MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 22, 2005

From: Topical Antiseptic Review Team

Through: Division of Nonprescription Regulation Development
Office of Nonprescription Products (ONP)

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

Subject: October 20, 2005 NDAC Meeting

Topical antiseptics are used to reduce the risk of infection by killing or inhibiting the growth of microorganisms on the skin. Currently available antiseptic products are diverse, targeted for different populations, use settings, and specific indications, as summarized in the table below. These products can be divided into three broad categories based on the proposed use: healthcare antiseptics, consumer antiseptics, and food handler antiseptics. Healthcare antiseptics are products intended for use by healthcare professionals and consist of healthcare personnel handwashes, surgical hand scrubs, and patient preoperative skin preparations. Consumer antiseptics, also called antiseptic handwashes, are largely marketed as antibacterial soaps (both liquid and solid dosage forms) and are intended for handwashing and general body cleansing. Food handler antiseptics are marketed for handwashing in a variety of food handling establishments. Each of these categories includes antiseptic products intended for use without water (leave-on products) that are marketed for hand cleansing and are called hand sanitizers. These category and product labels will be used for the purposes of the NDAC meeting.

Summary of Currently Available Antiseptic Products			
Product	Target Population	Marketed Use(s)	Use Setting
Healthcare antiseptics: Healthcare personnel handwash Patient preoperative skin preparation Surgical hand scrub Healthcare hand sanitizer	Healthcare professionals, Patients	To reduce bacteria on the skin prior to patient care or surgery To help reduce bacteria that potentially can cause disease	Hospitals, clinics, doctor's offices, outpatient settings, nursing homes

Product	Target Population	Marketed Use(s)	Use Setting
Consumer antiseptics: Consumer antiseptic handwash Consumer antiseptic bodywash Consumer hand sanitizer	General population	To reduce bacteria on the hands To reduce body odor To prevent infection	Homes, day care centers
Food handler antiseptics: Food handler handwash Food handler hand sanitizer	Commercial food handlers	To reduce the risk of food-borne disease	Commercial food establishments, e.g., restaurants, food processing plants

All categories of antiseptics are regulated as drugs by the U.S. Food and Drug Administration (FDA) under either the monograph or new drug application (NDA) process. The majority of antiseptic products are currently being marketed under the Tentative Final Monograph (TFM) for over-the-counter (OTC) Healthcare Antiseptic Drug Products, published in 1994. Manufacturers are not, however, required to comply with FDA's proposed monograph requirements. Compliance with a subsequent final monograph would be required. Manufacturers may continue to market products covered by the TFM subject to the risk that products not in compliance with the final rule will need to be made compliant. NDAC is being asked at this meeting to participate in ONP's ongoing development of policy for the final monograph.

The 1994 TFM encompassed healthcare antiseptics and some products from the consumer antiseptics category. Consumer antiseptic handwashes and consumer hand sanitizers were considered in the TFM to be components of an "antiseptic handwash" category. This category in the TFM did not include consumer antiseptic bodywashes for general body cleansing. Prior to the 1994 TFM, the term "antimicrobial soap" was used to describe the products that are now considered to be consumer antiseptic handwashes and bodywashes. The evolution of these categories has been of particular interest to the regulated industry who, in response to previous rulemakings, found the "antimicrobial soap" and "antiseptic handwash" categories overly restrictive (i.e., not inclusive of all relevant products) and proposed the alternative categories that are being used for the purposes of this NDAC meeting.

ONP is seeking input from NDAC about the role of topical antiseptics meant for use by consumers outside of healthcare settings. Recently, concerns have been raised about the potential hazards to either the individual or the community by using these products. Further, unlike the use of antiseptics in the hospital or healthcare setting where the potential risk and impact of infection is greater, the benefit of the use of consumer antiseptics is less clear.

NDAC will be asked to consider whether:

- antiseptics marketed for consumers are appropriate for the general population and have a valid use for this population

- consumer antiseptics should be regulated separately from healthcare antiseptics
- the evidence provided by the manufacturers of consumer antiseptics is sufficient to demonstrate a benefit for the consumer who uses these products
- the benefits of antiseptic hand and body products outweigh the potential risks to the consumer in nonhospital settings

This summary memo provides a further introduction to the NDAC discussion issues and the background material presented in this package. Points to consider in preparation for the meeting are presented in italics throughout this document (***NDAC TOPIC***). Following presentations of additional data at the October 20 meeting, FDA will seek NDAC input regarding the risks and benefits of antiseptics for consumers. A glossary of abbreviations and acronyms is provided at the end of this memo.

