarban and glucuronide conjugates, and slower elimination of sulfate conjugates (Ref. 8). Similarly, in humans, the major plasma metabolites are glucuronide conjugates, which were eliminated in urine with a half-life of about 2 hours (Ref. 1). Triclocarban sulfate conjugates are removed from plasma with a half-life of about 20 hours, presumably into the bile.

The majority of triclocarban and its metabolites are eliminated through the feces, with smaller amounts eliminated through the urine. In a human study where six male volunteers received a single oral dose of ^{14}C-labeled triclocarban in corn oil, 70% of the dose was eliminated in the feces and elimination was complete after 120 hours (Ref. 1). Twenty-seven percent of the dose was eliminated in urine, and the urinary excretion of triclocarban and its metabolites was complete by 80 hours after dosing.

Although there are some ADME data on triclocarban after oral exposure, there are little data after topical exposure. Gruenke et al. (Ref. 11) analyzed plasma and urine samples from human subjects who used triclocarban-containing bar soap. The major plasma metabolite was a sulfate of hydroxytriclocarban, with levels ranging from 0–20 ng/mL. The major metabolites found in the urine were triclocarban glucuronides, with typical levels averaging 30 ng/mL. The authors did not describe the frequency or length of time the subjects bathed with the soap; consequently, it is not known whether maximal exposure or steady-state levels were reached.

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

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

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

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

Triclocarban data on hormonal effects. Recent studies have demonstrated that triclocarban may have the ability to alter the activity of the androgen system (Refs. 12 and 13). Chen et al. (Ref. 13) reported that triclocarban enhanced the testosterone-induced androgen receptor-mediated response both in cell culture and in an in vivo rat model although triclocarban by itself had no activity. When castrated male rats were fed a diet containing 0.25% triclocarban and treated with testosterone propionate (0.2 mg/kg) for 10 days, all male sex accessory organs were significantly increased in size compared to rats treated with either triclocarban or testosterone alone. The implications of these findings on human health, especially for children, are not well understood.

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

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

- Human pharmacokinetic studies under maximal use conditions when applied topically, including documentation of validation of the methods used to measure triclocarban and its metabolites
- Animal ADME
- Data to help define the effect of formulation on dermal absorption
- Dermal carcinogenicity
- DART studies
- Potential hormonal effects
- Data from laboratory studies that assess the potential for the development of resistance to triclocarban and cross-resistance to antibiotics

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APPENDIX B9 – Safety Assessment of Triclosan

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

Summary of triclosan safety data

Triclosan human pharmacokinetics data. Although much of the human data relates to oral exposure, there are some human studies that examine triclosan pharmacokinetics after dermal exposure on the hands or body (Refs. 1-3). The dermal absorption of triclosan has been estimated or characterized using a variety of formulations and techniques, as described in this subsection. The available data show that dermal absorption of triclosan is low.

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

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

Using a reported industry estimate (Ref. 4) that a 10 ounce (295.5 mL) bottle contains enough body wash for 29 washes, the estimated amount of body wash per use would be 10.2 mL (295.5 mL/29 washes = 10.2 mL/wash). Assuming that an individual bathes twice a day with a 1% triclosan-containing body wash, the total mean volume estimate would be approximately 20.4 mL. This is less than the mean amount used in the handwash study (21.6 mL/day). Based on the pharmacokinetic data provided, steady-state was achieved during the study, indicating that the study was of sufficient length to evaluate the pharmacokinetics of chronically administered triclosan.

Another of the available studies (Ref. 2) addresses triclosan exposure as a result of multiple product use. Two groups of 84 subjects were enrolled in this 13-week study.

One group used triclosan toothpaste twice a day plus triclosan bar soap for face and handwashing twice a day plus triclosan deodorant once a day. The other group used triclosan toothpaste twice a day plus placebo soap and deodorant. Blood was drawn before product usage and at 3, 6, and 13 weeks.

At baseline, there was no significant difference in the mean triclosan plasma concentrations between groups. After product use, however, the mean triclosan plasma concentrations were significantly higher in the multiple triclosan-containing product group (highest achieved concentration: 31.04 ng/mL) than in the toothpaste only group (highest achieved concentration: 22.47 ng/mL) for all three time points. This suggests that the use of multiple triclosan-containing products can lead to higher triclosan exposure than from use of a single product. The concentrations observed in this study are substantially lower than the range of concentrations at steady-state that were observed in the handwashing study (Ref. 1). The substantial increase in triclosan concentration from baseline to 3 weeks indicates that the majority of the absorbed triclosan in this study was due to the use of the triclosan-containing toothpaste.

