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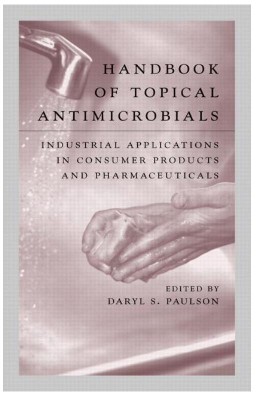

Handbook of Topical Antimicrobials
Industrial Applications in Consumer Products and Pharmaceuticals

Daryl S. Paulson

Healthcare Continuum: A Model for the Classification and Regulation of Topical Antimicrobial Products

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Healthcare Continuum: A Model for the Classification and Regulation of Topical Antimicrobial Products

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I. INTRODUCTION

It is commonly recognized that bacteria are ubiquitous in our environment. These bacteria are associated with a variety of disease conditions; therefore, it is important to hold the numbers of bacteria in check. As early as 1860, Semmelweis [1] demonstrated that, by reducing the level of bacteria on the skin, through handwashing, a corresponding reduction in the incidence of infection could be observed. Semmelweis recognized the advantage of using an antimicrobial product over water or plain soap and water. Through the years, the use of antimicrobial products in consumer and healthcare settings has grown. Antimicrobial wash products play an important role in improving personal hygiene and can help in the prevention of disease.

In the last 30 years the types and forms of antimicrobial products have evolved and now include bar soaps, liquid soaps, lotions, hand dips, hand sanitizers, foams, and rub products. In the United States the importance and need for antimicrobial products was recognized by an expert panel convened by the Food and Drug Administration (FDA) in 1972, and in two Tentative Final Monographs

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(TFM) for Healthcare Antiseptic Drug products subsequently issued in 1978 and 1994 by the FDA [2]. In an attempt to provide a tool to bring clarity to the area of antimicrobial wash products, a coalition of industry companies proposed the Healthcare Continuum Model (HCCM).

The Healthcare Continuum Model provides a flexible framework for characterizing use patterns and situational risks in order to establish efficacy requirements and appropriate labeling. The HCCM offers an initial six categories based on professional healthcare, foodworker, and consumer use patterns and risks. The six categories are preoperative skin preparation, surgical scrub; healthcare personnel handwash, foodhandler (worker) handwash, antimicrobial handwash, and antimicrobial bodywash.

The HCCM suggests an underlying philosophy of defining a product category or indication based on a thorough understanding of use patterns and attendant risks. Health hazards and characteristics of exposure are parameters of the framework. The result in the marketplace would be products that have been formulated for specific uses and thereby assure appropriate levels and types of active ingredients for each scenario. All antimicrobial products are not used for the same purpose, nor should they be. One of the results of implementation of the HCCM would be to avoid the inappropriate use of products, which could result in potentially negative consequences. Professional products, which are not typically formulated for general use, may irritate, stain, or contain complex use directions or warnings. This could result in a decrease in handwashing compliance. As a result of the potential for adverse effects, the process of establishing a category includes balancing the potential for disease acquisition or transmission with the product effectiveness and type of active ingredient.

Characteristics for each identified use pattern should be consistent with the specific risks associated with the use setting. These characteristics may include antimicrobial effectiveness versus transient or resident bacteria, persistent effect, speed of action, and spectrum of activity.

II. BACKGROUND

In a Centers for Disease Control and Prevention (CDC) study spanning the years 1980–1990, 62% of all nosocomial infections were attributed to bacterial pathogens [3]. An undefined number are due to bacteria transferred by and from the hands and skin. Products such as preoperative skin preparations and surgical scrubs have been used in hospital settings for the reduction of nosocomial infections. Products designed for these uses rapidly and dramatically reduce the levels of resident bacteria on the hands or skin immediately prior to invasive surgical procedures. By definition, they should exhibit a persistent effect. Persistence is prolonged or extended antimicrobial activity which acts to prevent or inhibit the

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growth or regrowth of organisms that remain on the skin after product use and/or the establishment of transient organisms that may contact the skin after product use. Healthcare personnel handwash products have been used by professional healthcare providers to reduce the incidence of nosocomial infections as well as to protect themselves or other patients from the transmission of microorganisms and consequently disease from infected patients. These products are designed to be used by the healthcare professional as many as 50–100 times per day. They should be fast-acting, effective against transient bacteria, and, if possible, mild to the skin.

