

BENEFITS OF TOPICAL OTC ANTIMICROBIAL PRODUCTS

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.

As background, it is important to note that the FDA in 1978 found that the reduction of flora, both transient and resident, has been sufficiently supported to be considered a benefit. The agency has embraced the reduction of skin flora by a pre-specified amount as a valid surrogate end-point for the efficacy of topical OTC antimicrobial products.

The Industry Coalition has concluded that the log reductions for non-professional antibacterial products are appropriate as cited by FDA in the June 17, 1994 Tentative Final Monograph, 59 Fed. Reg. 31402 (TFM) (*i.e.*, 2 log₁₀), as long as standardized ASTM methods (with neutralization of all sampling fluids) are employed in the Final Monograph. In addition, topical antibacterial products should be effective the first time they are used, and effectiveness should be demonstrated after a single wash. Demonstration of cumulative activity by a tenth wash is a redundant measure that should not be included in the Final Monograph.

Today's generation of topical OTC antimicrobial products provide a public health benefit by reducing bacteria on skin. Such products are formulated with active ingredients that have the capability of reducing transient or resident organism populations with greater effectiveness and efficiency than can be achieved through the use of non-antimicrobial products. 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).

Topical OTC antimicrobial products are currently available in many forms (bars, liquids, gels, wipes, etc.) and usually contain a single antimicrobial ingredient. In general, products should be used to appropriately address the risks associated with the specific tasks performed. Such tasks include

- Changing diapers
- Caring for sick, elderly or invalid family members
- Preparing family meals

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- Having contact with pets
- Attending daycare
- Attending school or work
- Using public restrooms and toilets

A summary of the major classes of topical antimicrobial drug products currently available is presented below.

Products used with water – These include hand wash products and body washes that contain an active ingredient that kills or controls bacteria that can cause illnesses or skin infections. Topical antimicrobial hand wash products generally have a broad spectrum of activity to reduce the number of bacteria on the skin and thus reduce the potential for transmission of disease-causing organisms.

Products used without water (i.e., hand sanitizers) – which are used to kill bacteria on skin without soap and water. These products are an appropriate choice when handwashing isn't possible.

In general, topical OTC antimicrobial products are designed to provide a prophylactic (i.e., preventive) benefit rather than a therapeutic benefit. The risks that are mitigated by topical OTC antimicrobial products are due to the acquisition of disease or illness from the transmission of transient organisms from oneself, others, or from environmental sources (e.g., fomites). In some cases reduction of resident flora may also be desirable (e.g., impetigo, eczema).

These product attributes fully support the current OTC drug indication of “to decrease bacteria on skin” and translate into tangible public health benefits such as:

- Reductions in the incidence of diarrhea
- Reductions in skin/eye diseases
- Reduction in illness rates (self-reported upper respiratory symptoms and secondary transmission of gastrointestinal illness)
- Reductions in absenteeism due to infectious disease (colds, flu, gastrointestinal disease)

In order to further demonstrate the benefits associated with this class of OTC drugs, it is necessary to

- (1) draw upon the large body of scientific evidence which shows that OTC antimicrobial products in a wide range of use patterns, product forms, and situations help mitigate the risk of infection or disease
- (2) indicate how topical OTC antimicrobial products are more effective at mitigating risk than non-antimicrobial products

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(3) show how modeling tools such as Qualitative Microbial Risk Assessments (QMRAs) can be used to demonstrate the prophylactic benefits of these products in light of the difficulties associated with conducting clinical tests

(4) illustrate how such products have been recognized by a variety of domestic and international public organizations for their role in reducing the potential risk of exposure to potentially pathogenic microorganisms in a variety of settings or situations. A discussion of each of these points is presented below.

1. Scientific Literature

Numerous scientific studies demonstrate that topical OTC antimicrobial products contribute to mitigating the risk of infection or disease when used in a variety of situations and settings (MacKenzie *et al.*, 1970; Aly and Maibach, 1981; Marzulli and Bruch, 1981; Taplin, 1981; Keswick *et al.*, 1996; Hoffmann *et al.*, 1999; Butz *et al.*, 1990; Hammond *et al.*, 2000; Breneman *et al.* 1998, Sugimoto *et al.* 1997, Akiyama *et al.* 1997, Guinan *et al.* 2002, Fendler *et al.* 2002, Shinder and Dyer undated; Dyer and Shinder, 2000; Falsey *et al.*, 1999; Samalonis, 1999; Rose and Haas, 1999; Shahin *et al.*, 1999; Leigh and Joy, 1993; Hendley and Gwaltney 1988; Peters and Flick-fillies, 1991; Ly *et al.*, 1997; Boddie *et al.*, 1997; Hicks *et al.*, 1981; Pankey *et al.*, 1983; Kovats, undated; Shel Drake and Hoare, 1981; Shel Drake and Hoare, 1983). In addition, a significant body of scientific evidence also exists to support the concept that the reduction of transient or resident flora helps to mitigate infection (FDA, 1978; Black *et al.*, 1981; Miller, 1982; Marshall, 1997; Krilove *et al.*, 1996; Hammond *et al.*, 2000; McFarland *et al.*, 1989; Boyce *et al.*, 1994; Isaacs *et al.*, 1989; Isaacs *et al.*, 1991; Rose and Haas, 1999; Montville *et al.*, 2002; Scott *et al.*, 1982; Roach, 1984; Noble, 1993; Gerba *et al.*, 1981; Cogan *et al.*, 1999; Gibson *et al.*, 1999; Scott, 1999). The industry coalition has previously submitted this information to the FDA under numerous docket submissions.

