SECTION 2
BENEFITS

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

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

- **A comprehensive literature review demonstrates the many significant benefits of topical antimicrobial products.**

Search Methodology

Topical Antimicrobial Products have been marketed since at least the 1870's. The body of evidence which demonstrates efficacy and benefit is extensive. To prepare this review, multiple sources were consulted. A literature search of electronic databases was conducted which covered literature from the mid 1960's through 2000. The databases included: PUBMED, PUBSCIENCE, MEDLINE, AGRICOLA, Pediatrics Online, WORLDNURSE, ARTICLEFIRST, INSPEC, ERIC, Optometry, and others. Examples of the search terms used include the following and combinations thereof:

> Antimicrobial, antibacterial, antiseptic, antisepsis, biocides, hygiene, skin, skincare, wash, hand washing, alcohol, Chlorhexidine gluconate, ethanol, hexachlorophene, iodine, isopropanol, methanol, PCMX, chloroxylenol, povidone-iodine, quaternary ammonium compounds, Triclosan, Triclocarban, hand sanitizer, hand disinfectant, skin, disinfection, deodorant soaps, soap, surgical scrubs, handwash, patient preoperative preparation, skin sanitizer.

A survey of the Internet was conducted focusing particularly on websites of scientific publishers, government dockets, and websites. A compilation of publicly available marketing and sales literature collected over the past 10 years was reviewed. Through review of the above literature, publications preceding the mid-1960's were collected and reviewed. In addition, previous SDA/CTFA submissions to the FDA were reviewed, including unpublished company data that were submitted to the FDA by the Industry Coalition in 1995 and 1996.

In conducting our literature review, we have considered studies using a variety of active ingredients: those currently under Monograph review, older active ingredients such as hexachlorophene, and products sold as OTC drugs under New Drug Applications. The reduction of bacteria on the skin is the key element in the prevention or mitigation of disease. The particular active ingredient used to reduce the number of bacteria is of lesser importance.

Many of the studies reviewed compare two or more disinfecting regimens, as in some cases it would be unethical to do studies without some cleansing and disinfecting step. This review has no bias for one active ingredient over another. It considers active ingredients that are NDA or prescription (e.g., hexachlorophene), as well as ingredients named in the 1994 TFM.

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

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

Historically, the benefit of using topical antimicrobial products has been to prevent or mitigate skin infections. Thus, the 1974 Proposed Rule, 39 Fed. Reg. 32103 (September 13, 1974) provides definitions for seven categories of products, five of which relate directly to skin infection stemming from invasive and non-invasive situations (Skin Antiseptic, Patient Pre-operative Skin Preparation, Surgical Hand Scrub, Skin Wound Cleanser, Skin Wound Protectant). The 1974 Proposed Rule also accepts the importance of reducing bacteria on the skin to prevent the transmission of disease to oneself or others (Healthcare Personnel Handwash, Antimicrobial Soap). It implicitly acknowledges the importance of reducing the normal resident and transient flora in areas and situations where prudent. This was formally recognized in the 1978 TFM in 43 Fed. Reg. 1210 (January 6, 1978).

The Healthcare Continuum Model (HCCM) considers the situational risk that topical antimicrobial products mitigate and retains many of the category designations put forth in the 1974 Proposed Rule. Unlike the 1974 Proposed Rule, it acknowledges that there is a continuum of risk and efficacy required to address that risk. It recognizes that there are many more product use situations that fall along the continuum such as food handling and "orphan" uses such as peritoneal lavage and perianal washes. In addition, for each situation there are a

number of different procedures or applications that may require differing levels of efficacy. For example, pre-operative skin preparations could include whole body wash products to be used on a number of occasions prior to surgery. To be effective, these would not need to have the same antibacterial performance as a pre-operative product applied only once at the time of incision.