Healthcare professionals and their patients represent a small but significant segment of the population that require specific antimicrobial wash products. Bacteria can cause infections outside of the clinical setting. An increasing segment of the population are seeking and using antimicrobial products designed as foodhandler handwash products. A study spanning the years 1983–1987 reports that poor personal hygiene by foodhandlers or food service workers is the second leading cause of foodborne illness [4]. Research supports the findings that the U.S. population lacks basic food safety information/skills and engages in food-handling and food-preparation practices that studies have linked to a significant number of foodborne illness outbreaks [5]. Foodhandlers require specific antimicrobial wash products not only to address their own personal hygiene needs, but also to protect those people who consume the food that they have prepared. Products designed for use by foodhandlers are used in restaurants, cafeterias, hotels, schools, hospitals, federally inspected meat and poultry plants, prisons, and airline food-preparation facilities. Today, more people in our society are assuming responsibility for food handling and preparation in the home and elsewhere [5]. Vulnerable sectors of the population more severely affected by foodborne illness are also increasing in size, including immunocompromised persons (e.g., persons with diabetes, cancer, chronic intestinal disease, organ transplants, or human immunodeficiency virus); and persons 65 years and older, a growing proportion of the population who are at increased risk due to normal decline in immune response. Foodhandler handwash preparations need to be fast-acting and effective against transient microorganisms, including foodborne organisms, and, if possible, exhibit persistence.

Every day, consumers are changing diapers, caring for sick, elderly, or invalid family members, preparing family meals, having contact with pets, gardening and performing yard work, having contact with other people, healthy or otherwise, attending daycare, attending school or work, and traveling and enjoying recreational activities. Topical antimicrobial products are used by consumers to provide a variety of end-user benefits. Antimicrobial handwash products help control the transient bacteria consumers acquire from contact with the environment. Consumers are constantly exposed to a variety of bacteria that have the potential to cause infection [6–12]. The transfer of transient bacteria via hands

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is recognized as a major factor in the spread of disease. Antimicrobial handwash products should have a broad spectrum of activity to reduce the number of these bacteria on the hands, thus reducing the potential for transmission of disease causing organisms. Additionally, antimicrobial activity should exhibit persistence, if possible.

Antimicrobial bodywash products are used for whole body cleansing, to reduce odor, and to help control bacteria, which may help prevent minor skin infections. Products for bodywashing are used for self-health and act as an aid in controlling the risk of pyogenic infection. Antimicrobial bodywash products can control the number of resident and transient microorganisms on the skin [13,14]. Antimicrobial bodywashes need to have an activity spectrum that will target the gram-positive resident flora. They may, in some instances, also target the gram-negative transient flora. A key characteristic of products in this category is persistence to reduce and maintain the microbial flora of the skin below baseline levels between washings.

III. THE HEALTHCARE CONTINUUM MODEL

Underlying the HCCM is a proposed framework for a system of broadly classifying topical antimicrobial use patterns, establishing transmission risks and etiology agents, and determining the pertinent characteristics of a topical formulation dictated by the situational risks. The following section describes the six initial use patterns proposed in the HCCM. The use pattern and attendant risks typical of microbial flora are described. Based upon the HCCM philosophy, formulary attributes and test methodology were proposed. Although the initial categories proposed within the HCCM are well established use patterns, development of new use patterns and new technology will drive the need to apply the flexible, underlying principles of the model to establish new categories in the future.

IV. GENERAL POPULATION PRODUCTS: ANTIMICROBIAL HANDWASH AND ANTIMICROBIAL BODYWASH

In everyday life, consumers encounter situations in which they are exposed to a variety of bacteria that have the potential to cause infection. It is well recognized that good personal hygiene can reduce the risk of infection. Antimicrobial washes can play an important role in improving personal hygiene. Antimicrobial washes are used for whole body cleansing, to reduce odor-causing bacteria, and to help control bacteria that can cause skin infections.

The routine use of personal antimicrobial wash products is beneficial to all. The potential benefits to consumers of antimicrobial washes, in addition to

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cleaning, are (1) to help reduce the incidence of pyogenic infections [15,16], (2) to help remove transient organisms which are potentially pathogenic [17], and (3) to reduce odor-causing bacteria [15]. Washing with antimicrobial washes or with nonmedicated washes will remove some bacteria from the skin due to the surfactancy of the base and the mechanical action of the washing procedure. However, antimicrobial washes deposit an active ingredient on the skin that can help control the number of organisms that survive and help prevent the colonization of potential pathogens, such as *Staphylococcus aureus*. Washing with nonmedicated products does not provide this persistent antimicrobial activity.

Antimicrobial washes are available in many forms (bars, liquids, gels, etc.) and usually contain a single antimicrobial ingredient. Products applied to the hands during handwashing reduce transient organisms on the hands and can reduce the possibility of disease transmission. Ehrenkranz and Alfonso point out that ''a pervasive misconception in infection control circles is that simple handwash reliably prevents hand transmission of transiently acquired bacteria'' [14]. Antimicrobial bodywashes can play a role in the prevention of pyogenic infections and help control odor-causing bacteria. Whole body use of antimicrobial products can control the number of organisms on the skin and has been demonstrated, in laboratory studies, to reduce the number of potential pathogens on the skin [18].

A. Antimicrobial Bodywash

Antimicrobial bodywashes are used to control the numbers of bacteria, where appropriate [15]. Because the organisms of potential concern are primarily Gram-positive, the activity of antimicrobial agents used in antimicrobial bodywashes should be suitable for that use and so may be of limited spectrum. Most importantly, this will enable a proportion of the normal flora to remain.