1. Regulation of Consumer Antiseptics

Consumer antiseptics are OTC drugs and currently are being evaluated under the Healthcare Antiseptic rulemaking. However, in the Final Rule for Healthcare Antiseptic Drug Products, consumer antiseptics may be placed in a separate category from healthcare antiseptics if they are deemed different from healthcare antiseptics. This way, FDA can address any differences in active ingredients, labeling, and testing criteria for consumer and hospital products. A separate category may also be made for food handler antiseptics.

1.1. What is the OTC Drug Review?

Certain – but not all – OTC drugs that were marketed before the beginning of the OTC Drug Review (May 11, 1972) may be marketed without specific approval pending publication of final regulations under the ongoing OTC Drug Review. Once a regulation covering a specific class of OTC drugs is final, those drugs must either -

- Be the subject of an approved **New Drug Application (NDA)**, or
- Comply with the appropriate **monograph**, or rule, for an OTC drug.

A more in-depth description of the regulation of OTC drugs is provided in **TAB 14**.

1.2. What information about consumer antiseptics has been published as part of the OTC Drug Review?

The following table is a summary of the Federal Register documents related to the development of the rulemaking for consumer antiseptic drug products. This information is available in the public record. A copy of the most recent document, the 1994 Tentative Final Monograph, is provided in **TAB 15** for your reference. ONP is working to finalize this monograph in the near future and would like to have a clear definition of the functions and attributes of consumer antiseptics**.**

Federal Register Notice	Information in Notice
September 13, 1974 (39 FR 33102) Establishment of a Monograph for OTC Topical Antiseptic Drug Products	FDA publishes the recommendations of the Advisory Review Panel on OTC Topical Antiseptic Drug Products (the Panel) on the following categories: (1) antimicrobial soap, (2) healthcare personnel handwash, (3) patient preoperative skin preparation, (4) skin antiseptic, (5) skin wound cleanser, (6) skin wound protectant, and (7) surgical hand scrub. ● Antimicrobial soaps were defined as products "designed to reduce the microbial flora of the skin. Both the resident and transient pathogenic and non-pathogenic flora of the skin may be reduced by the use of an antimicrobial soap." ➢ The Panel recognized that these products might be used repeatedly by consumers, possibly for a lifetime and noted their increasing presence in the OTC marketplace. ➢ Data evaluated by the Panel caused it to voice the hypothetical concern that the routine use of topical antimicrobials may have a long-term harmful effect by reducing the protective effect of the normal skin flora thus leading to an increase in certain kinds of skin infections. ➢ Studies to demonstrate the ability of antimicrobial soaps to prevent skin infection were not sufficient. ➢ There were no generally recognized as safe and effective active ingredients for antimicrobial soaps recommended by the Panel. ➢ Labeling claims were limited to antimicrobial or antibacterial soap and deodorancy. ➢ The Panel stated that only one of the drug product categories, skin antiseptic, needed clinical data to support the effectiveness of these products. The benefit of the reduction of transient and resident bacteria is sufficiently supported as an added benefit in all other products where antimicrobials are included in the formulation.
January 6, 1978 (43 FR 1210) TFM for OTC Topical Antimicrobial Drug Products	FDA publishes the TFM containing the Commissioner's tentative conclusions and proposed effectiveness testing of the drug product categories evaluated by the Panel. The TFM reflects the recommendations of the Panel and FDA's evaluation of comments and data submitted in response to the Panel's recommendations. ● The distinction between antimicrobial soaps and healthcare personnel handwashes was expanded. ➢ Antimicrobial soaps are intended to be used by the general public only in nonhospital settings.

