

**TAB 1 Comments from the SDA/CTFA Industry Coalition
Regarding the Benefit and Efficacy of Consumer
Antiseptics (75N-183H; CP16)**

The Consumer Products Citizen Petition

May 23, 2003

Submitted by

**The Soap and Detergent Association
and
The Cosmetic, Toiletry, and Fragrance
Association
Industry Coalition**

Executive Summary

The Soap and Detergent Association and The Cosmetic, Toiletry, and Fragrance Association Industry Coalition is submitting the following document to support development of the Monograph for all topical healthcare antiseptic drug products. This Petition complements the August 2001 healthcare professional products submission by providing data on the remaining product categories that comprise the Healthcare Continuum Model (HCCM), namely food handler, consumer hand and consumer body products.

The data submitted support the following key points:

- Healthcare is not limited to clinical settings but extends into the workplace and the home. There is a continuum of risk dependent upon a specific task or setting, and underlying conditions such as host susceptibility. Consequently, there should not be an artificial division of the products into “professional healthcare products” and “consumer products”.
- Topical healthcare antiseptic drug products largely provide a prophylactic benefit rather than a therapeutic benefit.
 - The benefits from the use of topical antimicrobial products to reduce bacteria on both hands (transient flora) and body (resident flora) have been demonstrated.
 - Risk Modeling has also been used to demonstrate prophylactic benefits in reducing both transient and resident flora.
- Finished product testing should be carried out using American Society for Testing and Materials (ASTM) standard methods. Standardized, defined, and peer-reviewed test methodology encourages reliability, reproducibility, and comparability of test results.
- In the 1994 Tentative Final Monograph for Health-Care Antiseptic Drug Products (“TFM”), FDA did not propose performance criteria for product categories other than the historical professional healthcare categories (pre-operative skin preparations, surgical scrubs and healthcare personnel hand products). FDA should adopt performance criteria that are applicable to all product categories and active ingredients, for the defined use situation. These criteria are:
 - Bacterial reductions of 1.5 log₁₀ after a single wash, as measured using ASTM E1174 Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations, reflect a level of efficacy that provides a benefit in a food preparation setting.
 - Bacterial reductions of 1 log₁₀ after a single wash, as measured using ASTM E1174 Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations, reflect a level of efficacy that provides a benefit in a domestic or institutional setting.
 - Bacterial reductions of 1.5 log₁₀ after a single wash, as measured using ASTM E1174 Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations, reflect a level of efficacy that provides a benefit in a domestic food preparation setting.
 - ASTM E 1173 Standard Test Method for Evaluation of a Pre-operative Skin Preparation can be used.
 - a. A significant reduction in resident flora compared to baseline levels as measured using ASTM E 1173 Standard Test Method for Evaluation of a Pre-operative Skin Preparation should reflect a level of efficacy that provides a benefit in a domestic or institutional setting.

OR

- b. A significant reduction in transient flora compared to levels attained with use of placebo/bland soap as measured using ASTM E 1874 Standard Test Method for Evaluation of Antibacterial Washes by the Cup Scrub Technique should reflect a level of efficacy that provides a benefit in a domestic or institutional setting.

Finally, we understand that FDA will address these remaining product categories of the Healthcare Continuum Model (HCCM) proposed in 1995 by the Industry Coalition (food handler products, consumer hand products and consumer body products) in the future. We request that the Agency formalize its intention to do so by a statement in the Final Rule for professional healthcare products.

INTRODUCTION

This document provides information in support of the rule-making for Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) 59 Fed. Reg. 31401 (June 17, 1994).

The Soap and Detergent Association and The Cosmetic, Toiletry, and Fragrance Association Industry Coalition (Coalition) has made a number of submissions to FDA providing data and comments pertinent to this rule-making¹. The Coalition continues to advocate that the Agency should develop a Monograph that encompasses all of the categories of topical antimicrobial products of the Healthcare Continuum Model² (HCCM) as many unresolved issues in the TFM are fundamental to all products in the HCCM. In August 2001, recognizing that the Agency was developing the rule-making for products designated as “healthcare professional products”, the Coalition submitted a Citizen Petition detailing proposed methods and performance criteria for pre-operative skin preparations, surgical scrubs, and healthcare personnel hand products. This Petition complements the August 2001 healthcare professional products submission by providing data on the remaining product categories that comprise the HCCM, namely food handler, consumer hand, and consumer body products.

The HCCM proposes that there is a continuum of risk from infection transmitted by microorganisms on the skin. The severity of the risk is dependent upon the specific task or setting and upon underlying conditions such as susceptibility of the host. While topical antimicrobial products should be formulated and labeled with indications to address specific situational risks, the actual level of risk to an individual may overlap one or more product categories, *i.e.*, there is a continuum of risk among the HCCM product categories. Splitting the healthcare professional products from the other HCCM categories is artificial and potentially misleading.

Healthcare is no longer limited to the health professions. It extends from the home through the surgical suite. The risks mitigated by the use of these healthcare professional products and the other categories overlap. Common issues of finished product test methodology and active ingredient status underpin all HCCM product categories. The Coalition requests that the Agency consider the entire HCCM, rather than addressing healthcare professional products separately from the other categories. If the Agency decides to split the topical antimicrobial monograph, we request that a statement be added in the Final Monograph for professional healthcare products that the remaining product categories of the HCCM will be addressed in future rule-making.

Products in this OTC Monograph largely provide a prophylactic benefit rather than a therapeutic benefit. The demonstration of a prophylactic benefit is more difficult than the demonstration of a therapeutic benefit. In the August 30, 2001 submission to the docket, the Coalition provided a summary of the benefit studies identified in the literature for both clinical and non-clinical settings. There are many more studies showing a benefit in hospital and other clinical settings, in part because the patients in those settings are very vulnerable and also because they are more easily

¹ These have included: comments on the TFM and the proposal of the Healthcare Continuum Model (June 15, 1995), compilations of efficacy data (December 13, 1995 and March 11, 1996), a detailed proposal on finished product testing methodology (September 29, 1999), a Citizen Petition for proposed labeling of HCCM product categories (April 2, 2001), a Citizen Petition addressing several OTC monograph flexibility issues (June 1, 2001), a Citizen Petition on surrogate end-point test methods (November 28, 2001), a Citizen Petition providing information in support of healthcare professional products (August 30, 2001) and a Citizen Petition requesting anti-viral claims based on testing and evidence of efficacy (January 17, 2003).

² Proposed by the Coalition in its June 13, 1995 submission to the docket, the HCCM proposes a framework for the regulation of topical antimicrobial drug products consistent with public health needs in domestic, institutional and commercial settings. Within the HCCM framework, product efficacy qualification is based on the need to mitigate the risk of transmission of organisms or acquisition of disease in specific situations. Finished product testing, using standardized and qualified American Society for Testing and Materials (ASTM) methods, must demonstrate that a product meets threshold performance criteria for that product category.

studied due to the relatively controlled conditions that exist in those institutions. Studies conducted in industrial or domestic settings are much more difficult to control, and the level of susceptibility of the individuals to infection varies considerably. Existing studies that show the benefit of antimicrobial products in non-clinical situations usually involve large numbers of subjects (often in institutional settings) or represent very specific use situations. A number of such studies have been conducted and are detailed herein.