B. Public Health Importance

Skin infections due to gram-positive organisms are recognized as a common and significant public health problem [19,20]. These skin diseases are most commonly caused by staphylococci and streptococci. They include pustules, folliculitis, impetigo, furuncles, and infection of cuts and scrapes. In addition to the staphylococci and streptococci, other gram-positive bacteria such as *Corynebacterium minutissimum* can cause contagious skin infections like erythrasma.

According to data obtained from the National Disease and Therapeutic Index (NDTI), on average from 1992 to 1994 there were approximately 2 million diagnosis visits per year to dermatologists, pediatricians, and general or family practitioners, and others for impetigo, pyoderma, and carbuncles/furuncles. It has been estimated that up to 8% of visits to dermatology clinics are a result of some

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form of pyoderma [21,22]. Skin-related problems constitute about 6.8% of the visits to general pediatric clinics [23]. Of these, about half are cutaneous infections, some of which can lead to frequent recurrence and intrafamilial spread. A recent survey estimated that 5.5 million office visits per year are due to skin infections. Children overwhelmingly constitute the population at greatest risk for bacterial skin infection, with those under 9 years of age having the greatest incidence [24]. The number of children worldwide with skin infections is estimated to be in the millions and constitutes a significant load on medical services [24].

Atopic dermatitis affects approximately 10–20% of the population. Clinical studies have shown that the skin flora of atopics is quantitatively and qualitatively different from the skin of the normal population [25]. It has been reported that these patients have increased numbers of skin flora and a higher frequency of colonization with *S. aureus*, not only on their skin, but also in their nares [26]. Due to the chronic presence of this organism, it is not surprising that patients with atopic dermatitis experience increased numbers of skin infections. In experimental staphylococcal infections, there is a direct relationship between the numbers of staphylococci applied to normal skin and the likelihood that infection will occur [17]. Many normal daily activities that result in minor cuts and scrapes have the potential to become contaminated with these transferred *S. aureus* and other organisms from environmental sources.

A survey of skin problems in the elderly identified skin infections in noninstitutionalized patients ages 68 and older [27]. It was strongly suggested that skin problems, including infections, were common. Also, bathing and shampooing were often substantially limited, adversely effecting personal hygiene.

Zimakoff and colleagues pointed out the importance of reinfection on the transmission of *Staphylococcus* within families and concluded that a residual effect is desirable to help prevent reacquisition of staphylococci that are shed into the household environment on sheets, towels, etc. [28]. Recently in the United States, special occurrences affecting many households were shown to increase the incidence of skin infections. Quinn et al. reported on medical care of families affected by Hurricane Andrew in 1992 [29]. For 2 weeks following the storm there were noted increases in pediatric dermatological infections, including impetigo, wound infections, and cellulitis.

The breach or destruction of the skin defenses, as a result of abrasions, cuts, burns, or the action of toxic chemicals, inevitably leads to increased colonization of the area by microorganisms. Thus, the likelihood of infection from the reduced defense capacity is increased. However, less severe and often barely detectable changes in the balance of the surface inhabitants of the skin can also increase the susceptibility to infection. These changes can be induced by alterations in host metabolism and other factors that modify the surface environment, even though they do not sever the epidermis [30].

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Skin infection with streptococci covers a range from simple colonization to primary and secondary infections. The skin provides an important portal of entry for systemic infection by these organisms. Minor trauma to the skin not prompting specific first aid attention, such as trivial cuts, abrasions, and scratches, may allow streptococci to initiate infection [17]. Staphylococci and streptococci are often found in mixed cultures from pyoderma lesions. There is still controversy over which is the more important pathogen. Most streptococcal skin infections occur among children and their contacts under conditions of overcrowding and poor hygiene, particularly in warm and humid parts of the world. Even in developed parts of the world, streptococci are commonly isolated from many clinical specimens. This is likely due to many factors, including the common asymptomatic carriage of organisms, the minor nature of most infections that are left untreated, and the opportunities for bacterial transmission that exist as people work, live, and play together.

Antimicrobial wash products are used for whole body cleansing, to reduce odor, and to help prevent minor skin infections. The efficacy of the ingredients used in antimicrobial washes against the types of organisms outlined has been well documented [31]. The regular use of these products results in the deposition of a bacteriostatic residue, which can significantly reduce the carriage of these organisms on the skin and play a role in the prevention of disease.

C. Antimicrobial Handwashes

There is consensus in the medical and scientific communities that transfer of transient bacteria via hands is a major factor in the spread of disease [32]. Hands can be viewed as unique in three respects. First, hands, more than any other part of the body, are in constant contact with the environment and, as such, reflect exposure to transient contaminants from many sources. Second, various parts of the hand, such as the nail folds and interdigital spaces, provide specific microenvironments, which can support organisms with varying growth requirements. Third, the flora of the skin of the hands are highly subject to modification because of the exposure to a number of varied household activities.