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. However, they may not meet the rigorous standards usually associated with pivotal, Phase III clinical trials due to logistical problems associated with controlling use behavior in a large number of subjects over a long duration, and to the institution of educational programs on hygiene at the time of product introduction.

Importantly, it is critical to note that hand hygiene studies in non-professional settings face greater challenges than in healthcare settings due to randomization, placebo control (especially for waterless products), and large sample size requirements in order to detect changes in infection rates. Despite these limitations, the collective results of the listed clinical evaluations demonstrate

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positive effects of routine hand hygiene in the reduction of community-related infections. The findings associated with non-professional healthcare settings are consistent with those seen in healthcare settings.

Furthermore, it is important to remember that topical OTC 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.

2. Efficacy of Topical Antimicrobial Products versus Soap and Water

The use of an antimicrobial product provides a reduction of the transient or resident microorganism population. This reduction is accomplished via the incorporation of active pharmaceutical ingredients (APIs) that have bactericidal properties and by the achievement of \log_{10} reductions. They are formulated to meet a minimum 2 \log_{10} bacterial reduction after a single wash (the same as healthcare personnel hand wash products). Standardized ASTM methods (with neutralization of all sampling fluids) are also employed. (See “Methods and Performance Criteria” in this document). Typical APIs used in consumer antimicrobial products include: alcohol, benzalkonium chloride, benzethonium chloride, triclocarban, and triclosan.

Non-antimicrobial washes function by mechanically removing pathogenic microorganisms from the skin and may not be sufficient to address the risk of disease acquisition or organism transmission. The reduction in bacterial load provided by topical OTC antimicrobial products translates to risk reduction, both in the transmission of potentially pathogenic organisms and in the potential for disease acquisition (Breneman *et al.* 1998, Rose and Haas 1999).

A study by Lucet *et al.* (2002) demonstrated the benefit of using an antimicrobial hand wash over using a non-antimicrobial handwash with a 10-second hand wash 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 hand wash. The authors concluded that handwashing with unmedicated soap does not reliably remove pathogenic bacteria from hands.

There are few studies which compare topical antimicrobial and non-antimicrobial products in large non-professional use situations. Just as in the case of professional topical OTC antimicrobial products, numerous confounding factors, logistical problems and unintentional interventions during the study make it difficult to use them for drawing conclusive evidence of benefits.

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Comparisons between topical antimicrobial and non-antimicrobial products in two recent studies (Larson 2004, Luby *et al.* 2005) illustrate these difficulties. In particular, sample sizes were too small in these studies to detect differences in changes in rates of infection, which could be of health significance, due to the antimicrobial active ingredients. In addition, targeted hygiene (a risk-based approach to target certain high risk situations), which is crucial in reducing transmission of infectious microorganisms, was not considered in these studies. Multiple interventions, such as hygiene promotion and education, visits by study personnel, etc., also likely affected outcomes. In the studies, there were no determinations as to whether topical OTC antimicrobial products reduced transient flora more effectively than non-antimicrobial products.

In reviewing such studies, it is important to note that several prominent hygiene experts have recognized the benefits of antimicrobial consumer products and have suggested several specific instances and indications for the use of these products that are beneficial to the general public (Larson and Rotter 1990, Keswick *et al.* 1996, Larson 2001, Luby *et al.* 2002, Luby *et al.* 2005).

The most notable of these recommendations, made by Larson (2001), states that there is indeed a need and place for topical OTC antimicrobial products in the home and that their use and indications should be reflective of their benefits. Proposed uses and indications include: “for close physical contact with persons at high risk for infection (*e.g.*, neonates, the very old, or immunosuppressed); close physical contact with infected persons; infection with an organism likely to be transmitted by direct contact (diarrhea, upper respiratory infection, skin infections); or work in a setting in which infectious disease transmission is likely (food preparation, crowded living quarters such as chronic-care residences, prisons, child-care centers, and preschools).” These indications are complementary to the current OTC indication (*i.e.*, to reduce bacteria on skin) and can certainly be added on product labels in order to further communicate recommended product uses.