In the 1974 Proposed Rule, topical antimicrobial products were organized into seven categories based on their use situation. In general two broad use situations were found: in the hospital/healthcare setting and in the home. In 1974, seriously ill patients were treated almost exclusively in hospital settings/nursing facilities and kept within the facility until the illness was largely resolved. In 2001 this is not the case. Many severely ill and/or immuno-compromised patients are treated in the home or on an outpatient basis. The patients themselves now do many procedures, such as injections and catheter maintenance, which were previously carried out only by trained healthcare professionals. The trend to transfer care and treatment to the patient and non-professional caregivers and family is increasing. Therefore, the sharp distinction between healthcare in institutional versus home settings is no longer valid. Rather, the more important division is one based on the risks of infection associated with invasive procedures and those associated with non-invasive procedures.

The risk of infection associated with breaking the skin barrier during invasive procedures such as surgery, catheterization, and injection is very real. The aim of skin disinfection is the quick removal and killing of as many of the skin flora as possible at the site of a planned invasive procedure in order to prevent their translocation into the underlying tissues by a knife blade or a needle. The organisms that are primarily associated with these types of infections are Gram positive bacteria derived from the patient or from the caregiver.

The risk of infection associated with non-invasive procedures is equally real. Here, the aim of skin disinfection and killing or inhibition of the skin flora is to: a) prevent the conveyance of transient bacteria from one person directly or via a fomite to oneself or another person, or b) reduce the resident bacteria and thereby control the risk of pyogenic infection, or c) decrease the numbers of resident bacteria associated with diseases such as atopic dermatitis. The organisms that are associated with these types of infections include Gram positive and Gram negative bacteria.

The following review of benefit studies separates them into invasive and non-invasive situations. Brief summaries of each study are provided in Appendix A. Appendix B contains all of the studies we identified in our literature search and provides a brief synopsis of them.

INVASIVE PROCEDURES

Interruption of infection in invasive situations due to the transfer of resident bacteria into wounds, incisions, injection sites or damaged skin

Studies examining clinical endpoints that support the benefits of using topical antimicrobial products in invasive procedures are summarized below. Some of the uses identified below are not encompassed in the traditional names for products used in invasive procedures (i.e., surgical hand scrub, patient pre-operative skin preparation). Yet these are valid and important uses of topical antimicrobial products.

A large number of studies were identified which involve mucous membranes. We have included information from one of these applications below, but have by no means done a comprehensive review of this specific application. Should the Agency desire more information on this topic, we will forward that data upon request.

The following summaries identify studies reporting benefits from the use of topical antimicrobial products in invasive procedures.

Clinical Settings

Surgery – Clinical studies have shown the benefit of using topical antimicrobial products to control the resident flora on surgeons' hands and at the site of incision in many different types of surgery including: intrathoracic procedures (Hughes *et al.* 1966; Klovekorn *et al*. 1985), gynecological surgery (Beaton undated), neurological procedures (Jackson 1972), intraperitonial procedures (Gruer *et al*. 1984; Brown *et al*. 1984), vascular surgery (Grinbaum *et al.* 1995; Denton 1991), and general or elective surgery (Georgiade *et al.* 1990; Brandberg *et al.* 1981; Cruse and Foord 1973; Connell and Rousselot 1964; Burkhardt *et al*. 1986; Berry *et al*. 1982; Denton 1991; Rubio 1987; Onesko and Wienke 1987).

Catheters, ventilators and intravenous lines – Contamination of these invasive prostheses comes from both the patient and from the hands of the caregiver. Examples where benefit from the use of topical antimicrobial products has been shown include:

Decrease in catheter related and ventilator associated infections due to the patient's flora (Levin *et al.* 1991; Maki *et al.* 1991; Garland *et al.* 1995; Beneda and Finney 2000; Tuominen *et al.* 1981).

Decrease in catheter related and ventilator associated infections due to the caregiver's hands (Gould 2000; Boyce *et al*. 1990; Brooks *et al.* 1999; Jones and Newman 2000; Amarante *et al*. 2000; Fauerbach *et al*. 2000).

Opthalmic surgery – Pre-operative preparations for the conjunctiva have been shown to decrease the bacterial contaminants in the eye (Isenberg *et al.* 1985; Isenberg *et al.* 1997; Apt *et al.* 1989).

Skin graft preparation – Use of topical antimicrobial preparations has been shown to minimize bacterial infection of the donor skin, potentially leading to a greater supply of skin for grafting (May *et al.* 1991).