The importance of the role of handwashing for infection control has been thoroughly reviewed for settings outside the home [32,33]. Although there are no definitive studies in the literature within home settings involving currently marketed products, there are numerous studies suggesting a role for antimicrobial washes in personal hygiene [31]. Regarding the absence of clearly definitive trials, Larson has written [34]: ‘‘I'm not convinced that even the definitive study for which we have been lobbying and waiting would, in fact, influence practice. What we know now from natural experiments, epidemiological studies and experimental models is that clean hands are associated with reduced risk of contact-

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spread infection in a variety of settings.'' [34]. It can be argued, based on the spread of disease among family members, that the added benefit of residual activity and of increased awareness of the need for handwashing reflected in the purchase of antimicrobial consumer products has a role for their use in the home.

Everyone picks up germs from contact with the environment, and antimicrobial soaps help to control these germs. Broad-spectrum activity is preferable because of the wide variety of potential sources of infection. However, rapid kill is not necessary because all soaps remove a portion of the bioburden on the hands through the detergency mechanism. Nonantimicrobial soaps do not provide the long-lasting persistent effect of antimicrobial soaps [13,35]. Typical consumer handwashing is incomplete. Rarely is it as thorough as in the hospital setting. Because of the lower level of consumer handwashing efficiency, persistence is desirable. Bartzokas et al. [36] reported that the efficacy of an antimicrobial handwash preparation ''was significantly augmented'' with repeated handwashing.

The flora on the hands and influencing factors have been studied. The transient bacteria lie free on the skin or are loosely attached with dirt [37]. The resident flora comprise a stable population in both size and composition. Washing readily removes some transients, but the resident flora are removed more slowly. Obviously, the flora that may be present on the hands as transients are greatly influenced by the activity related to a source of contamination and the environmental conditions. For the consumer, these include, among others, food preparation, contact with pets, gardening and yard work, contact with other people, changing diapers, assisting ill persons, daycare, school, work, travel, and recreation.

Surveys of the bacteria found in the home environment suggested four major sites of household contamination: dry areas (e.g., floors, linens, furniture, clothing), wet areas (e.g., baths, kitchens, sinks, toilets, drains), food, and people [6,7,38,39,40]. In many homes, animals (e.g., pets, farm animals) and outside work (gardening, yard work) should be included. Scott et al. [6] pointed out that, although it is accepted that the risk of infection in the general community is lower than that associated with hospitalized patients, increases in the number of outbreaks of household food-poisoning cases had been observed. In that survey, high bacteria counts were found mainly in wet areas associated with sinks, baths, and diaper pails [6]. High bacteria counts also were frequently recovered from washcloths, dishcloths, and cleaning towels. The survey included isolation for *Escherichia coli*, pseudomonads, *S. aureus*, and streptococci. Marples and Towers further established a model to study how contact transfer of *Staphylococcus* can occur from objects [41]. Borneff et al. examined households for organisms causing infectious enteritis and found 267 of 4683 samples contained staphylococci [42]. These studies support the need for handwashing and the desirability of antimicrobial soaps.

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The shift in recent years from home-based child care to group daycare further extends the household environment because of the likelihood of transmission back to the family and subsequent intrafamilial spread [43–47]. Surveys of the daycare center environment have found contamination of surfaces, toys, food areas, diaper-changing areas, and the hands of children and adults [48–52].

A number of other activities encountered at work lead to exposures to potentially harmful microorganisms. These include handshaking, exposure to ill colleagues in meetings, contact with the public, sharing objects such as public toilets, telephones, exercise equipment, and money, as well as other obvious situations such as those encountered by animal handlers or sanitation workers [17], The Mayo Clinic points out that it is critical to wash hands after using the bathroom, handling food, handling money, coughing, sneezing, etc. [53].

Black et al. first demonstrated the effectiveness of handwashing to prevent diarrhea in daycare centers [9]. Following the initiation of a handwashing program in several daycare centers, the incidence of diarrhea among children in the study was significantly and consistently lower (approximately half) than the incidence in the two control centers over the 35-week study period.

It is recognized that it is often difficult to attribute independent specific effectiveness to an intervention-and-control program because they are inherently multifaceted. For example, Butz et al. evaluated the effectiveness of an intervention program in daycare homes that included handwashing education, the use of vinyl gloves, disposable diaper changing pads, and an alcohol-based hand rinse [54]. Symptoms of enteric illness were lower in the intervention homes, but it was not possible to separate out the effects of each component of the intervention.

It can be demonstrated that antimicrobial washes reduce the numbers of organisms on the skin to a greater extent than nonmedicated wash. In addition, model systems have demonstrated the control of potentially pathogenic organisms on the skin [55]. For handwashing to be effective, it is important that any product also be acceptable for regular and frequent use by consumers: ‘‘As the value of frequent handwashing is well established, the choice of soap brand should be made with a view to encouraging frequent handwashing, while maintaining healthy skin’’ [56]. Antimicrobial ingredients, deposited on the skin, can also be of benefit when washing is perfunctory or inadequate, leaving behind organisms that can cause infection or be transferred to other skin sites. Appropriate degerming for consumers also does not present the risk of removing resident flora to the point of creating a flora shift. Aly and Maibach showed that prolonged use of antimicrobial soap on skin did not lead to overgrowth of undesirable flora [57]. Using this information collected on the antimicrobial handwash use pattern, the model details suggested product attributes and test methodology.

