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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Health-Care Antiseptic Drug Products; Reopening of the Administrative Record; Docket No. 75N-183H

Dear Sir or Madam:

The Soap and Detergent Association and The Cosmetic, Toiletry, and Fragrance Association Industry Coalition ("Industry Coalition") hereby submits the following comments in response to the above referenced rulemaking. These comments supplement previous submissions that the Industry Coalition has made to the FDA 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)[1]. The Industry Coalition continues to advocate that the Agency develop a Monograph that encompasses all of the categories of topical antimicrobial products used in domestic, institutional, and commercial settings.

[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 endpoint test methods (November 28, 2001), a Citizen Petition providing information in support of healthcare professional products (August 6, 2001), a Citizen Petition requesting anti-viral claims based on testing and evidence of efficacy (January 17, 2003), and a Citizen Petition providing information in support of consumer and food-handler products (May 23, 2003). We have been advised by FDA that it is not necessary to resubmit these documents filed since the rulemaking record closed.

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CTFA is the national trade association representing the cosmetic, toiletry and fragrance industry. Founded in 1894, CTFA has an active membership of approximately 300 companies that manufacture or distribute the vast majority of finished personal care products marketed in the United States. CTFA also includes approximately 300 associate member companies, including manufacturers of raw materials, trade and consumer magazines, and other related industries

The Soap and Detergent Association is the non-profit trade association representing some 120 North American manufacturers of household, industrial and institutional cleaning products; their ingredients; and finished packaging. SDA members produce more than 90% of the cleaning products marketed in the U.S.

In response to the reopening of the administrative record to admit additional data, we have developed a supplement to our August 6, 2001 healthcare professional products submission. It provides additional data, published since that submission, regarding the pre-operative skin preparation, surgical scrub, and healthcare personnel hand product categories. These papers were identified by on-going electronic search service based on appropriate keywords.

This submission reconfirms the key points discussed in the August 2001 submission:

- Healthcare professional products are used in a variety of home, institutional, and commercial settings. Such products provide many significant health benefits and are not intended to be solely used by "professional" or "healthcare" individuals.

- 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.

- FDA should adopt performance criteria that are applicable to all product forms and active ingredients, for the defined use situations. The performance criteria proposed in the 1994 TFM are overly stringent and inappropriate in that many products with proven efficacy and benefit (*e.g.*, alcohol, iodine and chlorhexidine gluconate products) fail to attain these levels of bacterial reduction.

We understand that FDA will develop a proposed rule for other product categories such as food handler products, consumer hand products, and consumer body products sometime in the future. We request that the Agency formalize its intention to do so by a statement in the Final Rule for healthcare professional products.

Finally, we are aware of a number of articles that are in preparation for submission or publication that support the efficacy and/or benefit of topical antimicrobial products. We urge the Agency to continue to accept additional data after August 27, 2003.

BENEFITS

Benefits from the use of topical antimicrobial products can be split into two classifications:

- Interruption of infection in an invasive situation due to the transfer of resident bacteria into wounds, incisions, injection sites or otherwise opened skin.
- Interruption of disease transmission to others and oneself in non-invasive situations due to: a) the acquisition of transient bacteria and their transfer to a point of entry into the host, and/or b) skin infections from one's own resident skin flora.

Topical antimicrobial products are an important part of healthcare infection control practices in institutional healthcare settings. Their importance is highlighted in the CDC Guideline for Hand Hygiene in Health-Care Settings (Boyce and Pittet 2002) prepared by the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force.

The examples provided below demonstrate the importance of a topical antimicrobial product in the overall infection control regimen, primarily in clinical settings. Many of the studies presented change more than one variable including the topical antimicrobial regimen. However, these studies demonstrate that the use of the topical antimicrobial plays a critical role in infection control.

Invasive Procedures

Blood cultures – Use of topical antimicrobial preparations on the skin prior to withdrawing blood has been shown to reduce the number of contaminated blood cultures. This reduces the number of times blood needs to be drawn and prevents the prescription of unnecessary medication to fight non-existent infections. Two additional studies are related to this benefit (Calfee and Farr 2002, Olmsted *et al.* 2002).

- No statistically significant difference in blood culture contamination rates was evident when 70% ethyl alcohol, tincture of iodine, or 10% povidone-iodine was used prior to percutaneous withdrawal of blood samples (Calfee and Farr 2002).