There have been several studies that attempted to estimate the absorption of triclosan following topical application in a variety of different formulations (Refs. 3, and 5-7). In these studies triclosan was delivered as a solution, in toothpaste, as a mouthwash, or in a cream. Despite the different properties of the dosage forms and vehicles used, the estimated absorption was approximately in the range of 5-15% of the applied dose. Based on these data, the impact of different formulations on the dermal absorption of triclosan appears to be minimal.

In summary, while 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 healthcare setting are not available.

Triclosan ADME data. Triclosan is readily metabolized in both humans and animals to two main parent conjugates, triclosan glucuronide and triclosan sulfate. Several other minor metabolites have been detected in animal studies (Refs. 8-11); however, the relevance of these minor metabolites to humans is unknown. In humans after oral or oral plus dermal triclosan exposure, triclosan glucuronide is the primary circulating metabolite in plasma (Ref. 2). After a single oral exposure to 4 mg of triclosan, the triclosan levels in human plasma increased rapidly and reached maximum concentration within 1 to 3 hours (Ref. 12). In this study, the majority of the triclosan in plasma was conjugated; the unconjugated fraction of triclosan in plasma was 30-35%. Triclosan was cleared from the plasma at a rate of 2.9 L/hour.

There also are some data to suggest that triclosan is metabolized during passage through the skin. Moss, Howes, and Williams (Ref. 5) examined dermal metabolism of triclosan in vivo in the rat and in vitro using rat or human skin in flow-through diffusion cells. In both species, triclosan was metabolized during passage through the skin to triclosan glucuronide and triclosan sulfate. Triclosan was more readily metabolized to the glucuronide conjugate, which was also more readily removed from the skin than the sulfate conjugate.

The elimination pattern of triclosan varies depending on the species. Triclosan is excreted mainly via urine in humans (Ref. 12) and hamsters (Ref. 9), while it is eliminated mainly through feces in mice (Ref. 10) and rats (Ref. 13). After a single oral administration of 4 mg of triclosan to human subjects, the majority of the triclosan was excreted in urine within the first 24 hours (Ref. 12). There was considerable variability among subjects; between 24 and 83% of the dose was excreted within 4 days after exposure. The urinary excretion half-life ranged from 7 to 17 hours, and excretion approached baseline levels by 8 days after exposure.

In the multiple exposure handwash study (previously described in this section (Ref. 1)), the mean elimination half-life for total triclosan after multiple dermal exposures was 33 hours. This is longer than the elimination half-life calculated after a single oral exposure (12 hours). The authors suggest the reason for this difference is that absorption through the skin takes longer than absorption from the gastrointestinal tract.

It is well documented that triclosan in aqueous solution can be degraded into 2,8-dichlorodibenzo-p-dioxin and other degradation products by heat or ultraviolet irradiation (i.e., photodegradation) (Refs. 14-20). Although the data support photodegradation in aqueous solution, we found no data regarding whether photodegradation of triclosan can occur on human skin. It is not known whether photodegradation products would be formed on human skin after topical application of triclosan-containing antiseptics and, if so, whether they would be absorbed or affect the skin. Because of this new information regarding photodegradation of triclosan, we propose that data are needed regarding the potential for formation of triclosan photodegradation products on human skin as a result of consumer antiseptic use and, if present, their effects on the skin.

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

New triclosan findings. A recent study evaluated the physiological effects of triclosan treatment on muscle function in mice and fish (Ref. 21). The authors observed a negative effect on both cardiac and skeletal muscle function as a result of a single triclosan treatment and identified a mechanism to explain the observed effect. While this finding suggests a previously unidentified toxicity of triclosan, it is a preliminary finding that has not been duplicated. Further, the mice were treated by injecting triclosan into the abdomen (i.e., intraperitoneal administration), rather than through a more relevant route of administration, such as the oral or dermal route. We invite comment on what these findings tell us about triclosan's potential impact on human health and the submission of additional data on this subject.

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

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

In contrast to the oral data, there are little data regarding dermal toxicity of triclosan. Short-term dermal toxicity studies in rats and mice show dose-related dermal adverse effects following a 14-day treatment period. Similar dermal effects were seen in a 90-day subchronic dermal toxicity study in rats. A long-term dermal carcinogenicity study could be used to assess the relevance of the short-term dermal toxicity findings to a chronic use situation; however, currently no long-term dermal carcinogenicity data are available. Because these data are not available but are needed to fully evaluate the safety of triclosan, FDA nominated triclosan to NTP for toxicological evaluation. The NTP studies will evaluate the dermal carcinogenicity potential following chronic dermal exposure to triclosan (Refs. 22-23) and these studies are ongoing.