The above discussion has clearly pointed out that improved hygiene can help prevent skin infections and interrupt the transmission of infectious disease

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as transferred by the hands. Therefore, the regular use of an antimicrobial soap for personal cleansing has a recognized role in the prevention of disease. Handwashing is repeatedly cited as the most important infection-control measure. It is no less important in the home than in these villages and institutional studies cited above.

D. Foodhandler Handwash

The importance of proper foodhandling during food preparation significantly contributes to the prevention of foodborne illness. As new and more virulent forms of bacterial pathogens appear, and as commercial preparation of food becomes more prevalent, our national strategies for prevention and control of foodborne disease will be increasingly tested.

Recent, well-publicized outbreaks of foodborne illness have reinforced the need to review foodhandling practices and how they are regulated. Two regulatory initiatives of note were the 1993 Food Code published by FDA [58] and the U.S. Department of Agriculture (USDA) regulation proposed in the Federal Register [59]. Both recommended the development of a Hazard Analysis and Critical Control Point (HACCP) system for foodhandling operations. HACCP principles call for the study of any system of food manufacture or preparation to determine the critical control points to protect food quality. HACCP has gained widespread acceptance. These evaluations of food preparation and serving practices identify personal hygiene on the part of foodhandlers as a critical point. The use of hand antimicrobials is cited as a measure available in a concerted effort to break the chain of transmission of disease.

Formerly USDA provided oversight for the use of hand cleaning and sanitizing products for meat and poultry processing plants [60]. However, products were only authorized by USDA if they were labeled for use in an inspected facility [59]. Many antimicrobial products intended for use by foodworkers in restaurants, hotels, schools, hospitals, and grocery stores were not considered for or required to have USDA authorization. As USDA discontinued the program in 1998, the HCCM offers a framework for regulation of this diverse group of product forms and use scenarios.

The cause of foodborne illness is widely recognized to be infection by pathogenic microorganisms [61]. Although preventable, no segment of the population is immune to the acute gastroenteritis caused by these pathogens. The exact symptoms of food poisoning vary but may include vomiting, diarrhea, abdominal pain, and fever and progress to the more severe blood clotting abnormalities, arthritis, kidney failure, autoimmune disorders, and death [62].

As the U.S. population ages and the proportion of immunosuppressed individuals continues to rise, the risk of foodborne illness will become an even greater threat [5]. This reinforces the need to prevent contamination of the nation's food

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supply. The bacterial organisms typically responsible for food poisoning are spread fecal-(food)-orally. The contamination may occur through an employee's hands transferring the contaminating organisms from raw food to noncontaminated food or prepared/cooked food, which is then consumed [63,64]. Bryan and Doyle reported findings from investigations of two poultry-processing facilities: ''[s]almonellae of the same serovars that were on incoming carcasses were found on 30% of hands, 38% of rubber gloves, and 31% of wire gloves of workers'' [33]. Microbial contamination may rapidly grow out of control when combined with poor refrigeration, inappropriate storage, or improperly sanitized equipment.

Bacterial food poisoning may be caused in two ways: either by the direct presence of bacteria in consumed food or by the production of a toxin that remains in the food. The organisms primarily responsible for toxins are *S. aureus*, *Bacillus cereus*, *Clostridium botulinum*, *Clostridium perfringens*, and *Vibrio cholera*. Those primarily responsible for direct infection include *Salmonella* spp., *Shigella* spp., *Campylobacter jejuni*, *E. coli*, *Listeria monocytogenes*, *Vibrio* spp., and *Yersinia enterocolitica*. These organisms may be transiently acquired from the soil, air, water, raw foods, hard surfaces, animals, or other contaminated food. They may also represent normal skin inhabitants. With the organisms that produce toxins, it is even more important to prevent their initial contact with food, since the bacteria may be killed by cooking while the toxin remains to affect the unsuspecting consumer [33,65].

The most well-known and frequently diagnosed foodborne pathogen in the United States is Salmonella. Some reports indicate that 25–64% of broiler chickens in the United States are contaminated with this organism [67]. Typically responsible for a short-lived gastroenteritis, which may be life-threatening in high-risk populations (elderly, children, immunosuppressed individuals), the infection may turn deadly if it enters the blood stream [62,68].

The CDC has released data derived from a composite review of several national surveillance systems [5]. These figures indicate that 7–33 million cases of foodborne illnesses occur each year, resulting in 7,000–10,000 deaths. The figures indicate that 17% of these deaths involve meat/poultry products contaminated by pathogenic microorganisms. These deaths are preventable with the appropriate precautions, including proper handwashing with an efficacious product. These numbers are suspected to be inaccurately low due to the voluntary nature of the programs and the innumerable cases that go undiagnosed and unreported.