Drawing upon the conclusions noted above, and in light of the results obtained in a variety of scientific and clinical studies sufficient evidence exists that efficacious consumer antimicrobial products provide benefits over non-antimicrobial products. These benefits clearly support the current labeling indication associated with this class of OTC drug products (*i.e.*, “to decrease bacteria on skin”) and also demonstrate that such products provide the consumer with an effective means through which to control the risks of infection from potentially pathogenic microorganisms in a variety of settings and situations.

Below is a discussion of how the employment of risk modeling tools such as Qualitative Microbial Risk Assessments (QMRAs) provides an important new tool for demonstrating the prophylactic benefits of antimicrobial products.

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3. Qualitative Microbial Risk Assessments (QMRA)

In general, the methods of QMRA are useful in estimating levels of risks or benefits difficult to establish by direct clinical or epidemiological study. QMRA is commonly used in U.S. government agencies for rulemaking and other regulatory matters. For instance, FDA's Center for Food Safety and Applied Nutrition (CFSAN) has used QMRA to project the risk of a number of foodborne pathogens (FDA 2001a, FDA 2001b, FDA 2001c); the U.S. Department of Agriculture and Centers for Disease Control and Prevention have jointly employed QMRA to ascertain the relative risks to public health from foodborne *Listeria monocytogenes*; and the U.S. EPA uses it extensively in the development of drinking and surface water regulations. Furthermore, the principals of QMRA have been endorsed as an important tool for making risk-based regulatory decisions by The Presidential/Congressional Commission on Risk Assessment and Risk Management in a 1997 report titled: "Risk Assessment and Risk Management in Regulatory Decision-making." (Presidential, 1997)

The advantage of QMRA is that it permits an assessment of the consequences of an exposure in the absence of direct experiments on human subjects. It uses experimental data and scientific data to develop appropriate discrete or probability distribution functions. Several QMRA studies have been conducted to ascertain the benefits of topical OTC antimicrobial products. In general, the results of these assessments indicate that topical OTC antimicrobial products can substantially reduce the risk of infection in a variety of consumer settings and situations. Examples of the types results obtained from several key QMRA studies are presented below:

- Bathing with a topical antimicrobial product provided a potential 20-fold reduction in the risk of skin infection by *S. aureus*, relative to use of a non-antimicrobial product (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 non-antimicrobial products (Chen *et al.* 2001).
- 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 indicated that two of the three most important factors were the use of waterless sanitizers and soap use. Antimicrobial products were shown to be more effective than non-antimicrobial products (Montville *et al.* 2002).
- A quantitative risk assessment model for transmission of Shigella, the bacterium most frequently associated with outbreaks of infectious intestinal disease in daycare settings, found that the use of antimicrobial products could reduce the probability of disease acquisition by a factor of

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20% beyond washing with a non-antimicrobial product (Gibson *et al.* 2002).

As seen from the results of these studies, QMRA offers a reliable alternative for demonstrating the benefits of consumer antimicrobial products.

4. Endorsements for Use

Consumer topical OTC antimicrobial products are currently recognized by a variety of domestic and international government organizations for their role in reducing the risks associated with potentially pathogenic microorganisms in a variety of settings or situations. A cursory review of such information indicates that virtually every major U.S. government agency, as well as State and local government agency has an official guideline, policy, or regulation in place recommending the use of these products in a variety of situations. Additionally, other domestic and international public health organizations and authorities also promote or regulate such products for numerous public health purposes, including infection control and hygiene. A comprehensive listing of these endorsements is presented in Appendix 1. These official guidelines, policies, regulations, and recommendations attest to the importance of these products from a risk management and public health perspective.

5. Conclusions

The log reductions for non-professional antibacterial products as cited in the 1994 Tentative Final Monograph (TFM) (*i.e.*, 2 log₁₀) are appropriate, as long as standardized ASTM methods (with neutralization of all sampling fluids) are employed in the Final Monograph.

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.

Consumer topical OTC antimicrobial products are designed to reduce transient or resident organism populations greater than can be achieved through the use of non-antimicrobial products. This additional reduction translates to risk reduction in the transmission of potentially pathogenic organisms and in the potential for disease acquisition. From a public health perspective, this implies that proactive risk management steps can be taken by consumers to help interrupt the transmission of potentially pathogenic microorganisms to oneself and to others as well as to inanimate objects that can become sources to others.