Additional support for the benefits of using topical antimicrobial products is provided by a number of studies using qualitative microbial risk assessment (QMRA), which are also included. QMRA can be used as a tool to provide systematic evaluation of the risk of potential infection associated with the acquisition or transmission of microorganisms in any setting. FDA has used QMRA to project the risk of a number of foodborne pathogens; EPA uses it extensively in the development of drinking and surface water regulations. The advantage of QMRA is that it permits an assessment of the consequences of an exposure in the absence of additional direct experiments on human subjects. It uses experimental data and literature data to develop appropriate discrete or probability distribution functions. A number of QMRA studies indicate that antimicrobial soaps can substantially reduce the risk of infection.

This Citizen Petition addresses three HCCM product categories, *i.e.*, food handler, consumer hand, and consumer body products and is complementary to the Citizen Petition for professional healthcare products submitted by the Coalition on August 30, 2001.

Section 1 reviews situations where food handler products, consumer hand products, and consumer body products are used and the range of expected exposure to microorganisms.

Section 2 briefly reviews the benefits of these products in domestic and institutional settings, proposes performance criteria and appropriate methods, and summarizes the data supporting these proposals.

Appendix A provides a tabular display of the efficacy data used to support the performance criteria.

Appendix B includes the Coalition's proposed labeling for the three categories discussed. This was previously submitted on April 2, 2001.

Finally, the Coalition is committed to working with the Agency to resolve all of the issues associated with this Monograph.

Section 1: The Healthcare Continuum Model

The Healthcare Continuum Model (HCCM) is based on situational risk due to the specific task or setting, or due to underlying conditions, such as susceptibility of the host. Health hazards and exposure characteristics are the main parameters of the framework. The HCCM framework for topical antimicrobial products addresses the need to mitigate the risk of acquiring or transmitting organisms or disease in specific situations. 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 exposure, and consequently the risk, to populations of varying susceptibility determines the desired drug performance and the attributes necessary to mitigate the risk (e.g. fast-acting and persistent).

In September 1999, the Coalition submitted a briefing document to FDA proposing finished product efficacy testing of healthcare antiseptic drug products³. We concur with FDA on the approach of using both *in vitro* and *in vivo* efficacy testing. We recommended conducting Time Kill Tests (*in vitro*) to demonstrate the potential speed of antibacterial activity of a topical antimicrobial product. We also recommended conducting simulated use tests (*in vivo*) specific to the use scenario of the product.

In August 2001, the Coalition submitted a Citizen Petition that summarized the benefits of all topical antimicrobial products and suggested performance criteria using the appropriate *in vivo* simulated use test for three product categories: patient pre-operative preparation, surgical hand scrub, and healthcare personnel handwash. In this submission the Coalition proposes performance criteria using the appropriate *in vivo* simulated use test for three additional product categories: consumer body products, consumer hand products, and food handler preparations.

Situations Considered Herein

The home plays an important role in a number of public health and hygiene issues including the spread of foodborne infections and gastrointestinal infections, the common cold and other respiratory infections, and the development of skin infections (Scott *et al.* 2001, Kagan *et al.* 2002).

A number of surveys of bacterial contaminants of the home have been conducted. Moist areas of kitchens, bathrooms and fabrics (e.g. towels) are frequently found to be highly contaminated with potentially pathogenic organisms. The human body and its wastes are believed to be one of the major sources of these organisms. *Staphylococcus aureus* was isolated from 44% of hand towels and 20% of bathroom floors (Finch *et al.* 1978). *Escherichia coli* and other gram-negative bacteria were found to commonly contaminate wet areas such as sinks, drains, sponges, and dishcloths. They were also found, less frequently, on hard surfaces where there had been hand contact (Scott *et al.* 2001). Additionally, contaminated foods, e.g., chicken carcasses, eggs, produce, serve as another source of pathogenic organisms in kitchens. The likelihood of the transfer of these organisms, either directly from one person to another or indirectly via inanimate objects or ingestion of contaminated foods, will depend upon the hygiene practices of the residents. The risk of infection will depend upon the exposure to the pathogen and the underlying health status of the person acquiring the pathogen.

Rubin (1988) estimated that when one person in a household becomes sick with a *Salmonella* infection, there is a 60% chance that at least one other family member will also become infected. These secondary infections are caused, in large part, by both direct and indirect cross-contamination in the home. It is likely that a similar pattern is true for other infections transmitted

³ Additional data relating to finished product test methodology was submitted to the docket as a Citizen Petition on November 28, 2001.

by the fecal-oral route. Studies have shown that up to 50% of family members become infected when a child contracts *Shigella sonnei* dysentery. This is primarily a result of cross-contamination involving both the hands and inanimate surfaces (Thomas and Tillett 1973).

There is growing consensus among food experts that most cases of foodborne illness originate from food eaten in the home (Fein *et al.* 1995). In a US study of an *E. coli* 0157 outbreak, it was found that 80% of the likely source of contamination (hamburger) was eaten at home, and food preparers in those homes were significantly less likely to report washing their hands or work surfaces than were food preparers in the control households (Mead *et al.* 1997).

A number of studies have demonstrated the potential for hand transfer of either naturally occurring or seeded bacteria from contaminated food products (Humphrey *et al.*, 1994; Cogan *et al.* 1999). The potential for cross-contamination in the kitchen to cause foodborne illness was found to range as high as 39% (Djuretic *et al.* 1996, Evans *et al.* 1998).

The potential for the transmission of pathogens to oneself or to others in the home via direct or indirect means is significant. Topical antimicrobial products are used in domestic situations for both body and handwashing for the purpose of decreasing the overall bacterial load on the skin and thereby reducing the risk of transmission of disease to oneself or to another.

The reduction of the bacterial load on the skin is also important in reducing the transmission of disease to oneself or others outside the home. Topical antimicrobial products are used in many situations outside the home. Examples of institutional and commercial settings include, but are not limited to:

- public restrooms
- schools
- restaurants
- day-care centers
- long-term and residential care facilities
- prisons and correctional facilities
- manufacturing sites, e.g. pharmaceutical manufacturing
- food manufacturing and processing facilities
- offices of physicians, dentists, and other healthcare providers

In these cases, there is a need to reduce the numbers of bacteria and viruses that can be transferred to shared inanimate objects, food, or to other people. In many of these cases, a single source of infection can transfer that infection to many other people through direct or indirect contact. Reducing the bioburden on the skin has been shown to reduce the risk of disease transmission. (Black *et al.* 1981, McFarland *et al.* 1989, Boyce *et al.* 1994)

Exposure

Within the HCCM framework are two main levels of risk: risk of invasive exposure, i.e. the skin barrier is broken, and risk of disease transmission via non-invasive routes. Risk of non-invasive exposure is further sub-divided into risk of microbial transmission to others, either directly or indirectly, and risk to oneself e.g., fecal-oral transmission.

i. Invasive

This submission will not discuss purposeful invasion of the skin integrity due to injections, surgery or catheterization⁴. However, invasive procedures that break the skin barrier are not restricted to a hospital environment. For instance, individuals in the home receiving home-dialysis, self-injecting drugs, or maintaining in-dwelling catheters are at serious risk of infection if hygienic conditions are not maintained. Topical antimicrobial products specifically designated for use in healthcare settings would be the preferred prophylactics in these situations. However, products designed for use by the general population could also be used, assuming they meet the appropriate criteria.