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

Triclosan DART data. In the 1994 TFM, we stated that we were evaluating the data from a two-generation study of the reproductive toxicity of triclosan in rats. In this study, rats that were exposed to a high dose (3,000 ppm) of triclosan in utero showed lower neonatal survival and lower mean body weights compared to untreated controls. The offspring of these rats (i.e., F2 pups) had a lower rate of survival to weaning compared to untreated controls. Based on the findings from this two-generation study, we recommended that a segment II study should be conducted to address the decreased survival among the high dose-treated litters.

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

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

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

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

Triclosan data on hormonal effects. Recent studies have demonstrated that triclosan has effects on the thyroid, estrogen, and testosterone systems in several animal species, including mammals (Refs. 24-31). In addition, effects were also seen in the hamster carcinogenicity study (e.g., a reduction or absence of spermatozoa, abnormal spermatogenic cells, and partial depletion of one or more generations of germ cells in male testes in the high dose-treated group). The implications of these findings on human health, especially for children, are still not well understood.

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

Triclosan resistance data. Much of the recent data looking at cross-resistance between antiseptic active ingredients and antibiotics involve an evaluation of triclosan. Several bacterial species that showed reduced susceptibility to triclosan were also resistant to one or more of the tested antibiotics (Refs. 32-44). This trend was seen for both gram-negative (*E. coli*, *Pseudomonas aeruginosa*, *Salmonella enterica*, *Stenotrophomonas maltophilia*, *Acinetobacter*, and *Campylobacter*) and gram-positive (*Staphylococcus aureus*, including MRSA) organisms. Although the clinical relevance of these studies is not clear, the possibility that triclosan contributes to changes in antibiotic susceptibility warrants further evaluation.

One of our concerns stems from the observation that triclosan exposure can lead to changes in bacterial efflux pump activity. Several studies (Refs. 34, 36, 38, and 45) suggest that an efflux mechanism is responsible for the observed reduced triclosan susceptibility. In addition, overexpression of efflux pump regulatory genes also leads to reduced triclosan susceptibility in *E. coli* (Ref. 46).

In addition to bacterial efflux activity, other mechanisms have been documented that may also contribute to reduced antiseptic susceptibility and cross-resistance, e.g., changes in bacterial membrane (Ref. 47). This type of nonspecific mechanism, in theory, could work against multiple antibiotics or antiseptics.

Other data suggest that different mechanisms of action may occur at different triclosan concentrations. In the laboratory, at low concentrations triclosan has a specific action against a bacterial enzyme (FabI), while high concentrations act against less specific targets, such as the cell membrane (Ref. 48). Currently, there is not enough information to know which scenarios, if any, could occur under actual use conditions.

Although numerous studies have evaluated the antiseptic and antibiotic susceptibility profiles of clinical or culture collection strains, there are few studies that evaluate the susceptibility profiles of bacterial isolates from real world settings. In a pair of studies (Refs. 49-50), Lear and colleagues collected, identified, and measured antimicrobial susceptibilities of bacteria from industrial sources. Samples were taken from a factory and laboratories of companies that manufacture products containing triclosan, where it

was likely that the organisms were exposed to this ingredient. Of approximately 100 industrial isolates, two triclosan-tolerant isolates were chosen for further study (*Acinetobacter johnsonii* and *Citrobacter freundii*).

The authors then determined the antibiotic susceptibility profiles of the two industrial isolates compared to standard culture collection strains (Ref. 49). The authors saw no difference in the antibiotic susceptibility patterns of the industrial and standard strains of *A. johnsonii*. In contrast, the *C. freundii* industrial isolate was more resistant to 12 of 14 antibiotics tested. These changes in antibiotic susceptibility were quite modest, however. While this industrial isolate showed only modest changes in susceptibility for most of the tested antibiotics, it still demonstrates a change in the antibiotic susceptibility pattern after triclosan exposure. Unfortunately, the number of sites that were sampled was low (50 total sites), only two isolates were studied, and the time and extent of triclosan exposure is unknown.

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. 32-44)
- Data define triclosan's mechanisms of action and demonstrate that these mechanisms are dose dependent (Ref. 48)
- Data demonstrate that exposure to triclosan changes efflux pump activity, a common nonspecific bacterial resistance mechanism (Refs. 34, 36, 38, and 45)
- Data show that low levels of triclosan may persist in the environment (Refs. 51-58).

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

- Data to characterize the concentrations and antimicrobial activity of triclosan in various biological and environmental compartments (e.g., on the skin, in the gut, and in environmental matrices);
- Data to characterize the antiseptic and antibiotic susceptibility levels of environmental isolates in areas of prevalent antiseptic use, e.g., in the healthcare 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.

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, including documentation of validation of the methods used to measure triclosan and its metabolites
- Animal ADME
- Dermal carcinogenicity
- Data regarding the potential for formation of photodegradation products on human skin and their effects on the skin

- Potential hormonal effects
- Data to clarify the relevance of antimicrobial resistance laboratory findings to the healthcare setting

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