	➢ The different circumstances of use require different labeling for consumer antimicrobial soaps and healthcare personnel handwashes. ➢ FDA felt that some common claims for healthcare personnel handwashes could be misleading to the average consumer. ➢ Labeling claims for the prevention of infection or reduction in skin bacteria suggested by the comments were not accepted by FDA. ● FDA stated its concern about the proliferation of triclosan-containing products and concluded that if the number of sources of the ingredient appears dangerously high the availability of triclosan-containing products should be curtailed, especially in bar soaps, which provide total body exposure on a repeated daily basis.
July 22, 1991 (56 FR 33644) Amendment to the TFM for OTC First Aid Drug Products	FDA amends the TFM to establish a monograph for OTC first aid antiseptic ingredients. This antiseptic category is indicated for the prevention of skin infection in minor cuts, burns, and abrasions. ● The distinction between antimicrobial soaps as drugs and cosmetics is clarified. ➢ Antiseptic products that include antimicrobial labeling, e.g., kills the germs that cause body odor, are drugs and are required to demonstrate effectiveness.
June 17, 1994 (59 FR 31402) Amendment to the TFM for OTC Healthcare Antiseptic Drug Products (**TAB 15**)	In this notice, FDA amends the TFM to establish a monograph for OTC healthcare antiseptic drug products. This category is generally intended for use by healthcare professionals. ● FDA concludes that antimicrobial soaps are a dosage form and removes them from evaluation as a drug product category. ● FDA recognizes the need for an antiseptic handwash for repeated or daily use over an extended period of time. ➢ The current definition of an antiseptic handwash is a product "used by consumers on a more frequent, even daily, basis and includes products for personal use in the home, such as when caring for invalids and during family illness." ➢ These products may contain the same active ingredients as professional use products, but are labeled and marketed for different intended uses. ➢ The TFM makes no distinction between healthcare personnel handwashes (i.e., hospital products) or antiseptic handwashes (i.e., consumer products) with

	regard to testing criteria or effectiveness requirements. ● FDA concludes based on new information that proliferation of triclosan-containing antiseptics is not a concern.

In addition to the Federal Register documents, two public NDAC meetings have been held on topics that relate to the current issues for consumer antiseptics. On January 22, 1997, NDAC held a joint meeting with the Anti-Infective Drugs Advisory Committee (AIDAC) to discuss antibiotic and antiseptic resistance issues related to the Healthcare Continuum Model (described in section 3) for professional use products. At that time, the committees concluded that decreased susceptibility to antiseptics was not a concern. However, they recommended that on-going surveillance for the possible development of resistance to these agents is prudent.

More recently (March 23, 2005), an NDAC meeting was held regarding surrogate endpoints used to demonstrate the effectiveness of antiseptic products used in healthcare settings. Despite limited information about the correlation between the effectiveness criteria based on clinical simulation (e.g., bacterial log reduction) studies and clinical benefit, NDAC did not feel that sufficient evidence was presented to justify lowering the efficacy standards proposed in the TFM for professional use products. These standards are also proposed in the TFM for application to the consumer antiseptics.

2. Defining Consumer Antiseptics

Antiseptics are used to prevent infection by killing or inhibiting the growth of microorganisms. Because these products are used in or on humans or animals, they are considered drugs and are approved and regulated by FDA. In contrast, *disinfectants* are used on inanimate surfaces or objects to destroy or irreversibly inactivate infectious microorganisms. Consequently, disinfectants, even if they contain the same active ingredient as an antiseptic, are regulated by the U. S. Environmental Protection Agency (EPA).

The term *consumer antiseptic* refers to a class of antimicrobial drug products marketed or proposed for use by the general public in a variety of settings. Currently, consumer antiseptics are marketed as antibacterial soaps, hand sanitizers, and antibacterial wipes. In previous rulemakings, products that now belong in the consumer antiseptic class were designated as either antimicrobial soaps (1974 Notice of Proposed Rulemaking and 1978 Proposed Rule) or antiseptic handwashes (TFM). In the 1974 and 1978 publications, antimicrobial soaps were broadly defined as a soap containing an active ingredient with in vitro and in vivo activity against skin microorganisms. Moreover, the proposed use of these products was not limited to handwashing. The TFM proposes to limit consumer products to handwashes and defines an antiseptic handwash as an antiseptic-containing preparation designed for frequent use. These products should reduce the number of transient microorganisms on intact skin to an initial baseline level after adequate washing, rinsing, and drying. Also, they should be broad-spectrum, fast acting, and if possible, persistent. As

previously discussed, Industry has defined consumer antiseptic more broadly to encompass both hand (antiseptic handwash) and body cleansing (antiseptic bodywash).

2.1. What is the function of a consumer antiseptic? Who should use a consumer antiseptic?

As mentioned previously, the TFM defines antiseptics meant for consumer use as antiseptic handwashes. The antiseptic handwash indication proposed in the TFM is limited to reduction of bacteria on the skin after certain activities. The proposed labeling allows an indication statement "For handwashing to decrease bacteria on the skin" which may be followed by one or more of the following: "after changing diapers," "after assisting ill persons," or "before contact with a person under medical care or treatment." The phrase "recommended for repeated use" also is an allowable indication. No specific claims for the prevention of infection have been proposed by FDA.