In the healthy general population, the risk of invasive exposure is usually limited to infection primarily by resident bacteria of overt cuts and scratches or microscopic openings in the skin caused by poor skin condition. The normal resident flora of the skin consists predominately of coagulase negative staphylococci, micrococci and coryneforms. Certain individuals are also carriers of *Staphylococcus aureus* and streptococci. In situations where the skin is stressed, these bacteria have been shown to cause overt disease e.g., impetigo (Noble 1992), and/or to further aggravate skin conditions such as atopic dermatitis (Williams *et al.* 1990) or acne (Brown 1977). Topical antimicrobial products can be used to control the numbers and types of bacteria on the skin and can help to mitigate the risk of overt infection or the aggravation of skin conditions.

ii. Non-Invasive

There is a risk of transmission of microbial contaminants, primarily transient organisms, to oneself or from one person to another, either directly through hand-to-hand transmission or indirectly via transmission from food or other inanimate objects.

Transient organisms are those that may be found on the skin but do not normally colonize the skin; many are potential pathogens (Ayliffe 1980). The transfer of transient bacteria via hands is recognized as a common factor in the spread of disease (Maki 1978, Doebbling *et al.* 1992, Bryan *et al.* 1995, Boyle and Pittet 2002). The acquisition of illness may be associated with transmission of transient organisms on the skin to oneself via fecal-oral or respiratory routes. In addition, disease may be transmitted via the hands directly or indirectly to others, which may lead to food poisoning, other enteric diseases, and respiratory infections. An example of direct transmission is seen in daycare situations. Several studies of environmental surfaces in daycare settings have shown that fecal contamination is widespread. Approximately 30% and 20% of hands of children and adult caregivers, respectively, were shown to be contaminated (Ekanem *et al.* 1983, Weniger *et al.* 1983, Van *et al.* 1991). An example of indirect transmission involves currency. Studies of US currency found potential pathogens on 3-18% of the coins and 7-42% of the bills tested (Abrams and Waterman 1972, Jiang and Doyle 1999). These pathogens included *E. coli*, *Pseudomonas aeruginosa*, and *S. aureus*.

The total population is exposed daily to a variety of transient microorganisms depending upon the activities of the individual. The risk of developing an infectious disease depends on many factors, including the virulence and dose of the microorganism and the susceptibility of the host.

The primary means of interrupting the spread of infection are the application of sound principles of personal hygiene, disinfection of contaminated materials, and skin antisepsis. Risk management steps by the individual can interrupt transmission to oneself and to others as well as to inanimate objects that can become sources to others. (Marshall 1997; Krilove *et al.* 1996; Caturelli *et al.* 1996; Hammond *et al.* 2000; Isaacs *et al.* 1989; Isaacs *et al.* 1991).

⁴ August 30, 2001 Citizen Petition addressed the use of topical antimicrobial products in these situations.

While plain soaps can remove pathogenic microorganisms from the skin, topical antimicrobial products can provide an incremental improvement in reducing the numbers of contaminants by either inhibiting or killing the microorganisms left on the skin in addition to removing microorganisms from the skin during the washing process (Montville *et al.* 2002, MacKenzie 1970, Keswick *et al.* 1997)

Summary

Control of microorganisms found on the skin of individuals is important to public health. The potential for the transmission of opportunistic pathogens to oneself or to others is significant, in the home, in institutional and commercial settings, as well as in 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 exposure and, consequently, the risk to populations of varying susceptibilities determine the drug performance desired and the attributes necessary to mitigate the risk.

Products such as consumer hand wash, consumer body wash and food handler products are intended to reduce resident and transient organism populations greater than can be achieved through the use of plain soap. This additional reduction translates to risk reduction in the transmission of potentially pathogenic organisms and in the potential for disease acquisition (Breneman *et al.* 1998, Rose and Haas 1999).

Section 2: The Relationship of Benefit to Efficacy

BENEFITS

The literature review submitted in 2001⁵ demonstrated the benefits of topical antimicrobial products in a wide variety of situations and for purposes not discussed in the 1972 Panel's review. It demonstrated the continuum for risk of infection and the need for different efficacy levels to address those risks. It further illustrated the need to view the entire class of products as appropriate prophylactics for use in home, institutional, and traditional healthcare settings in terms of invasive (e.g., surgery) and non-invasive (e.g., hand washing, body washing) situations.

The scientific literature shows many and varied benefits from the use of topical antimicrobial products. A wide range of use patterns, product forms, and situations were found where the use of topical antimicrobial products contributes to mitigating the risk of infection or disease. The benefits of topical antimicrobial products were observed in institutional and domestic settings for both invasive and non-invasive applications.

Some of the identified studies present confounding issues. Institution of educational programs on hygiene at the time of product introduction, lack of double blind control, or changes in other parameters make quantitative comparisons difficult. Nevertheless, these studies provide a significant body of evidence that supports the concept that the reduction of the transient and resident flora helps to mitigate infection. Furthermore, it is important to remember that topical antimicrobial products are used as part of an overall hygiene regimen and should not serve as the only means of infection control. Even though the variables are not well controlled in many of the studies, the weight of the available evidence demonstrates that *the use of the topical antimicrobial product plays a critical role in infection control.*

Reduction of organisms on intact skin

The effectiveness of washing with non-antimicrobial soap in infection control has been explored for hand transmission sources as well as whole body bathing (Ayliffe 1980, Bartzokas *et al.* 1987, Ehrenkranz 1992, Aly and Maibach 1987). When properly used, these products are effective in the immediate removal of transient organisms from the skin. However, handwashing is frequently incomplete, based on individual practices in terms of the amount of product used (as soaps are "dose less"), and the time of product use and/or product rinsing.

Washing with non-antimicrobial soap leaves no persistent effect as is seen with some topical antimicrobial products. The use of an antimicrobial hand or bodywash provides a reduction of the target microorganism population greater than can be achieved through the use of plain soap. This additional reduction translates to a demonstrable risk reduction in the potential for disease acquisition, or organism transmission.