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 (Schifman and Pindur 1993; Tanaka *et al.* 1988).

Surgical glove failure – Use of topical antimicrobial preparations reduced the number of skin bacteria released through pinholes of punctured gloves (Furuhashi and Miyamae 1979).

Pre-operative or post-operative body wash – Use of topical antimicrobial preparations for washing patients either before or after surgery was shown to significantly reduce the number of bacteria on patients' skin (Stuart Pharmaceuticals 1986c; Garibaldi *et al*. 1988; Kaiser *et al*. 1988; Hayek *et al.* 1987).

NON-INVASIVE PROCEDURES

Interruption of disease transmission in non-invasive situations to others and oneself due to the acquisition of transient bacteria and their transfer to a point of entry into the host

Studies examining both clinical and non-clinical endpoints support the effectiveness of topical antimicrobial products in non-invasive procedures. Some of these applications are not encompassed in the traditional names for products used in non-invasive procedures (i.e. consumer hand preparation, consumer body preparation, food handler preparation), yet these are valid and important uses of topical antimicrobial products.

The following summaries identify studies reporting benefits from the use of topical antimicrobial products in non-invasive procedures.

Clinical Settings

Reduced nosocomial infection rates – A number of studies showed significant reduction in infection rates in clinical settings from the use of handwash products: hospital nursery (Frappier-Davignon *et al.* 1959; Johnson *et al.* 1976; Cooper and Gibson 1974; Forfar *et al*. 1968; Murray and Calman 1955); dialysis unit (Malone

and Larson 1996); transplant unit (Klausner *et al*. 1999; Thompson *et al.* 2000); and intensive care units (Doebbeling *et al.* 1992; Maki and Hecht 1982; Maki 1989; Onesko and Wienke 1987; Sakata *et al*. 1989; Conly *et al*. 1989; Denton 1991; Webster *et al*. 1994; Webster 1992; Facagal *et al*. 1999).

Control of Methicillin Resistant *Staphylococcus aureus* – Studies have shown the benefit of using topical antimicrobial products for hand and body washing to control or eradicate MRSA (Brady *et al.* 1990; Bartzokas *et al.* 1984; Webster *et al*. 1994; Zafar and Butler 1999; Onesko and Wienke 1987; Tyzack 1985; Majury *et al*. 2000; Mitsuda *et al*. 1999; Tuffnell *et al*. 1987).

Reduction in transfer of bacteria from patients' to caregiver hands – A significant decrease was seen when topical antimicrobial products were used for routine handwashing (Casewell and Phillips 1977; Mortimer *et al.* 1962).

Significant reduction in total bacterial load on caregivers' hands – Routine use of topical antimicrobial products led to a demonstrated reduction in the bacterial flora of hands (Amortegui and Buffenmyer 1978; Kirita *et al.* 1993; Stuart Pharmaceuticals 1986; Goldblum *et al.* 1983).

Significant reduction in *Staphylococci* and other Gram positive organisms – *S. aureus* is a pathogenic strain frequently isolated from the hands and in the nares of carriers. A number of studies have shown that the use of topical antimicrobial products reduces the Gram positive flora on various body sites (Voss 1975; Stuart Pharmaceuticals 1986; Gould *et al*. 2000).

Significant reduction in Gram negative organisms – Routine use of topical antimicrobial products led to a demonstrated reduction in the Gram negative flora on patients' skin and transferal to caregivers' hands. (Eckert *et al.* 1989; Eckert *et al*. 1989a; Ehrenkranz *et al.* 1991; Gilmore *et al.* 1984; Ayliffe *et al*. 1975; Stuart 1986; Knittle *et al.* 1975; Casewell and Phillips 1977; Raimondi *et al*. 2000).

Institutional Settings

School absenteeism reduced – Use of hand sanitizer reduced absenteeism among elementary school teachers and students (Hammond *et al.* 2000; Shinder and Dyer, undated).

Reduction in respiratory infection rate in adult day care centers – Use of a hand sanitizer as a supplement to handwashing was implicated in the significant reduction of respiratory infections in three adult day care centers (Falsey *et al*. 1999).