Consumer antiseptics often do not adhere to TFM labeling and many are currently labeled with only general claims for the reduction of bacteria on the skin or as antibacterials. These products are also heavily promoted with implied claims that range from use as an adjunct in the prevention of infection in a variety of settings to the reduction of body odor. Consumer antiseptics are marketed to address the consumer's need for products to reduce the number "harmful bacteria" in their environment.

As mentioned above, the purpose of an antiseptic is to prevent infection. The general population is exposed to bacteria from a variety of sources, both at home and in the community. Consequently, there are many situations in the domestic/community setting where hand hygiene is important to help reduce the transmission of infection. However, the question arises: is soap-and-water handwashing sufficient, or are antiseptics necessary.

In certain situations, such as food preparation, other domestic infection control measures are often used in conjunction with hand hygiene. This may include surface disinfection and proper handling of raw food. As a result, it often is not clear what contribution consumer antiseptics make relative to washing with plain soap and water.

In contrast to the handwash products, antiseptic bodywashes are marketed "to kill the germs that cause body odor." However, manufacturers of these products suggest that they may be useful in the prevention and treatment of certain skin infections. The consequence of repeated whole body exposure to these products over the course of a lifetime may be of concern.

Antiseptics also play a part in other home-based activities such as day care of children and care of ill family members. Increasingly, the line between healthcare and consumer is becoming less defined as more patients with serious illnesses are being treated at home. Even though these individuals are not in a hospital, they may be at risk for serious infections due to underlying conditions.

Potential consumer antiseptic users range from healthy adults to immunocompromised individuals. Listed below are just some of the populations that might use consumer antiseptics:

Healthy adult or child	Hospital outpatient at home
Elderly	Person living with cancer
Day care worker	Person with HIV/AIDS
Domestic food preparer	Immunocompromised individual

NDAC TOPIC: *What should the function of a consumer antiseptic be? Is there a need for healthy adults to use consumer antiseptics? Should home caregivers be using consumer antiseptics or healthcare (hospital) antiseptics?*

2.2. What benefit and antimicrobial effect should consumer antiseptics have?

Consumer antiseptic handwashes, like healthcare antiseptic handwashes, are meant to reduce the number of *transient* microorganisms on intact skin after use. The TFM proposes that antiseptic handwashes meant for consumer use should be subject to the same requirements as healthcare personnel handwashes. The currently proposed testing consists of both in vitro and in vivo studies. In vitro studies are designed to demonstrate the product's spectrum and kinetics of antimicrobial activity, as well as the potential for the development of resistance associated with product use.

In vivo test methods and evaluation criteria are based on the premise that bacterial reductions translate to a reduced potential for infection and that bacterial reduction can be adequately demonstrated using tests that simulate conditions of actual use. These studies are designed to demonstrate effectiveness of a product in the presence of a bacterial challenge. The hands are artificially contaminated with a marker organism, and the reduction from the baseline numbers of the contaminating organism is determined after use of the test product. This contamination and handwash procedure is repeated 10 times, and bacterial reductions are determined after the first, third, seventh, and tenth wash. This aspect of the study design is intended to mimic the repeated use of the product. The product must achieve a specified reduction after the first and tenth washes.

The TFM also states that antiseptic handwashes should be broad-spectrum, fast acting, and if possible, persistent. Persistence refers to the ability of the antimicrobial ingredient to remain on the skin after one application of the product. The property of persistence is one of the advantages of antiseptics compared to nonantimicrobial soap. However, specific testing guidelines to demonstrate product persistence are not provided in the TFM. The current efficacy testing for antiseptic handwashes includes a greater log reduction after ten applications. This is meant to show the cumulative, or additive, effect of the product.

Antiseptic bodywashes are generally formulated to target resident organisms, which may cause odor or skin infections. There are no proposed requirements for antiseptic bodywashes since this category has not been included in FDA's 1994 proposal.

NDAC TOPIC: *Should consumer antiseptics be held to the same testing requirements as professional use products? Should consumer antiseptics demonstrate persistence? If so,*

how should persistence be demonstrated? What testing criteria should be used to demonstrate the efficacy of bodywashes?

2.3. What active ingredients are used in consumer antiseptics?

Antiseptics are formulated using antimicrobial chemicals known as biocides. *Biocide* is a general term for a chemical or physical agent that kills all living organisms, both pathogenic and non-pathogenic. Chemical biocides are incorporated into a wide variety of other products in addition to antiseptics, such as surface disinfectants, plastics, fabrics, and paint. In contrast to antibiotics, which have a specific mechanism of action, biocides are generally thought to have multiple target sites within the bacterial cell or more than one mechanism of action.