The risks mitigated by topical antimicrobial products used on intact skin are skin infection due primarily to one's own resident skin flora and the acquisition of illness due to transmission of transient organisms from oneself or others via fecal-oral or respiratory routes.

Products used primarily for the control of the resident flora of the skin include soaps, leave-on products, wipes and other dosage forms containing antimicrobial ingredients. These are designed for use on face, hands and body. Products with different modes of action, different means of application, and different effectiveness levels should be used to appropriately address the risks associated with the specific tasks performed.

⁵ SDA/CTFA Industry Coalition Citizen Petition providing information in support of healthcare professional products August 30, 2001.

A growing body of evidence demonstrates that topical antimicrobial products provide a benefit by reducing the number of organisms on intact skin. Because the incidence of skin infection is low and because the desired effect of topical antimicrobial products on the resident flora is small (yet significant), large studies would be required to demonstrate the benefit of these products. Large-scale studies with numerous participants increase clinical study variability, as more parameters need to be controlled. Thus, most of these studies which show the control of skin infection and transmission of disease are conducted with institutionalized subjects whose diets, activities, climate, environment, and other parameters are somewhat controlled.

In domestic, institutional, and commercial settings, the risk of invasive exposure is largely limited to infection, primarily by resident bacteria, of overt cuts and scratches or through microscopic openings in the skin caused by poor skin condition. Almost all of the published studies in this area were conducted in institutional settings. Improvements in infection rates and wound healing were seen following bathing with topical antimicrobial products in institutional facilities (Dubow and Winter 1967, Hoffmann *et al.* 1999) and military academies (MacKenzie *et al.* 1970).

- A significant reduction in the number of infections of moderate to severe lacerations occurred with the use of an antimicrobial soap (0.75% hexachlorophene, 0.75% triclocarban) for daily bathing and wound cleansing (Dubow and Winter 1967).
- Use of a triclosan-containing hand lotion after washing with a chlorhexidine product resulted in a 60% reduction in skin/wound infections compared to using the chlorhexidine product alone in a 3-month trial (Hoffmann *et al.* 1999).
- A significant reduction in the incidence of cutaneous infections resulted from the daily use of an antimicrobial soap (0.75% hexachlorophene, 0.75% triclocarban) at a military academy (MacKenzie *et al.* 1970).

Certain disease states may also be associated with increased bacterial colonization. Two examples are atopic dermatitis, a superficial inflammation of the skin, and acne. Topical antimicrobial products have been shown to help in mitigating these conditions particularly when used as an adjunct to traditional therapies. To be clear, the Coalition is not recommending that the topical antimicrobial products be labeled as treatments for acne or atopic dermatitis, rather it is providing this information to further support the benefits of these products for use by the general public.

The numbers of *S. aureus* isolated from the skin of patients with atopic dermatitis is reported to be greater than those isolated from normal skin (Breuer *et al.* 2002, Leyden *et al.* 1974). This is a complicating factor in the clinical management of this disease even though it is unclear whether *S. aureus* has a specific pathogenic role in atopic dermatitis or if its presence simply represents an opportunistic colonization of the bacteria at a more susceptible site. Reduction of the resident flora has been shown to provide a benefit when used by subjects with atopic dermatitis (Breneman *et al.* 1998, Akiyama *et al.* 1997, Sugimoto *et al.* 1997).

Topical antimicrobial products have also been used as an adjunct treatment for acne (Brown 1977, Franz *et al.* 1978, Jampani *et al.* 2000a, Jampani *et al.* 2000b, Stoughton and Leyden 1987) and erythrasma (Somerville *et al.* 1970).

- Acne patients used povidone-iodine foam twice daily for 6 months in conjunction with their normal acne therapy. A significant improvement in the condition was seen in 56% of the patients, while another 28% showed a moderate benefit (Brown 1977).
- Patients using an anti-acne product containing 0.1% triclosan for 8 weeks showed a substantial decrease in the numbers of inflamed (43-44%) and non-inflamed (21-22%) lesions and a reduction of overall inflammation (Franz *et al.* 1978).

- An alcohol-containing hand gel was used on the face by patients with acne or secondary bacterial inflammations with pseudofolliculitis barbae for 12 or 8 weeks, respectively. Significant improvements in skin condition were observed (Jampani *et al.* 2000b).
- A significant reduction of acne papules plus pustules count as well as comedones was seen following a 12-week treatment regimen using 4% chlorhexidine gluconate. The formulation was effective in resolving existing lesions and preventing new lesions (Stoughton and Leyden, 1987).
- Use of an antimicrobial bar soap containing triclosan, triclocarban and cloflucarban resulted in a significant reduction in scaling and incidence of erythrasma following 6 weeks of use (Somerville *et al.* 1970).
- Use of an antimicrobial bar soap containing 1.5% triclocarban for 9 weeks caused a significantly greater improvement in the severity and extent of skin lesions (atopic dermatitis) than the placebo soap regimen in patients that were carriers of *S. aureus* (Breneman *et al.* 1998).
- Following use of a 10% povidone-iodine solution for two weeks, atopic dermatitis patients had decreased levels of erythema and exudation in patients colonized with moderate numbers of *S. aureus* (Akiyama *et al.* 1997).
- Use of 10% povidone-iodine solution as part of a treatment regimen for atopic dermatitis led to significant improvement of skin condition (Sugimoto *et al.* 1997).

Reduction of organisms transmitted between individuals and/or fomites.

Microorganisms that are deposited on the skin but do not colonize it are called transient flora to distinguish them from resident skin flora that do colonize the skin. One important hygienic distinction between resident and transient bacteria is the greater ease of removal of transient bacteria either by washing with soap and water or by use of topical antimicrobial products (Lilly and Lowbury 1978). When non-antimicrobial soap is used, handwashing efficacy appears to depend on the effects of the surfactant along with friction applied during the washing and rinsing process. Rinsing removes bacteria by dilution (Lucet *et al.* 2002).

Handwashing compliance is poor. Surveys of the US population (ASM "clean hands" initiative, 1996 and 2000) repeatedly reflect poor hand hygiene habits of the general population. People frequently fail to wash their hands following use of the toilet or prior to handling food, despite surveys in which people say they always wash their hands in those situations. Other studies (Li-Cohen and Bruhn 2002, Larson *et al.* 1986) support the conclusion that, for a variety of reasons, handwashing is not performed as frequently as it should. Even when handwashing is performed, it frequently is not as rigorous as might be desired to limit infectious disease transmission. A study of handwashing behaviors in public lavatories, homes, and schools (Toshima *et al.* 2001) indicates that the average handwash is significantly less than 30 seconds and in most cases less than 10 seconds. The use of surfactant-based product is also low in many of these settings, i.e. many people only rinsed their hands. In fact, it is very likely that the only time hands are washed for greater than 20 seconds and with a surfactant-based product is during bathing/showering, or during pursuit of certain household tasks such as hand dishwashing.