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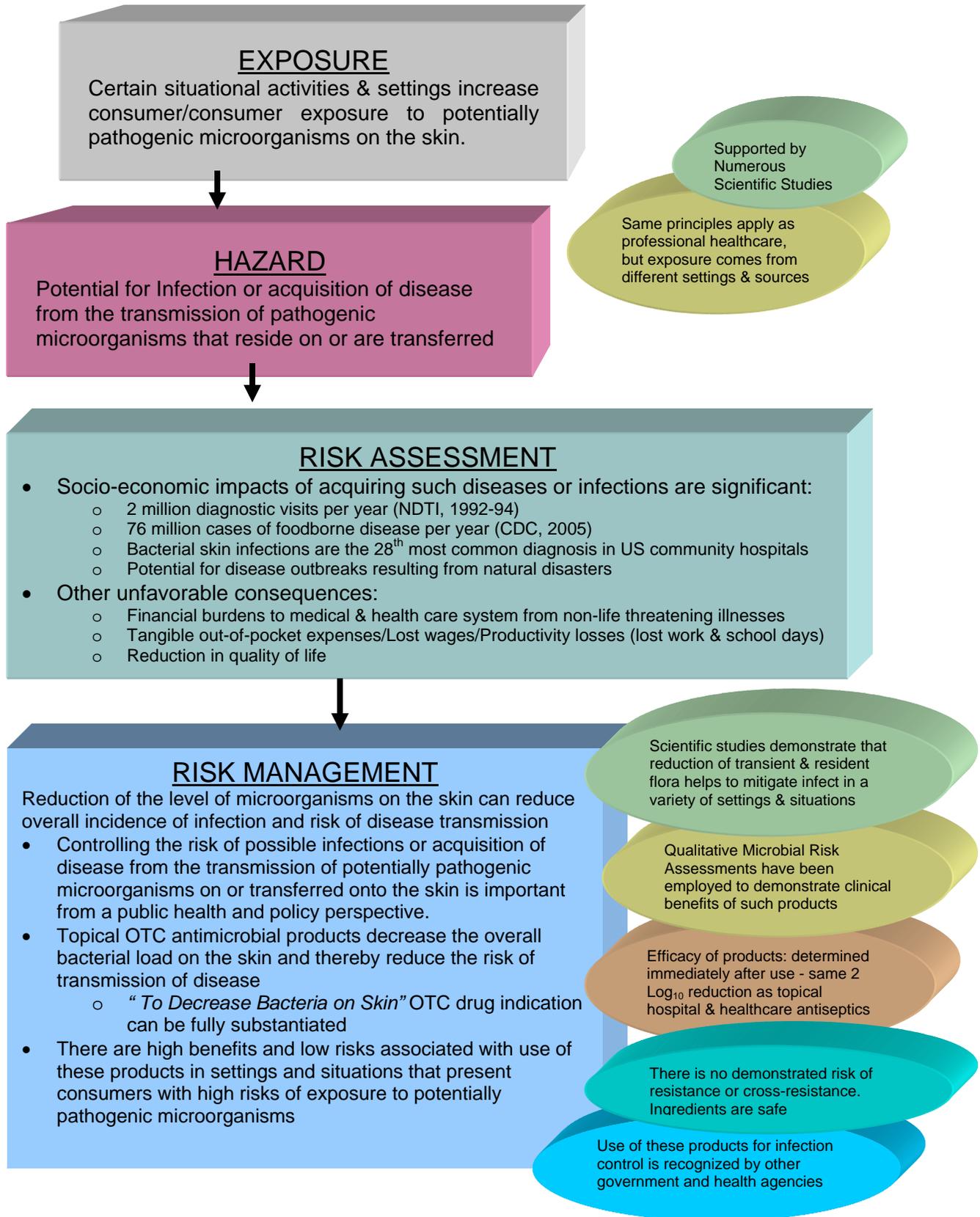
Topical OTC antimicrobial products have a broad spectrum of activity to reduce the number of bacteria on the skin and thus reduce the potential for transmission of disease causing organisms from a wide variety of potential sources of infection. Topical OTC antimicrobial products achieve their efficacy via the use of active pharmaceutical ingredients (APIs) that have activity against a broad spectrum of bacteria and microorganisms. In general, the following APIs may be used: alcohol, benzalkonium chloride, benzethonium chloride, triclocarban, and triclosan. The safety and efficacy of these products have been affirmed by the ingredient manufacturers via data submissions to the OTC docket.

Topical OTC antimicrobial products have been shown to be effective in decreasing the overall bacterial load on the skin and thereby reducing the risk of transmission of disease to oneself or to another in a variety of consumer settings and situation. Thus, from a public health perspective they provide an important public health benefit to the consumer and should continue to be readily available for use.

An overview of the benefits and risk management attributes of topical OTC antimicrobial products is presented in Figure 1.

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Figure 1. Overview of the Overall Benefits and Risk Management Attributes of Topical OTC antimicrobial products



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