The TFM currently lists only two active ingredients as generally recognized as safe and effective (GRAS/E) for antiseptic and healthcare personnel handwashes: 60-95% alcohol and 5-10% povidone-iodine. Other active ingredients that were considered by the Advisory Review Panel for use in consumer or healthcare personnel handwashes were benzalkonium chloride, benzethonium chloride, cloflucarban, para-chloro-meta-xylenol (PCMX), 70-91.3% isopropyl alcohol, methylbenzethonium chloride, triclocarban, triclosan, and others. At that time, the Panel did not classify these active ingredients as GRAS/E due to insufficient data on their safety and/or effectiveness.

The following table lists active ingredients that are used in consumer antiseptics.

Product Type	Active Ingredient					
	ALC	BKC	BZC	PCMX	TCC	TCS
Rinse-off handwash			●	●	●	●
Leave-on handwash	●	●	●			
Bodywash				●	●	●

ALC, alcohol; BKC, benzalkonium chloride; BZC, benzethonium chloride; PCMX, para-chloro-meta-xylenol; TCC, triclocarban; TCS, triclosan.

3. Industry Position on Consumer Antiseptics

The manufacturers of consumer antiseptics, primarily represented by the Soap and Detergent Association (SDA) and the Cosmetic, Toiletry, and Fragrance Association (CTFA) Industry Coalition, have submitted several comments to the Healthcare Antiseptic rulemaking regarding the clinical benefit and efficacy of consumer products. These comments have included proposed labeling and efficacy testing requirements. In addition, the Industry

Coalition has provided their position on the development of antimicrobial resistance to topical antimicrobials.

3.1. What information has industry submitted regarding consumer antiseptics?

In 2003, the SDA/CTFA Industry Coalition submitted a citizen petition (CP16; **TAB 1**) regarding consumer antiseptic products. This petition was meant to complement a previous submission regarding healthcare antiseptics that described the Industry Coalition's Healthcare Continuum Model (HCCM; **TABS 2 - 4**). The HCCM encompasses products for healthcare, consumer, and food handler uses, and is based on situational risk due to the specific task or setting, or due to underlying conditions, such as the susceptibility of the host. The general population, food service and food preparation workers, and healthcare professionals use topical antimicrobial products in domestic, institutional, commercial, and healthcare settings. The risk of infection or acquisition of disease from the transmission of microorganisms can be correlated to specific tasks in all of these settings. The Industry Coalition suggests that the exposure, and consequently the risk, to populations of varying susceptibility should determine the desired drug performance and the attributes necessary to mitigate the risk.

To support its position, the Industry Coalition submitted published articles and technical reports regarding the clinical benefit and efficacy of consumer antiseptic handwashes and bodywashes. FDA's review of these articles can be found at **TABS 5** and **6**.

3.2. What is industry's proposal for efficacy criteria for consumer antiseptics?

The Industry Coalition considers the performance criteria specified in the TFM for antiseptic handwashes to be overly stringent. The HCCM recommends lower bacterial log reduction criteria for in vivo testing of consumer products than what is proposed in the TFM. This recommendation is based in part on data submitted to FDA, which is reviewed in TABS 5 and 6. The proposed efficacy criteria from the latest industry proposal (CP16; TAB 1) is summarized in the table below and compared to the 1994 TFM bacterial log reduction criteria for testing of consumer antiseptic handwashes.

The effectiveness criteria proposed by industry, like that proposed in the TFM, is based on surrogate endpoints that have uncertain clinical relevance. Performance criteria for the three professional use categories of healthcare antiseptic products were discussed at a recent NDAC meeting (March 23, 2005). At that time, NDAC believed that there was not sufficient evidence to change the current performance criteria for professional use products.

The Industry Coalition proposes that efficacy should be determined following a single handwash procedure (immediately after product use), with an option for similar sampling after multiple washes to demonstrate cumulative microbial reduction.

Proposed Antiseptic Handwash Efficacy Criteria		
	Bacterial Reduction after 1st wash	Bacterial Reduction after 10th wash
TFM proposal: Antiseptic handwash, all uses	2 $\log_{10}$	3 $\log_{10}$
HCCM proposal: Antiseptic handwash, domestic use	1 $\log_{10}$	Optional
HCCM proposal: Antiseptic handwash, domestic food preparation and food handlers	1.5 $\log_{10}$	Optional

The HCCM proposal does not provide specific bacterial log reduction criteria for antiseptic bodywashes. Instead, the Coalition recommends that a consumer body product should either a) show a significant reduction in resident flora compared to baseline levels as measured using the American Society for Testing and Materials (ASTM) pre-operative skin preparation method, or b) show a significant reduction in transient flora compared to levels attained with use of placebo/bland soap as measured using the ASTM cup scrub technique for antibacterial washes. The TFM does not propose testing or efficacy requirements for antiseptic bodywashes since this category was not identified in any previous rulemakings.