  In a randomized, crossover, investigator-blinded study conducted in an emergency department and the inpatient wards of a university hospital, 70% ethyl alcohol, tincture of iodine, or 10% povidone-iodine was used to prepare the skin prior to percutaneous withdrawal of blood samples. A total of 333 (2.62%) of 12,692 blood cultures was contaminated during the

study period. There were no statistically significant differences in the blood culture contamination rates among these three antiseptics. However, there was some evidence suggesting greater efficacy among the alcohol-containing antiseptics.

- Tincture of iodine reduced overall contamination of blood culture rates from 4% to 2% (Olmsted *et al.* 2002).

  A health system intended to standardize use of pre-operative preparations during blood culture collection. Iodine tincture was to replace 2% iodine tincture in 47% alcohol or 70% isopropyl alcohol. However, the change was made to 10% Povidone-iodine system-wide, not iodine tincture. Before standardization, the system-wide frequency of blood culture contamination was 2.5% .The system-wide rate rose to 4% when 10% Povidone-iodine was used. When iodine tincture was substituted for 10% Povidone-iodine, the rate fell to 2%.

Catheters and Intravenous Lines – Contamination of these invasive prostheses comes from both the patient and from the hands of the caregiver. Additional examples of benefit from the use of topical antimicrobial products have been shown (Chaiyakunapruk *et al.* 2002, Kinoshita *et al.* 2002).

- Decrease in urinary tract infections was seen with the introduction of using povidone-iodine after washing the genital area with soap (Kinoshita *et al.* 2002).

  In an intensive care unit, the urinary tract infection rate (number of infections/1000 days) before employment of povidone-iodine was 11.0 (n=142), and 0 (n=332) following use of povidone-iodine after washing with soap.

- In a meta-analysis of eight studies, patients with intravascular catheters had a 2% rate of bloodstream infections when skin disinfection used povidone-iodine (Chaiyakunapruk *et al.* 2002).

  The meta-analysis reviewed 8 hospital-based studies involving a total of 4143 catheters and compared infection rates where povidone-iodine or chlorhexidine gluconate preparations were used as skin antiseptics. The rate of infection using povidone-iodine was 2%, and the rate was 1% with chlorhexidine gluconate.

Non-invasive Procedures

Reduced Infection Rates – Three additional studies showed significant reduction in infection rates: in clinical settings from the use of alcohol hand sanitizers (Fendler *et al.* 2002; Hilburn *et al.* 2003), and in a non-clinical setting from the use of 1.2% triclocarban (Luby *et al.* 2002).

- A 30.4% decrease in infection rate was seen with the use of an alcohol gel hand sanitizer by caregivers in an extended care facility.

  The primary infection types found were urinary tract, respiratory tract and wound infections. In a comparison of the infection types and rates for the two units where hand sanitizer was used with those for the control units where hand sanitizer was not used, there was a 30.4% decrease in infection rates for the 34-month period in the units where hand sanitizer was used (Fendler *et al.* 2002).

- A 36.1% reduction in infection rate was seen with use of an alcohol hand sanitizer by patients and caregivers.

  In an orthopedic surgical unit of an acute care facility the primary infection types found were urinary tract and surgical site infections. Infection types and rates for the unit during the period the alcohol hand sanitizer was used were compared with the infection types and rates for the same unit when the alcohol hand sanitizer was not used (baseline). The results demonstrated a 36.1% decrease in infection rates for the 10 month period that the hand sanitizer was used (Hilburn *et al.* 2003).

- A significant reduction in the incidence of impetigo in a non-clinical setting was seen among children living in a low-income neighborhood of Karachi, Pakistan following the routine use of 1.2% triclocarban soap (Luby *et al.* 2002).

  The routine use of triclocarban-containing soap by children living in a community with a high incidence of impetigo was associated with a 43% reduction in the incidence of impetigo among Pakistani children living in 81 households receiving a 1.2% triclocarban soap, as compared to children in 79 control households with no intervention ($P = 0.02$).

  When compared to children in 81 households receiving placebo soap, a 23% reduction in the incidence of impetigo was seen among children living in households receiving a 1.2% triclocarban soap, as compared ($P = 0.28$) with children receiving a non-antibacterial control soap.

Mathematical Modeling – Two mathematical models were published providing quantitative assessment of risk reduction from hand washing with antibacterial soaps (Gibson *et al.* 2002, Marie *et al.* 2002).