In addition, there is increasing evidence that the wash protocols recommended in surgical and other hospital settings, as well as in food service institutions (*i.e.*, typically handwashing with a surfactant-based product for 20 or more seconds followed by a thorough rinse) are not performed in those settings (Snyder 1998, Kerr *et al.* 1993, Fein *et al.* 1995).

An estimated 65-81 million Americans contract a foodborne illness from food prepared in the home, even though most reported foodborne infection outbreaks occur from ingestion of food prepared and consumed outside the home (Albrecht 1995). However, most consumers believe that foodborne illness occurs less frequently in the home than outside. This common misconception may explain the extent of unsafe food handling practices in the home. A national survey of US consumer handling practices of fresh produce was conducted, and almost half of the respondents indicated they did not always wash their hands before handling fresh produce (Li-Cohen and Bruhn 2002).

Scott (1999) reviewed several aspects of hygiene within the home, and concluded that hygiene in the home plays an important role in public health issues. The critical role of hygiene in the home was demonstrated, particularly its effect on the transmission of foodborne illness. In her review Scott cited data from studies done in England and Wales (Sockett *et al.* 1993) and the Netherlands that show that more than 80% of Salmonella and Campylobacter infections are acquired in the home. Data from Italy (Scuderi *et al.* 1996) indicate that more than 70% of Salmonella infections are acquired in the home.

Uthoff (1997) reviewed several studies that showed how contaminated surfaces and transfer of contaminants to the hands could transmit foodborne infections. There is a growing body of evidence that the likelihood of infection from direct contact with a contaminated surface, and subsequent ingestion by such mechanisms as hand-to-mouth contact is a common means of disease transmission. One such study (Borneff *et al.* 1988) stated that infections in the home were three times more frequent than in commercial settings. The authors attribute this to the fact that transmission control measures are not taken in the home.

Topical antimicrobial products have been repeatedly demonstrated to aid in mitigating the risk of transmission of transient microbial contaminants directly from one person to another, or indirectly via inanimate objects including food.

Chamberlain *et al.* (1997) studied the effect of a 10-second handwash using non-antimicrobial products on naturally-acquired contaminants and artificially contaminated hands. They found that the mean reduction on naturally-acquired contamination was less than 50%, *i.e.*, there was little effect on reducing the numbers of naturally-acquired bacteria. When artificially contaminated hands were sampled following a 10-second handwash, a 90% reduction was seen.

A recent study by Lucet *et al.* (2002) demonstrated the benefit of using an antimicrobial handwash over a non-antimicrobial handwash with a 10-second handwash in a managed care setting. While the non-antimicrobial handwash provided a significant reduction in naturally-acquired contaminants as opposed to no washing, use of the antimicrobial handwash provided an even greater reduction (statistically significant) than the non-antimicrobial handwash. They concluded that handwashing with unmedicated soap does not reliably remove pathogenic bacteria from hands.

The risk of transmission of microbial contaminants, primarily transient organisms, to oneself or from one person to another either directly or indirectly via food and other inanimate objects is significantly impacted by the use of topical antimicrobial products. Benefits have been demonstrated in both institutional and domestic settings.

- Use of a triclosan-containing hand lotion after washing with a chlorhexidine product resulted in a 71% reduction in eye-infections and an overall reduction in infections when compared to only washing with the chlorhexidine product. This 3-month trial was conducted in a long-term care facility (Hoffmann *et al.* 1999).
- Symptoms of enteric disease (diarrhea and vomiting) were significantly reduced over a one-year period in family day care homes using an intervention regimen that included an alcohol-based hand rinse (Butz *et al.* 1990).

- Student absenteeism due to infection was reduced by 19.8% in elementary schools that used an alcohol gel hand sanitizer (62% ethanol) compared to control schools using soap and water. Teacher absenteeism decreased 10.1% in the schools where hand sanitizer was used (Hammond *et al.* 2000).
- The number of absences in 5 independent schools over a 3-month period was 50.6% lower ($p < 0.01$) with a regimen that included a one-hour education session and use of alcohol based hand sanitizer (Guinan *et al.* 2002).
- A 30.4% reduction in infection rates was seen in units using an alcohol gel hand sanitizer as compared to units using soap and water handwashes in an extended care facility for a period of 34 months (Fendler *et al.* 2002).
- A consistent and dramatic decrease in illness-related absenteeism of elementary school children resulted from the use of an alcohol-free instant hand sanitizer when compared to normal hand washing (Shinder and Dyer undated, Dyer *et al.* Shinder 2000).
- A significant reduction in the rate of respiratory infection was seen when staff used alcohol foam over a 4-month period in three adult day care centers (Falsey *et al.* 1999).
- A retrospective review of 427 contact lens wearers with eye infections showed that 89% used non-antimicrobial soaps, while only 11% used antimicrobial soaps. When the source of infection was determined for 62 contact lens wearers with eye infections, *S. aureus* or *S. epidermidis* was the case in 52% of non-antimicrobial soap uses, and only 30% of antimicrobial soap users (Samalonis 1999).
- Use of a 4% chlorhexidine wash product and a 1% chlorhexidine powder decreased the carriage levels of *S. aureus* by 86% after 8 days of use and significantly lowered the rate of recolonization and cross-contamination of family members (Leigh and Joy 1993).
- Regular disinfection of the fingertips with a 2% iodine solution resulted in a significant reduction in the acquisition of respiratory disease (12.5%) when compared to a placebo (36%) (Hendley and Gwaltney 1988).
- *Ad libitum* use of a hand disinfectant (ethanol) by new mothers in a hospital maternity ward significantly decreased the incidence of puerperal mastitis (Peters and Flick-fillies 1991).
- Use of an alcohol based hand wipe after washing with soap and water significantly reduced the rate of transfer of bacteria from the hands to contact lens (Ly *et al.* 1997).

Quantitative Microbial Risk Assessment (QMRA)

QMRA has increasing acceptance as a predictive and decision-making tool for assessing the consequences resulting from human exposure to infectious agents. Ongoing improvements in data-gathering, mathematical modeling, validation testing as well as real-world experience have led to the growing importance of QMRA for the evaluation of antimicrobial interventions under a variety of conditions. For example, the US FDA has published several QMRA studies of food-borne pathogens (FDA 2001a, 2001b). Further refinements of QMRA are a high research priority according to FDA/CFSAN's joint three-year research plan of the National Food Safety initiative (FDA 2001c). Several QMRA studies indicate that topical antimicrobial products can substantially reduce the risk of infection.