4. Benefits of Consumer Antiseptics

Consumer antiseptics would offer an advantage relative to nonantimicrobial soaps if they a) reduced the numbers of bacteria on the skin over and above the mechanical action of plain soap, b) provided a residual effect (i.e., persistence), or c) demonstrated both actions. The submitted efficacy studies were not designed to address either of these actions.

4.1. To what extent does the published literature submitted by industry establish the clinical benefit of consumer antiseptics?

The SDA/CTFA Industry Coalition submitted numerous journal articles and abstracts to support a clinical benefit from the use of consumer antiseptic handwash products. The majority of the references are clinical studies and were reviewed previously for the March 2005 Healthcare Antiseptic advisory committee meeting. The remaining references describe the clinical benefit of hand sanitizers in elementary schools, microbial risk assessment models, and other experimental models. In addition, a number of references were submitted to demonstrate the benefit of antiseptic bodywashes. A review of the clinical benefit and efficacy data submitted in CP16 can be found at **TAB 5**. A review of the data on the benefit of antiseptic bodywashes can be found at **TAB 6**.

Although the elementary school studies suggest a trend toward reduced germ transmission, they are not designed to address the efficacy of the antiseptic product versus supervised hand

hygiene alone. The studies were open-label and employed multiple interventions, such as educational programs. Also, there were no controls, such as washing with plain soap. Furthermore, they were not formally randomized and did not address their cluster designs in data analysis. Overall, the results of these studies must be interpreted with caution.

Of the remaining studies submitted to support the clinical benefit of consumer antiseptic handwashes, none were designed to address a clinical benefit. In fact, only one study provided infection rate data; however, these investigators did not address antiseptic use. As a whole, these studies provide interesting experimental models, but do not demonstrate reduced infection rates as a result of using consumer antiseptic products.

The Industry Coalition suggests that antiseptic bodywashes should be used for whole body cleansing, to reduce odor-causing bacteria, and to help control bacteria that can cause skin infections (see TAB 3). Most of the submitted bodywash data were not relevant because the investigators studied the use of antiseptic bodywashes as part of treatment regimens for atopic dermatitis, erythrasma, or acne. Treatment of specific disease states like secondary infection of atopic dermatitis or erythrasma are not considered an OTC use for an antiseptic bodywash. Moreover, the majority of the studies were inadequately designed to address the contribution of the antiseptic to the treatment regimen because they employed multiple treatment measures (e.g., topical corticosteroids in addition to the antiseptic bodywash). Thus, there were no data presented to address the impact of antiseptic bodywashes in the prevention of skin infection, and no definitive data demonstrating the contribution of these products to the treatment of skin infection.

4.2. Does the published literature establish a clinical benefit from using consumer antiseptics?

FDA review staff performed a literature search to determine if there is a correlation between use of antiseptic handwashes and a reduction in illness rates in homes, schools, or day care centers (**TAB 7**). A search of the medical literature did not reveal any studies that were able to demonstrate a link between the use of a specific consumer antiseptic and a reduction in infection rates. The one randomized, blinded clinical trial (Larson et al., 2004) that studied triclosan-based soap showed no reduction in symptoms of infectious disease or disease transmission. Furthermore, the literature suggests that consumer handwashing techniques may not result in a clinically significant bacterial log reduction.

NDAC TOPIC: *Is there an added benefit to using consumer antiseptics* in addition *to other infection control measures (e.g., soap-and-water handwashing, surface disinfection) used by consumers in the home? Do antiseptic bodywashes provide any benefit?*

5. Concerns about Consumer Antiseptics

One of the major concerns regarding topical antiseptics is that use of these products may lead to the development of antimicrobial resistance. The importance of this factor is uncertain, largely because the current data are conflicting and unclear.

The Council on Scientific Affairs of the American Medical Association published their findings from a review of the literature on the effectiveness of antiseptic ingredients in consumer products and the implications of such use on antimicrobial resistance (**TAB 8**). They concluded, "The use of common antimicrobials for which acquired bacterial resistance has been demonstrated should be discontinued in consumer products unless data emerge to conclusively show that such resistance has no effect on public health and that such products are effective at preventing infection."