Some estimates report that 70% of foodborne illnesses occur due to restaurant incidents and 20% occur due to home food preparation incidents. The CDC reports that 20–30% of food-poisoning incidents are the direct result of consumer mishandling of food [69]. With the dramatic increase in the number of restaurants and their popularity in our society, this rate is expected to continue to rise.

Our risk of exposure due to cultural and societal changes is increasing. This, coupled with the aging of the population and the increase in the percentage

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of immunocompromised citizens, contributes to the risk of foodborne illness. Bean et al. reviewed cases of foodborne disease outbreaks reported to the CDC [4]. These are cases from food service rather than food production. The article states: ''[f]or each year from 1983 to 1987, the most commonly reported food preparation practice was improper storage or holding temperature, followed by poor personal hygiene of the foodhandler.'' They report that, of 127 total reports of bacterial incidents in 1983, 13.4% concluded poor personal hygiene was a contributing factor. The reports also noted from 1983 to 1987 that approximately 25% of cases were in the home, 32% in restaurants, 5% in schools, and 3% in churches [4].

Restaino and Wind provide a survey addressing antimicrobial effectiveness of handwashing for food establishments [70]. They conclude that washing reduces the number of viable organisms remaining (that would be available to contaminate handled food) and that use of an E2 (USDA antimicrobial wash category) level product produces a measurably greater reduction as compared to washing with plain soap. From this understanding of the hand-to-food transmission risks, the model offers specific test methodology to elucidate the minimum performance characteristics.

E. Healthcare Personnel Handwash

Transmission is defined as the conveyance of disease from one person to another. The transfer of transient bacteria via hands is recognized as a factor in the spread of disease [71,72]. Nosocomial infections represent major sources of morbidity and mortality for hospitalized patients and constitute a serious public health problem. These hospital-acquired infections add significantly to the impact of the underlying diseases alone. The most complete study to date of the incidence of nosocomial infection rates in the United States was the Study of the Efficacy of Nosocomial Infection Control (SENIC) Project conducted by the CDC [73]. This study covered patients hospitalized during 1970 and 1975–76. SENIC Project estimates of the incidence of nosocomial infection rates at 6449 acute care hospitals in the United States for the period 1975–76 were 5.7 infections per 100 admissions, 7.18 per 1000 patient-days, and over 2 million total for a 12-month period. The same study estimated that the total rate of infection in 1983, including nursing homes, could approach 4 million cases per year and that related deaths placed nosocomial infections among the top 10 causes of death in the United States. The epidemiology of nosocomial infections has been affected by the introduction of the prospective payment system, which changed the economic basis of U.S. healthcare delivery [74]. Patients admitted to hospitals today tend to be more seriously ill or require sophisticated and, sometimes, high-risk procedures only suitable for inpatients. They are also usually discharged earlier, and care is often continued at home or in nursing facilities.

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The sites of nosocomial infection are diverse, and microorganisms transmitted on the hands of healthcare workers may cause infection at these sites. The extensive contact that patients have with healthcare workers and the high concentration of organisms often present in wound drainage, catheter drainage bags, urine, and feces makes them efficient disseminators of these flora, often to the hands of the healthcare workers. Studies have shown that the major reservoir of nosocomial infection in the hospital is the infected or colonized patient, and the primary mode of transmission of organisms between patients is on the hands of medical personnel [75]. Carriage of microorganisms on the hands has been implicated in numerous nosocomial outbreaks [71]. Most transmittable infections are transmitted by the hands of healthcare workers [76].

The importance of handwashing by medical personnel in the prevention of nosocomial infections was recognized over 100 years ago [2]. The literature concerning a causal link between handwashing and infection has been extensively reviewed by Larson and coworkers [32,33,77]. Today, handwashing to remove transient organisms acquired from patients or the environment and to prevent cross-infection is generally regarded as one of the most fundamental infection-control practices. Use of antimicrobial handwash products within this context is similarly widely established. Several agencies and organizations have published guidelines and standards regarding the use of topical antimicrobial products for skin hygiene. These include the Association for Professionals in Infection Control and Epidemiology (APIC) [78], the CDC [79], and the Association of Operating Room Nurses (AORN) [80]. In general, these organizations propose a similar approach to selection and use of antiseptic handwash products based upon infection control considerations.

Antimicrobial handwash products for use in the healthcare setting have been routinely and widely available for decades. The history of these products can be followed by examination of the evolution of active ingredients, regulatory practice, and clinical standards. The modern use of antimicrobial healthcare personnel handwash products has been said to have begun with the use of hexachlorophene following World War II. The decline in the use of hexachlorophene led to the proposal and use of a number of alternate active ingredients for healthcare personnel hand antisepsis. These included *para*-chloro-*meta*-xylenol (chloroxylenol, or PCMX), triclosan, iodine and iodophors, alcohol, triclocarban, tribromsalan, cloflucarban, and others. Chlorhexidine gluconate (CHG) was widely used in Europe and Canada and was introduced in the United States in the mid-1970s.