- Bathing with a 1.5% triclocarban product provided a potential 20-fold reduction in the risk of skin infection by *S. aureus*, relative to use of a non-antimicrobial product. In this study (Rose and Haas, 1999), the dose response data measured the rate of skin infection following inoculation with *S. aureus* (Singh *et al.* 1971).
- The probability of infection from contamination of raw meat during meal preparation was predicted to be significantly lower among users of topical antimicrobial hand products than among users of regular soap (Marie *et al.* 2002). These results supported previous conclusions from QMRA showing the importance of handwashing in the reduction of infection during food preparation (Chen *et al.* 2001).
- Montville *et al.* (2002) conducted a risk assessment based on data collected from the scientific literature and from laboratory experiments to discern the primary factors influencing final bacterial counts on the hand in the preparation of foods. Two of the three most important factors were sanitizer use and soap use. Antimicrobial soap was shown to be more effective than plain soap.
- Gibson *et al.* (2002) developed a quantitative risk assessment model for transmission of Shigella, the bacterium most frequently associated with outbreaks of infectious intestinal disease in daycare settings (Van *et al.* 1991). They found that the use of an antimicrobial soap could reduce the probability of disease acquisition by a factor of 20% beyond washing with a non-antimicrobial product.

Based on the studies identified above, the Coalition agrees with the finding of the Jan. 6, 1978 TFM, OTC Topical Antimicrobial Products (43 Fed. Reg. 1210), that “the reduction of the normal flora, both transient and resident, has been sufficiently supported to be considered a benefit. The only determination that remains, therefore, is how much of a reduction in microbial flora will be required to permit claims for the various product classes.” The proposed methods to demonstrate efficacy for each product class and performance criteria are discussed below.

EFFICACY

The efficacy of topical antimicrobial products can be defined as the ability to mitigate the risk of disease transmission and/or the ability to mitigate the risk of skin infection. Where the risk mitigated is primarily that of disease transmission, i.e., for consumer hand and food handling products, the product should be effective with each and every use. The user should not have to wash or apply the product repeatedly in order to obtain efficacy. The first wash of the day should provide benefit as well as the last. For antimicrobial body products, where the primary risk addressed is that of skin infection, a cumulative and/or persistent effect⁶ is appropriate. The risk of skin infection is low and the use of a prophylactic antimicrobial product can further lower that risk (Rose and Haas, 1999).

Theoretically, the incidence of infection should be directly related to a specified dose of organisms that cause that infection. However, numerous mitigating factors influence whether an infection can become established, including immunological status of the host, viability and virulence of the infectious agent, and route of infection. These factors make it difficult to calculate precisely the level of bacterial reduction needed to demonstrate the benefit of a prophylactic agent. However, it is possible to demonstrate a significant incremental benefit from the use of topical antimicrobial products.

⁶ Cumulative effect is defined as a progressive decrease in the numbers of microorganisms recovered following repeated applications of a test material. This effect manifests itself in *in vivo* surrogate endpoint test as an increase in the log₁₀ reductions of products following two or more applications. Cumulative effect should not be confused with persistence that is time dependent, rather than application dependent.

While there are many studies demonstrating the benefit of using topical antimicrobial products, very few present data on the reduction of bacteria at the treated site. However, there are many other studies, without a clinical endpoint, that measure the reduction of bacteria on treated skin using topical antimicrobial products that are known to be efficacious and shown to provide a benefit. Many of these studies evaluate these topical antimicrobial products using methods based on the pertinent ASTM method. More importantly, some studies evaluate product performance versus the natural flora in situations that mimic typical use patterns. This makes it possible to extrapolate the results from an efficacy study to a benefit study that uses a clinical endpoint. However, this approach does not take into consideration many of the other factors cited earlier that affect the benefit of using the product.

Two factors that must be considered in reviewing the data are the initial bacterial load and neutralization of samples. For studies using marker organisms or natural flora, the initial bacterial load must be considered as it has been shown to affect the overall outcome of efficacy studies (see August 30, 2001 submission). Also, most active ingredients are substantive and may continue to affect bacterial growth and viability during the processing of sampling fluids. If they are not effectively neutralized, their efficacy may be overestimated.

Food Handler

Bacterial reductions of 1.5 log₁₀ after a single wash as measured using ASTM E1174, Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations, reflect a level of efficacy that provides a benefit in a food preparation setting.

The criterion is appropriate for inclusion in the Final Monograph provided neutralizer is incorporated into all sampling fluids.

Food workers have been shown to be significantly more likely to carry food pathogens on their hands than the general public. For example, Kerr *et al.* (1993) surveyed the hands of workers in food retail and manufacturing sites for *Listeria*. Twelve of the 99 food workers surveyed carried *Listeria* spp. and 7% carried *L. monocytogenes*. Upon observation only one of the *Listeria* carriers was deemed to have washed his hands “adequately”; the others failed to use soap/antimicrobial handwash or washed for less than 10 seconds.

Topical antimicrobial products labeled for food handling situations are formulated, marketed, purchased, and used as aids in preventing the transmission of foodborne illness. Both the FDA Food Code (FDA 2001d) and the USDA recommend the development of Hazard Analysis and Critical Control Point systems for food preparation establishments. Both refer to the use of hand antimicrobials as a measure available in a concerted effort to break the chain of transmission of diseases.

Historically, the US Department of Agriculture (USDA) regulated the products used in USDA inspected meat and poultry processing facilities (USDA 1974). USDA authorized these products using a system that classified them as follows:

- E2 Hand Cleansers with documented sanitizing efficacy. The USDA Food Safety and Inspection Service (FSIS) required the use of the Association of Official Analytical Chemists (AOAC) Chlorine (Available) in Disinfectants Test to demonstrate that the product is equivalent to 50 ppm available chlorine *in vitro* (AOAC 2000). This test is commonly referred to as the AOAC Chlorine Equivalence Test. USDA reviewed, tested and authorized products in this category from 1970 to 1998. Common active ingredients included chloroxylenol (PCMX), triclosan, triclocarban, alcohols, quaternary ammonium compounds, chlorhexidine gluconate and iodophors.

E3 Hand Sanitizers that do not possess cleansing capabilities. The efficacy of these products was also measured using the AOAC Chlorine Equivalency Test. Typically, they were dips, shakes or rubs. They are applied in the prescribed manner and are not rinsed off the hands. USDA reviewed and authorized products in this category from 1958 to 1998. 21 CFR 178.1010 restricted the active ingredients in this category to iodine or quaternary ammonium chloride.

Prior to 1998, products authorized for use in meat and poultry processing plants inspected by USDA were identified in the List of Proprietary Substances and Nonfood Compounds that was issued annually. Since that time Food Inspectors have had a difficult time in ascertaining the appropriateness of products used for hand cleansing and sanitation in meat and poultry plants. Subsequently, non-government organizations, such as National Sanitary Foundation⁷ (NSF) and Underwriter's Laboratories (UL)⁸, have stepped in to provide fee-based nonfood compounds registration programs that provide registration marks for products used in these facilities. Product testing is usually not part of the review unless requested by reviewers on a case-by-case basis.

We believe FDA needs to provide statutory leadership by setting standards for these products in this Monograph. The fact that these non-statutory registration programs can develop different standards for these products could cause even greater confusion in the future. Furthermore, the E-classification system was applied only to products used in meat and poultry plants and did not apply to the many antimicrobial products sold for use in kitchens, non-meat/poultry food processing plants, delicatessens, restaurants, bakeries, supermarkets, and other sites where food is prepared for consumption.