The SDA/CTFA Industry Coalition submitted a comment to FDA regarding the issue of development of bacterial resistance to antiseptic ingredients (**TAB 9**). They state that the information in their submission shows that:

- there is evidence of decreased susceptibility of bacteria to antiseptic agents in laboratory settings;
- there is no evidence, to date, of decreased susceptibility of bacteria to antiseptic agents under use conditions or in the environment;
- there are reviews of the available data by other institutions that have concluded that decreased susceptibility, i.e., resistance, is not a problem at the present under current use conditions; and
- there are existing surveillance programs that are available to monitor the possible emergence of resistance to antiseptic agents.

Furthermore, the Coalition cites conclusions from the January 1997 joint NDAC/AIDAC meeting that the evidence to date indicates that antiseptic wash products do not contribute to antimicrobial resistance. However, the committees also suggested that on-going surveillance for the possible development of resistance to these agents is prudent.

5.1. Do bacteria become "resistant" to antiseptics in actual use?

The recent proliferation of consumer products containing antiseptic ingredients (i.e., biocides) has raised concerns that overuse or misuse of these products may lead to decreased bacterial susceptibility to biocides, similar to the bacterial resistance seen from the overuse and misuse of antibiotics. Bacterial resistance refers to a change in susceptibility such that a previously susceptible organism no longer can be killed or injured by the biocide. The term resistance can only be properly applied to antibiotics where a change in susceptibility to the drug can lead to treatment failure. In contrast, since biocides may affect multiple targets in the bacterial cell, reduced susceptibility does not always correlate with treatment failure at use concentrations. For this reason, a reduction in bacterial susceptibility to a biocide will be noted in the ONP discussion as nonsusceptibility, rather than resistance.

The mechanisms of biocide action are poorly understood. Biocides are believed to have a non-specific mechanism of action and may act on multiple targets in the bacterial cell. Even though biocides are chemically diverse, the damage inflicted on the bacterial cell may be similar. Many biocides affect the integrity of the bacterial cytoplasmic membrane in some way. As a result of either multiple or non-specific mechanisms of action, it is thought that changes in specific bacterial targets leading to biocide nonsusceptibility does not occur. However, recent studies have shown that this may not be true.

The literature suggests that it is relatively easy for bacteria to become less susceptible to a biocide after growth in amounts of the biocide that was not lethal to the bacteria. Notably, reduced susceptibility to moderate-to-high concentrations of triclosan and benzalkonium chloride occurred after exposure to sublethal doses. Many of the published studies examined both clinical isolates (bacteria isolated from hospital infections) and laboratory type strains (bacteria maintained by culture collection laboratories). In general, there was no difference in the adaptive capabilities of clinical or type strains. Moreover, biocide nonsusceptibility was often stable. Taken together, this suggests that biocide nonsusceptibility can occur after exposure to small amounts of biocide and that this phenomenon may occur in the real world. In other words, biocide 'resistance' may not be limited to the laboratory.

Further information on bacterial mechanisms of resistance to biocides and similarities to antibiotic resistance mechanisms is provided in **TAB 10**.

5.2. Is it possible to develop cross-resistance to antibiotics?

Development of biocide nonsusceptibility may also be a concern if bacteria with decreased susceptibility to biocides are also found to be less susceptible to antibiotics, possibly due to common resistance mechanisms. In theory, the use of biocides in consumer products could select for bacterial strains which also are resistant to clinically important antibiotics. This, in turn, could exacerbate the clinical antibiotic resistance problem and make treatment of bacterial infections even more difficult.

FDA review staff performed a literature search to find evidence of a correlation between reduced susceptibility to biocides and antibiotic resistance (**TAB 11**). In most of the studies, bacterial strains that showed reduced susceptibility to biocides also demonstrated antibiotic resistance. However, no clear association was established between biocide nonsusceptibility and antibiotic resistance. For the most part, antibiotic resistance was against second-line drugs or drugs not usually used for therapy. In addition, nearly all of the articles describe laboratory experiments whose relationship to the real world situation is not defined. Although bacterial susceptibilities to antibiotics are fairly well characterized, currently the relevance of a change in the minimum inhibitory concentration of an antiseptic is unknown. Nevertheless, even though the mechanism has not been identified, it is of concern that growing clinical isolates in doses of a biocide that does not kill the bacteria can lead to changes in the organism such that antibiotic resistance profiles also are changed.