- Adequate washing of hands after diapering reduces the risk of transmission of *Shigella.* The risk can be further reduced by a factor of 20% by the use of an antibacterial soap (Gibson *et al.* 2002).

  A probability of infection model and an exposure assessment based on microorganism transfer were used to evaluate the efficacy of different soap formulations in reducing the probability of disease following hand contact with *Shigella,* an enteric pathogen. Those exposed to asymptomatic shigellosis who used a non-antibacterial control soap had a risk between 49/100,000 and 53/100, and those who used a 1.5% triclosan soap reduced the risk to between 21/100,000 and 43/100. For exposure to symptomatic shigellosis, the probability of infection was 24/100 to 91/100 for those using non-antibacterial control soap, and 15/100 to 91/100 for those using a 1.5% triclosan soap.

- The use of antimicrobial hand wash products after handling raw chicken reduces the probability of infection with *Salmonella* by 3 to 5 orders of magnitude (Marie *et al.* 2002).

  A quantitative microbial risk assessment model was developed to calculate the probability of infection after preparing raw chicken. The most sensitive parameter in the model was the occurrence of *Salmonella* on raw chicken. The second most sensitive parameter was the initial $\log_{10}$ reduction.

EFFICACY

In its August 6, 2001 submission, the Industry Coalition proposed performance criteria for Surgical Scrub Preparations, Pre-operative Preparations, and Healthcare Personnel Handwash Preparations based on an analysis of the data found in the published literature and upon our knowledge of the ASTM methods used to evaluate these products. Table 1 compares the performance criteria proposed in the 1994 TFM and those proposed by the Industry Coalition. Appendix 1 contains a series of tables prepared from the studies described below where the appropriate ASTM methods (ASTM 2002a, ASTM 2000b, ASTM 2000c) were used and the microbiological data were reported.

Surgical Scrub Preparations

In its August 6, 2001 submission, the Industry Coalition reviewed the literature regarding the efficacy of surgical scrubs and, based on an analysis of that data, proposed the following performance criteria: a 1 $\log_{10}$ reduction of the natural flora after a single wash as measured in ASTM E1115 Standard Test Method for Evaluation of Surgical Hand Scrub Formulations (ASTM, 2002a). This reflects a level of efficacy that provides a benefit in the surgical suite. The criterion of a 1 $\log_{10}$ reduction of the natural flora after a single wash is appropriate for inclusion in the Final Monograph provided the baseline contamination level is greater than 5 $\log_{10}$ and neutralizer is incorporated into all sampling fluids.

The level of activity of a surgical scrub preparation depends upon the baseline bacterial level, topical antimicrobial product used, and other factors such as amount of product, scrub time, etc. Since the August 6, 2001 submission, two additional studies on surgical scrubs have been published, one of which includes microbiological efficacy data (Bryce *et al.* 2001).

- Bryce *et al.* (2001) compared a 70% isopropyl alcohol surgical scrub to "traditional" surgical scrubs, *i.e.*, either 4% chlorhexidine gluconate or 7.5% povidone-iodine (use of these products was not separated) in actual surgical situations. The alcohol hand rinse was equivalently effective in reducing microbial hand counts as the traditional pre-surgical scrub, both immediately after hand disinfection and at the end of the surgical procedure.

- Parienti *et al.* (2002) compared a 75% alcoholic solution (propanol-1, propanol-2 and mecetronium etilsulfate) with 4% povidone iodine or 4% chlorhexidine gluconate in actual surgical situations. There was no statistical difference in the surgical site infection rates.

Pre-operative Preparations

In its August 6, 2001 submission, the Industry Coalition reviewed the literature regarding the efficacy of pre-operative preparations and based on an analysis of that data proposed the following performance criteria: bacterial reductions of 1 $\log_{10}/cm^2$ for injection sites and 2 $\log_{10}/cm^2$ for a moist site as measured in ASTM E1173 Standard Test Method for Evaluation of a Pre-operative Skin Preparation (ASTM 2000b). This reflects a level of efficacy that provides a benefit in preparation of skin immediately prior to invasive procedures. These criteria are appropriate provided the baseline contamination level is greater than 4 $\log_{10}$ and neutralizer is incorporated into all sampling fluids.