Healthcare personnel handwashes on the market today are predominantly liquid detergent formulations with sufficient active antimicrobial ingredient levels to achieve targeted organism reductions in both in vitro and in vivo tests as specified in the 1978 TFM. The most commonly used active ingredients are PCMX (0.24–3.75%) and triclosan (up to 1%) [58]. Formulations are typically optimized systems rather than plain soap to which an antimicrobial agent has been added.

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The trend in formulation of these products is toward low irritating systems using mild surfactants, emollients, and moisturizers. Contrary to popular belief, antiseptics are not necessarily more irritating to the skin than plain soaps [81,82].

The distinguishing characteristics of a healthcare personnel handwash/antiseptic focus on its intended use as a fast-acting, broad-spectrum antimicrobial antiseptic designed for rapid removal and/or kill of transient skin microorganisms encountered in a healthcare setting. These products are designed for very frequent use, up to 50–100 times per workday. A persistent antimicrobial effect is a desirable characteristic but is not necessary since these products are used frequently throughout the day.

F. Surgical Products: Preoperative Skin Preparations and Surgical Scrubs

The definitive role of antimicrobial surgical scrubs and preoperative preparations in reducing nosocomial infections has been consistently debated over the past 50 years. The nature of the relationship is a complex interaction that comprises the condition of the patient, the transient and resident flora of the patient, the operating room (OR) team, the sterility of the devices involved, and other factors [71].

The hazardous microorganisms are primarily derived from the patient's own resident flora. In addition, patients in medical environments are frequently exposed to a wider variety of pathogens and potentially more antibiotic-resistant organisms than the general population.

During invasive procedures, the primary barrier function of skin is significantly compromised. Examples of invasive procedures include surgery, catheterization, and injection. There are a variety of situational risks associated with invasive medical procedures [77]. For example, incisions into the skin during surgery and placement of IV and other catheters provide the greatest risk of infection, while a lesser risk is realized during injection. The degree of effectiveness of the products should be related to the severity of the risk of infection within the use situation.

The 1994 TFM defined a patient preoperative preparation to be ''fast-acting, broad spectrum, and persistent antiseptic-containing preparation that significantly reduces the number of microorganisms on intact skin.'' The purpose of surgical scrubs and preoperative skin preparations are similar [85]. Lowbury emphasized that ''skin disinfection'' eliminates the transient microorganisms and reduces or kills the resident flora at the operative site [83]. A preoperative product remains on the skin to offer antimicrobial protection during the procedure and may be used to postoperatively cleanse the wound.

Current surgical scrub formulations typically contain the following active ingredients: chlorhexidine gluconate, chloroxylenol, hexachlorophene, triclosan,

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iodophors, and alcohol. Active ingredients found in preoperative preparations are commonly formulated with chlorhexidine gluconate, iodine, alcohol, and iodophors [78,84]. Although not covered under the current monograph, many new products are now available which may prove to aid in the prevention of wound infections when used in combination with the preoperative preparation.

In 1994, Larson put aside the controversy of definitively proving the infection prevention benefit of topical antimicrobial soaps and refocused attention in a practical direction. She stated, ''Although a definitive, double-blind clinical trial of the effects of handwashing with an antiseptic product on nosocomial infection rates may not be feasible, it appears that, at least in certain high-risk situations, such antimicrobial products are beneficial. Two major dilemmas facing Infection Control Practitioners in healthcare settings today, however, are when to use antiseptic agents and which agents to use'' [78].

The 1994 TFM defined a surgical scrub as ''an antiseptic containing preparation that significantly reduces the number of microorganisms on intact skin; it is broad spectrum, fast acting, and persistent'' [58]. AORN states that the purpose of the scrub is to ''[r]emove debris and transient microorganisms from the nails, hands, and forearms; reduce the resident microbial count to a minimum; and inhibit rapid rebound growth of microorganisms'' [85].

The nature of the use pattern of these products results in this category holding a high risk of infection for the patient; however, the category risk is of limited scope due to the small percentage of the population who require surgery. The Association of Operating Room Nurses has published practices that address when to use surgical scrubs and preoperative preparations [85].

V. EFFECTIVENESS TEST METHODS

The purpose of surrogate endpoint test methods within this public health framework is to demonstrate that a product is efficacious in reducing risks of infection or acquisition of disease within a given situation. As such, the methods must address the key performance criteria for the product under conditions that simulate use situation(s). The key performance parameter for topical antimicrobial products is effectiveness against a spectrum of bacteria representative of those encountered in the targeted situations. Depending on the situation and task, speed of action and residual activity may also be key parameters.

In an OTC monograph, the characterization of an active ingredient is carried out prior to finalization of the monograph. Minimum inhibitory concentration (MIC) testing and other methods are used to determine the spectrum of antimicrobial activity. As a consequence, testing of an active ingredient to determine its spectrum of activity in a formulation should not be necessary

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Several general principles can serve as guidance for determining appropriate test methods.