In the 1994 TFM FDA asked for comments on how to best regulate products used by the food industry as hand sanitizers or dips⁹. The Coalition proposed the Food Handler category to cover all institutional, commercial and retail food preparation sites including those previously regulated by the USDA¹⁰. A proposal for labeling this category of products was submitted April 2, 2001¹¹. This submission proposes appropriate efficacy methods and performance criteria (following sections).

In the Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations (ASTM E1174-00), hands are artificially contaminated with a marker strain. As these products are largely designed for removal of transient species, this is an appropriate method for evaluation of these food handler handwash products. There is a provision within this method for modification to allow for the evaluation of handrubs and sanitizers.

Montville *et al.* (2002) conducted a risk assessment based on data collected from the scientific literature and from laboratory experiments which discerned the primary factors influencing final bacterial counts on the hand. Two of the three most important factors were sanitizer use and soap use. Antimicrobial soap was shown to be more effective than plain soap. The authors estimated that transfer rates of a gram-negative indicator species from hands to lettuce was about 1%. They estimated that is equivalent to approximately a 2 log₁₀ reduction. In simulation predictions, the use of an antimicrobial hand product, paper towels, a sanitizer, no hand jewelry, and a touch-free hand washing system would result in a ≤ 3 log₁₀ CFU reduction on hands about

⁷ NSF Registration serves as a gateway for a product to be included in the NSF White Book, which is published in hardcopy, on CD-Rom, and online. NSF Registration requires NSF Review (formulation and label review) against the NSF Registration Guidelines for Proprietary Substances and Nonfood Compounds (previously the USDA Guidelines for Obtaining Authorization of Compounds to be Used in Meat and Poultry Plants), which include the FDA 21 CFR. Further information on NSF is available on their website www.nsf.org/usda.

⁸ Further information on U/L is available on their website www.ul.com.

⁹ FR 59 No. 116 p. 31440, Comment 28.

¹⁰ Citizen Petition filed June 13, 1995.

¹¹ The Citizen Petition for proposed labeling of HCCM product categories (April 2, 2001) is appended.

92% of the time. As this recommendation is based on the use of more than one antimicrobial product, it supports our proposal of a 1.5 log₁₀ for a single product.

Active ingredients commonly used in foodservice applications include: chlorhexidine gluconate, alcohol, iodine, triclosan, chlorine and quaternary ammonium compounds. We reviewed the efficacy data generated using the healthcare personnel handwash method on chlorhexidine gluconate, alcohol, iodine, triclosan, and PCMX in our August 2001 submission on healthcare applications. That body of evidence demonstrated that formulations containing these ingredients could meet the more stringent criteria put forth for healthcare personnel. Consequently, those products containing chlorhexidine gluconate, alcohol, iodine, triclosan, or PCMX would also meet the requirements for food service applications.

In addition, chlorine and quaternary ammonium compounds should be considered for the food handler category. These ingredients have been used successfully in the food preparation and service industry for many years under the regulation of the USDA. Please note that while chlorine is not listed as a potential active ingredient in the 1994 TFM, chlorine was used in these applications prior to 1972 and has served the food preparation industry well as both a standard and as a product. We are able to present only limited data for chlorine, as most efficacy testing has been conducted using the AOAC Chlorine Equivalency Test (AOAC 2000), which uses chlorine as a standard. As seen in Tables 1 and 2, preparations containing benzalkonium chloride or chlorine can meet the performance criteria proposed for this category.

The Coalition believes that adoption of its proposed methodology, performance criteria, and labeling (see Appendix C, Table 4) will provide users engaged in commercial, institutional, and consumer food preparation with efficacious products that will help to reduce the transmission of foodborne illnesses. We believe that with this labeling, the FDA regulation would provide USDA inspectors with an assurance of appropriateness of products for use in food preparation settings.

We also believe that the justification for use of these products in industrial and institutional food preparation illustrates the natural extension of the continuum of topical antimicrobial use to the consumer sector where food preparation is an ever-present activity. If a consumer-targeted product were to have claims specific to the use of the product to help prevent the transmission of foodborne pathogens, the Coalition proposes that it should also meet the efficacy criterion of a food handler product.

Consumer Hand Product

Bacterial reductions of 1 log₁₀ after a single wash as measured using ASTM E1174, Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations, reflect a level of efficacy that provides a benefit in a domestic or institutional setting; and bacterial reductions of 1.5 log₁₀ after a single wash as measured using ASTM E1174, reflect a level of efficacy that provides a benefit in a domestic food preparation setting

These criteria are appropriate for inclusion in the Final Monograph, provided neutralizer is incorporated into all sampling fluids.

In the Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations, hands are artificially contaminated with a marker strain. As these products are largely designed for removal of transient species, this is an appropriate mechanism for evaluation of these products. There is a provision within this method for modification to allow the evaluation of handrubs and sanitizers.

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.

Using ASTM E 1174, test products should be compared to baseline. An internal control should be used to demonstrate that the procedure used at a testing facility is valid under the test conditions on the day the procedure is conducted. Inclusion of an internal control standard should be routine in simulated in-use tests.

In a three month trial at a long-term care facility, Hoffmann *et al.* (1999) found that use of a triclosan-containing hand lotion after washing with a chlorhexidine product resulted in a 71% reduction in eye-infections and an overall reduction in infections when compared to only washing with the chlorhexidine product. The reduction of transient flora cannot be measured in this type of study. The log₁₀ reduction in resident flora on the hands from use of the antimicrobial lotion after washing with an antimicrobial wash approximated 0.125 log₁₀. This report indicates that a benefit can be seen from controlling the microflora even by very small reductions in the bacterial numbers.

Gibson *et al.* (2002) developed a microbial quantitative risk assessment model to examine the risk reduction achieved from using non-antimicrobial and antimicrobial wash products after diaper changing. They demonstrated that adequate washing of hands after diapering reduced the risk, and it can be further reduced by a factor of 20% by the use of an antimicrobial product. The model was based on handwashing data (Bartzokas *et al.* 1987) that showed a mean reduction of 0.06 to 0.25 log₁₀. This demonstrates again that a small reduction in the number of pathogens on the hand can have a significant impact on disease transmission.

Data support the suitability of the active ingredients commonly used in consumer hand applications, which include alcohol, triclosan, parachlorometaxyleneol (PCMX), quaternary ammonium compounds, and triclocarban. We reviewed the efficacy data generated using the healthcare personnel handwash method on alcohol, triclosan, and PCMX in our August 2001 submission on healthcare applications. That body of evidence demonstrated that formulations containing these ingredients could meet the more stringent criteria put forth for healthcare personnel handwashes. Consequently, those products would also meet the requirements for consumer hand applications. In addition, Table 9 includes data from another study on triclosan.