The level of activity of a pre-operative preparation depends upon the baseline bacterial level, topical antimicrobial product used, and other factors such as amount of product. Since 2001, one additional study on pre-operative preparation has been published.

- Hibbard *et al.* (2002) compared a product containing 2% chlorhexidine gluconate and 70% isopropanol with both 70% alcohol alone and with 2% chlorhexidine gluconate alone. The baseline contamination level on abdominal sites was approximately 2.9 $\log_{10}/cm^2$. Ten minutes after treatment, a 2.52 $\log_{10}$ average reduction was seen for the combination product, compared with 2.54 $\log_{10}$ for alcohol and 2.3 $\log_{10}$ for chlorhexidine gluconate alone.

Healthcare Personnel Handwash Preparations

In its August 6, 2001 submission, the Industry Coalition, reviewed the literature regarding the efficacy of Healthcare Personnel Handwash preparations and, based on an analysis of that data, proposed the following performance criteria: bacterial reductions of 1.5 $\log_{10}$ after a single wash as measured in ASTM E 1174 Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel or Consumer Handwash Formulations (ASTM 2002c). This criterion reflects a level of efficacy that provides a benefit in a healthcare setting. It is appropriate provided neutralizer is incorporated into all sampling fluids.

The level of activity of a healthcare personnel handwash preparation depends upon the baseline bacterial level, topical antimicrobial product used, and other factors such as amount of product, duration of washing, etc. Since the August 6, 2001 submission, a number of additional studies on Healthcare Personnel Handwashes have been published.

- Trick *et al.* (2003) compared the effects of using plain soap and water to using either a 62% alcohol gel or a 1% benzethonium chloride wipe on the presence or absence of transient flora of the hands of 66 surgical intensive care unit nurses. Transient organisms were defined as all organisms other than methicillin-resistant coagulase-negative (MRCN) staphylococci. Compared with the use of plain soap and water, hands cleansed with alcohol-based hand gel were significantly less likely to be contaminated with MRCN staphylococci, *Candida* species, or any transient organism.

- Sickbert-Bennett *et al.* (2002) compared the efficacy of handwashing products in removing *Serratia marcescens* at an exposure time representative of health care workers' observed behavior, a handwashing

time of 10 seconds rather than the ASTM 1174-94 standard time of 30 seconds. Reductions in order of decreasing efficacy were:

- 4% chlorhexidine gluconate (CHG) – 3.77 $\log_{10}$
- 2% CHG – 3.63 $\log_{10}$
- 1% triclosan – 2.49 $\log_{10}$
- 61% ethanol (waterless wash) – 1.77 $\log_{10}$
- non-antimicrobial soap – 1.64 $\log_{10}$
- 0.5% PCMX/40% SD alcohol (waterless wipe) – 0.76 $\log_{10}$
- 62% ethanol (waterless wash) – 0.67$\log_{10}$.

- The efficacies of 2% chlorhexidine gluconate, 61% ethanol hand gel, and chlorine-containing hand wipes were compared with soap and water using *Bacillus atrophaeus* spores as a surrogate of the pathogen *Bacillus anthracis*. Under the use conditions of the test, reductions for 2% chlorhexidine gluconate (1.5 to 2.0 $\log_{10}$) were greater than for chlorine-containing wipes (1.3-2.2 $\log_{10}$). Alcohol, which, contrary to use instructions, was not allowed to dry, showed the lowest reduction. (Weber *et al.* 2003).

- Voss and Goroncy-Bermes (2000) compared a chlorhexidine containing handwash with an alcohol-based hand disinfectant and a non-medicated soap. The average reduction factors after product use were 1.93 for the alcohol product, 0.48 for the chlorhexidine product, and 0.36 for the non-medicated soap.

METHODOLOGY

Since November 28, 2001, when the Industry Coalition submitted its briefing document on the evaluation of health care antiseptic drug products by *in vitro* and *in vivo* surrogate end-point test methods, a number of articles have been published on various aspects of the methodologies proposed for use in this monograph.

Surrogate Organisms

For *in vitro* testing a limited number of culture-collection strains of bacteria should be used as surrogate organisms. These strains should be representative of bacteria encountered in the situations where the products are intended to be used.

- Broek *et al.* (2000) performed a pilot study on an internal medicine ward to determine which bacterial species could be used to monitor transmissions. The results showed *Escherichia coli* is a good candidate for monitoring transmission events in a standard clinical ward, and is thereby a good surrogate or indicator organism for the efficacy of topical antimicrobial ingredients.