Standardized, defined, and peer-reviewed test methodologies ensure reliability, reproducibility and comparability of test results.
Appropriate methods should duplicate or simulate actual use conditions, present a minimum of hazard to investigator and subject, be reasonably economical, and be flexible enough to handle a variety of product forms.
Antimicrobial test methods should also utilize a reliable supply of standardized microorganisms.
In situations where product form or ingredients interfere with a method, use of an equivalent method should be allowed provided it meets the general guidelines embodied in the original test method.

ASTM (American Society for Testing and Materials) methods are proposed for testing because they embody the above principles. Use of ASTM procedures ensures that periodic peer review of the methods will maintain their validity, currency, and reproducibility.

To be consistent with an ingredient-based monograph approach, a regimen incorporating both in vitro and in vivo tests is used to demonstrate the speed of action and spectrum of activity of a final formulation and its ability to meet the effectiveness criteria to support product claims and indications. The monograph criteria should correspond to a reduction in risk in a given situation.

An active ingredient listed in an OTC monograph as effective and safe (category I) has had the breadth of its efficacy attributes established during the formal drug review process. Therefore, when such ingredients are used in product formulations, only limited testing is needed to confirm the level of effectiveness of the ingredient at the use concentration and to assess the impacts of other ingredients in the formulation on its effectiveness. Supplemental methods may be used to demonstrate attributes to support other truthful and not misleading statements, not necessarily indications or label claims.

To demonstrate the speed of action and spectrum of activity of a final formulation, an in vitro time-kill methodology is used. This is a suspension test method that demonstrates that there is a reasonable expectation of antimicrobial activity within a time frame that is relevant to the use situation for that product.

Specific in vivo tests are performed on final formulations in order to support specific indications. The surrogate endpoint effectiveness criteria proposed for these tests should be correlated to clinical performance, where possible, or statistical risk models. The criteria should reflect the severity of the risk associated with the performance of the task.

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A. Reduction of Transmission Primarily to Oneself (Bodywash)

In vivo testing to support indications for products used to reduce the incidence of minor skin infection must demonstrate either: activity against resident organisms to reduce their numbers to a specified level or the maintenance of bacterial levels remaining after washing to below initial levels. If a decrease in transient skin microorganisms from the gut that are left on the hands after washing is claimed, activity against transient organisms down to effective levels must be demonstrated. The surrogate criteria are based on data from either clinical studies, or microbial risk modeling.

In most cases, criteria for these products will overlap with the criteria for products that interrupt transmission between individuals, and the methodology and efficacy criteria should be the same. Appropriate methods include ASTM E1174 (the Healthcare Personnel Handwash test), the Cade method, and the Cup Scrub. Persistent activity could be demonstrated using the same methods.

B. Reduction of Transmission Between Individuals/ Fomites (Handwash)

In vivo testing must demonstrate that the drug product reduces the number of transient organisms. The effect should be immediate and greater than or equal to surrogate reduction criteria in order to support indications that the use of a product reduces transient organisms on the hand. Efficacy criteria should be reflective of the risks encountered in various settings. They are based on clinical or risk modeling data from studies that look at these specific scenarios. The method of primary utility is ASTM E1174, the Healthcare Personnel Handwash Method. This method allows for evaluation of various product forms and uses, including waterless products. This method is flexible enough to allow the products to be tested under use conditions specified on the label.

In cases where activity against transient and resident flora on the hands needs to be demonstrated, ASTM E1874, the Cup Scrub method, would be appropriate in addition to E1174.

C. Reduction of Transmission During Presurgical/ Surgical, Preinjection Procedures (Surgical Scrub, Preop Prep)

In vivo testing must demonstrate the immediate and significant reduction of the resident and transient flora, reflective of the highest potential for acquisition of disease, and the increased risk associated with breaching the skin barrier. In some

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cases residual activity over a period of hours should also be demonstrated. ASTM E1173, the Preoperative Preparation method, can be used to demonstrate the in vivo activity of products labeled for preoperative skin preparations and for injection site preparation as well. This method samples primarily resident flora using the Cup Scrub technique. It is flexible to allow evaluation of various product forms under conditions of use. Substantiation of residual activity against resident bacteria can also be demonstrated with this method. In cases where immediate and persistent activity against transient and resident flora on the hands needs to be demonstrated, ASTM E1115, the Surgical Scrub method would be appropriate.

VI. SUMMARY

The six categories proposed in the Healthcare Continuum Model illustrate the underlying principles of defining performance attributes following a thorough understanding of the use pattern, user population, and microbiology. Any model as complex and detailed as the HCCM answers many old questions while stimulating new questions: Are other use patterns in practice that should be included? Should certain categories be combined or refined? Are there additional details concerning the use patterns that need to be addressed? Should additional attributes and test methodology be considered? The regulation of topical antimicrobial products remains a work in progress. The HCCM offers a flexible system to quickly define additional categories to meet the challenges of emerging disease and technology. We have pointed out only a few of the obvious questions that remain and restated the need for a flexible, cohesive regulatory framework.

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