Reduced symptoms of enteric disease – Hand rinses significantly reduced these symptoms in family day care homes (Butz *et al.* 1990).

Reduced eye and skin/wound infection rates – Use of a topical antimicrobial product significantly reduced infection rates in a long-term care facility (Hoffmann *et al*. 1999).

Healing of scrapes and scratches – Bathing with topical antimicrobial products and use of those products to clean cuts, scratches and abrasions led to a significant improvement in wound healing and a lower frequency of infection (Dubow and Winter 1967; MacKenzie 1970; Somerville *et al*. 1970).

MRSA eradicated in a day care setting – An antimicrobial regimen including the daily use of a topical antimicrobial product was reported to have cleared up within three months an MRSA infection in one child and two other infected contacts (Shahin *et al.* 1999).

Home Settings

Atopic skin – Use of topical antimicrobial preparations improved the overall health of the skin as measured by a decrease in areas affected by atopic dermatitis and significantly fewer bacterial numbers on the skin (Breneman *et al.* 1998; Akiyama *et al.* 1997; Sugimoto *et al.* 1997).

Skin infection risk – A mathematical model showed that the use of antibacterial soap would result in a considerable reduction in the risk of infection (Rose and Haas 1999). Use of topical antimicrobial preparations reduced the recurrence of infective skin lesions (Leigh and Joy 1993).

Adjunct to acne treatment – Use of topical antimicrobial preparations decreased inflammation and improved skin condition when used as an adjunct treatment in acne patients (Brown 1977; Franz *et al.* 1978; Jampani *et al*. 2000a; Jampani *et al.* 2000b; Stoughton and Leyden 1987).

Reduced respiratory illnesses in mothers – Hand disinfecting treatments significantly reduced respiratory illnesses in mothers caring for sick children (Hendley and Gwaltney 1988).

Reduced puerperal mastitis rate in nursing mothers – Use of a hand disinfectant significantly reduced the incidence of puerperal mastitis (Peters and Flick Fillies 1991). There is considerable precedence for this in the dairy literature which repeatedly shows the importance of topical antimicrobial products in preventing the transfer of *Staphylococci* during the milking process (Boddie *et al*. 1990; Boddie *et al.* 1997; Hicks *et al.* 1981; Pankey *et al.* 1983; Kovars 1985; Sheldrake and Hoare 1981; Sheldrake and Hoare 1983; National Mastitis Council Research Committee 2000).

Reduced eye infection – Use of an antibacterial hand soap correlated with fewer staphylococcal infections of the eye (Samalonis 1999).

Reduction of bacteria on contact lens – It is prudent to keep contact lens as free of bacteria as possible, not only by sterilization of the lens, but by decreasing the risk of bacterial transfer from the hands to the lens (Ly *et al.* 1997).

Topical Antimicrobial Products have been shown to provide many significant benefits.

The scientific literature shows many and varied benefits from use of topical antimicrobial products. A wide range of use patterns, product forms, and products used in many different situations were found where topical antimicrobial products contribute to mitigating the risk of infection or disease. Some of the studies identified have a number of confounding issues, such as institution of educational programs on hygiene at the time of product introduction, lack of double blind control, or changes in other parameters such as patient cohorting. 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 many of the studies have additional and different variables, the weight of the evidence available demonstrates that *the use of the topical antimicrobial product plays a critical role in infection control*.

Conclusion

An extensive search of the scientific and marketing literature using state-of-the-art electronic search engines as well as more traditional means identified a substantial body of evidence demonstrating the benefits of topical antimicrobial products.

The literature review conducted to confirm the benefits of topical antimicrobial products shows that these products are used in a wide variety of situations and for purposes not discussed in the 1972 Panel's review. It demonstrates the continuum for risk of infection and the need for different efficacy levels to address those risks. It further illustrates 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 (hand washing, body washing) situations.

Based on the studies identified above, the Industry Coalition believes the reduction of the normal flora, both transient and resident, is sufficiently supported to be considered a benefit. The question of how much of a reduction in microbial flora is required for various product claims." This topic is addressed in Sections 3 and 4.