- Fischler *et al.* (2003) compared the efficacy of a 4% chlorhexidine gluconate product and a triclosan containing product against both *S. marcescens* and *E. coli* using the Healthcare Personnel Handwash method. The results supported the use of *E. coli* as an appropriate surrogate organism in this test.

Neutralization

Immediate and complete neutralization of the active ingredient in all test time points is necessary in order to provide accurate evaluation of the test material. Validation of the neutralizing system should be conducted.

- Fischler *et al.* (2002) demonstrated the importance of immediate and effective neutralization in developing valid results using the Healthcare Personnel Handwash methodology.

- Jones and Morrison (2002) showed that a delay in neutralization of the active ingredient could increase the reduction of viable bacteria by more than 1 $\log_{10}$ in the Healthcare Personnel Handwash methodology. This could lead to an overestimation of the efficacy of the product.

- Voss and Goroncy-Bermes (2000) demonstrated that with proper neutralization, the level of reduction seen with use of chlorhexidine gluconate products is significantly less than seen in previous studies where neutralizer was either not incorporated or was inadequate.

Water Temperature

Water temperature during washing is one variable that does not appear to have an effect on the reduction of bacteria during hand washing.

- Michaels et al. (2001) demonstrated that the water temperature used in hand washing (over the range of 4.4°C to 48.9°C) had no effect on transient or resident bacterial reduction during normal handwashing.

CONCLUSIONS

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 that are appropriate for each intended use. 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 domestic, institutional and commercial 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 by the Industry Coalition 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 Industry Coalition believes that this and previous submissions demonstrate the benefit of using topical antimicrobial products in domestic, institutional, and commercial settings. Together with the August 30, 2001 submission and the May 23, 2003 submission, we believe we have demonstrated the potential for topical antimicrobial products to provide the level of efficacy needed to deliver that benefit. The Industry Coalition has also provided extensive comments on the *in vitro* and *in vivo* methodologies used to evaluate these products for all categories (September 29, 1999 and November 28, 2001).

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In closing, the Industry Coalition applauds FDA for reopening the administrative record in this rulemaking to formally admit important new data and information on ingredients and testing criteria for consideration in developing the Final Monograph. We ask the Agency to consider the extensive body of scientific

evidence provided by the Industry Coalition over the last eight years, and to modify the test methodologies and performance criteria as delineated in our submissions to ensure the continued availability of safe and effective products with proven health benefits.

Sincerely,

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Vice President – Legal &
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The Cosmetic, Toiletry, and
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Richard I. Sedlak
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cc: Charles J. Ganley, M.D. (HFD-560)
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Table 1:

Comparison of Performance Criteria proposed in 1994 TFM and August 2001 Submission

	1994 TFM Reductions			2001 Industry Coalition Proposed Reductions	
Surgical Scrub Preparations	**Day 1, Wash 1**	**Day 2, Wash 2**	**Day 5, Wash 11**	**Day 1, Wash 1**	
	1 $\log_{10}$ in 1min AND Bacterial count does not exceed baseline within 6 hours on day 1	2 $\log_{10}$ in 1 min	3 $\log_{10}$ in 1 min	1 $\log_{10}$ in 1 min	
Comments	Surgical scrubs should be effective following a single use. A cumulative effect should not be a requirement as alcohol, a Category 1 ingredient, and potentially other effective active ingredients may not provide a cumulative effect.				
Patient Pre-operative Preparations	**Dry Site**	**Moist Site**	**Injections**	**Moist Site**	**Injections**
	2 $\log_{10}/cm^2$	3 $\log_{10}/cm^2$	1 $\log_{10}/cm^2$	2 $\log_{10}/cm^2$	1 $\log_{10}/cm^2$
Comments	As pre-operative preparations are marketed for all surgical site preparations, not just dry or moist sites, it is proposed that only the worse case scenario should be evaluated, i.e. the moist site.				
Healthcare Personnel Handwashes	**Wash 1**	**Wash 10**	**Wash 1**		
	2 $\log_{10}$	3 $\log_{10}$	1.5 $\log_{10}$		
Comments	Healthcare Personnel Handwash products should be effective following a single use. A cumulative effect should not be a requirement as alcohol, a Category 1 ingredient, and potentially other effective active ingredients may not provide a cumulative effect.				