Benzalkonium chloride data were presented in the context of the food service industry. Again, as that body of evidence demonstrated that formulations containing benzalkonium chloride could meet the more stringent criteria put forth for food service, those products would also meet the requirements for consumer hand applications. Triclocarban has been used extensively for the past 30 years in antimicrobial bar soaps. While its spectrum of activity is directed primarily to gram-positive bacteria, it can be formulated to provide a wider spectrum of activity¹². Table 4 presents examples of the efficacy of triclocarban as measured by the healthcare personnel handwash assay. In these examples triclocarban-containing products meet the efficacy criteria for a consumer hand product.

The actual level of risk to an individual may overlap one or more product categories, *i.e.*, there is a continuum of risk among the HCCM product categories. Therefore, the Coalition proposes that if a product formulated for consumers were to make claims specific to the use of the product to help prevent the transmission of foodborne pathogens, it should meet the efficacy criterion of a food handler product as well.

¹² In the 1994 TFM, FR59 No. 116. p. 31408 comment C6 FDA notes that when properly formulated in a final product, the spectrum of activity of antimicrobial ingredients with a targeted spectrum of activity (such as triclocarban, chlorxylenol or triclosan) can be broadened to include additional activity against the test microorganisms.

Consumer Body Product

- A significant reduction in resident flora compared to baseline levels as measured using ASTM E 1173 Standard Test Method for Evaluation of a Pre-operative Skin Preparation should reflect a level of efficacy that provides a benefit in a domestic or institutional setting.
OR
- A significant reduction in transient flora compared to levels attained with use of placebo/bland soap, as measured using ASTM E 1874 Standard Test Method for Evaluation of Antibacterial Washes by the Cup Scrub Technique should reflect a level of efficacy that provides a benefit in a domestic or institutional setting.

Either criterion is appropriate for inclusion in the Final Monograph provided neutralizer is incorporated into all sampling fluids.

ASTM E1173 and ASTM E 1874 each use a scrub cup technique. The pre-operative method (ASTM E 1173) uses the scrub cup technique to sample specific body sites having a specified resident bioload. In the cup scrub method (ASTM E 1874) the bioload may be either the resident flora or transient flora. For transient bacteria, surrogate markers can be used to ensure a sufficient level of bacteria to allow measurement.

In a quantitative microbial risk assessment, antimicrobial soaps were shown to have the potential to substantially reduce the risk of infection by *S. aureus* (Rose and Haas, 1999). The study used experimental dose response data which measured the rate of skin infection following inoculation with *S. aureus* (Singh *et al.* 1971). Risk as a function of both dose and time of contact with the skin was characterized using a 1.5% triclocarban product. Rose and Haas (1999) generated data on growth kinetics to interpret the dose-response and characterize the risk of skin infection. They found a nearly twenty-fold reduction in exposure and risk from the use of the germicidal soap compared with use of the control soap.

Breneman *et al.* (1998) demonstrated the improvement of skin condition following use of a 1.5% triclocarban product. Measurement of the resident flora after product use showed a reduction of carriage of *S. aureus* of approximately 0.3 log₁₀ as compared to baseline. Those patients identified as *S. aureus* carriers at baseline showed a reduction of 1.9 log₁₀.

Akiyama *et al.* 1997 showed an improvement in skin condition following two weeks of use of a 10% povidone-iodine solution. All subjects carried greater than 3 log₁₀ *S. aureus* in the areas affected by atopic dermatitis. Following use of the povidone-iodine solution, only 3 of 26 subjects still had carriage of greater than 3 log₁₀; 11 of 26 subjects had levels less than 2 log₁₀. In the placebo group, only 5 of 21 subjects showed any improvement in *S. aureus* carriage, and only one of those had less than 2 log₁₀. These results indicate that improvement can be seen by controlling the microflora, reducing their levels by one log₁₀ or less.

Active ingredients commonly used in consumer body applications include: triclosan, PCMX, quaternary ammonium compounds, and triclocarban. Alcohol, iodine, and chlorhexidine are less frequently used currently, but nothing precludes their use in these applications.

We reviewed the efficacy data generated using the healthcare personnel handwash method on alcohol, triclosan, and PCMX in the Coalition's August 2001 submission on healthcare applications. That body of evidence demonstrated that formulations containing these ingredients could meet the more stringent criteria put forth for healthcare personnel handwashes. Consequently, those products would also meet the requirements for consumer hand applications. Benzalkonium chloride data were presented in the context of the food service industry. Again, as that body of evidence demonstrated that formulations containing these ingredients could meet the more stringent criteria put forth for food service, those products would also meet the requirements for consumer hand applications.

Optional Labeling Information

In addition to the appropriate efficacy testing detailed above, final formulations may be tested to support other truthful and non-misleading statements. The above methods could be used for this purpose as well as other methods including but not limited to: the AOAC Chlorine Equivalency Assay (AOAC 2000), Agar Patch Technique (ASTM E 1882), Modified Cade Technique (ASTM E 1883) and the European Committee for Standardization (CEN) Techniques,

As discussed in Section 12 of the CTFA/SDA Proposal for Finished Product Testing of Health Care Antiseptic Drug Products submitted September 29, 1999, these methods have been used in the past to support product claims and demonstrate the efficacy of topical antimicrobial products. Tables 3, 5, 6a, 6b, 7, and 8 of Appendix A present data demonstrating the efficacy of products containing triclosan, triclocarban, or benzethonium chloride using the Cade and Cup-scrub techniques.

Other Categories

The uses and benefits of topical antimicrobial products are not limited to the active ingredients currently found to be Category I for safety and efficacy, nor are they limited to the six product categories detailed in this submission and the August 2001 submission.

Summary

The HCCM proposes that there is a continuum of risk from infection transmitted by microorganisms on the skin. The severity of the risk is dependent upon the specific task or setting, and underlying conditions such as host susceptibility. Topical antimicrobial products should be formulated and labeled with indications to address specific situational risks, however, the actual level of risk to an individual may overlap one or more product categories, *i.e.*, there is a continuum of risk among the HCCM product categories.

There is compelling evidence that topical antimicrobial products contribute to mitigating the risk of infection or disease acquisition over a wide range of situations, product forms, and use patterns. The performance criteria for *in vivo* simulated use tests proposed herein for food handler, consumer hand, and consumer body products reflect the levels of efficacy that provide benefits in the situations where they are used. These criteria provide an appropriate measure of efficacy that can be related to a significant incremental benefit from the use of such topical antimicrobial products as compared to non-antimicrobial products.

The Coalition believes that significant support has been shown for the benefit of all six categories proposed in the HCCM. Together with the August 30, 2001 submission, we believe we have demonstrated the potential for topical antimicrobial products containing monograph active ingredients to provide the level of efficacy needed to deliver that benefit. The Coalition also provided extensive comments on the *in vitro* and *in vivo* methodologies used to evaluate these products for all categories (September 29, 1999). Consequently, we urge the Agency to consider issuing a single monograph encompassing all topical antimicrobial categories.

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