NDAC TOPIC*: *Based on the available data, should cross-resistance between antibiotics and antiseptics be considered a concern associated with the use of consumer antiseptic products?

5.3. What effect do consumer antiseptic ingredients have on the environment?

Another concern relating to consumer antiseptics is that the biocides found in antiseptics, as well as disinfectants and other products, may be released into the environment and have ecotoxic effects. Most antiseptic products are disposed of down residential drains, where they undergo treatment by local wastewater treatment plants. During wastewater treatment, many of the chemicals, including biocides, are removed, but some chemicals enter the environment via release to surface waters (e.g., rivers and lakes). Until recently, no one

looked for the presence of biocides from antiseptics in the environment. No municipal wastewater treatment plants are currently engineered to remove these chemicals.

While FDA does not monitor or regulate biocides in the environment, we felt it was important to get NDAC feedback on the importance of this issue to drug regulation. FDA is required under the National Environmental Policy Act of 1969 (NEPA) to consider the environmental impacts of approving new drug and biologics applications (NDAs and BLAs) as an integral part of its regulatory process. For these environmental assessments, FDA considers harm to the environment to include not only toxicity to environmental organisms, but also environmental effects other than toxicity, such as lasting effects on ecological community dynamics. In contrast, environmental assessments are not usually considered as part of the OTC drug review.

FDA review staff performed a literature search to summarize the published data on the fate and effects of biocides used in consumer antiseptics (**TAB 12**). Nearly all the information we found pertained to the occurrence and fate of triclosan in the environment. Recent studies examining rivers and streams in the US and Europe suggest that many organic contaminants, including triclosan, survive wastewater treatment and biodegradation, and can be detected at low levels in the environment, particularly in surface waters and sediment.

Despite continual introduction of triclosan into water sources, a number of mechanisms for its removal have been identified. Some of the triclosan leaves surface waters and wastewater treatment plant influent via sedimentation. In addition, several investigators have shown that triclosan in surface waters can be degraded in the presence of sunlight. However, studies also suggest that this photodegradation can result in harmful products, such as dioxin.

Finally, triclosan has been shown to have some adverse effects on aquatic organisms. Triclosan appears to inhibit the growth of algae and reduce algal species diversity. This is notable because the biocide is affecting organisms at the bottom of the food chain, with unknown consequences on organisms higher up the chain. In higher organisms, triclosan appears to be toxic to early life-stages of fish, but does not appear to have an adverse effect on their reproductive capabilities. However, triclosan induced behavioral changes in both tadpoles and fish that may affect their ability to evade predators or feed properly.

NDAC TOPIC*: *How significant is the environmental impact of these products to the evaluation of the risk from consumer antiseptics?

5.4. Are there other pathways of exposure to biocides?

As mentioned above, biocides may not be completely removed during wastewater treatment. As a result, humans may be exposed to minute quantities of these chemicals via alternate routes of exposure, such as drinking water, with unknown consequences. Moreover, some biocides may enter the terrestrial environment when biosolids from wastewater treatment facilities, which contain adsorbed material, are applied to land. Application of biosolids to land is subject to regulation by the EPA or an appropriate State authority.

5.5. Do consumer antiseptics lead to an increased incidence of allergies?

There is a current theory that inadequate exposure to microbial antigens may lead to incomplete immune system development and explains the increased incidence of asthma and allergies. This is known as the *hygiene hypothesis*. Recent emphasis on disinfection, via antiseptics, surface cleaners, etc., may make our environment too clean. Consequently, our immune systems are not exposed to enough antigens to develop properly. This is a controversial theory, and other theories have been proposed to help explain recent increases in the incidence of asthma and allergies. Review articles on the hygiene hypothesis, and an alternate theory, are provided in **TAB 13**.

Glossary of Abbreviations and Acronyms

AIDAC	Anti-Infective Drugs Advisory Committee
ALC	alcohol
ASTM	American Society for Testing and Materials
BKC	benzalkonium chloride
BLA	Biologic Licensing Application
BZC	benzethonium chloride
CP	citizen petition
CTFA	Cosmetic, Toiletry, and Fragrance Association
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GRAS/E	generally recognized as safe and effective
HCCM	Healthcare Continuum Model
NDA	new drug application
NDAC	Nonprescription Drugs Advisory Committee
NEPA	National Environmental Policy Act
ONP	Office of Nonprescription Products
OTC	over-the-counter
PCMX	para-chloro-meta-xylenol
SDA	Soap and Detergent Association
TCC	triclocarban
TCS	triclosan
TFM	Tentative Final Monograph