

**TAB 6 FDA Reviewer's Evaluation of the SDA/CTFA Submissions
(C12, CP7, CP16) Regarding Benefit of Antiseptic Bodywashes**



CONSUMER ANTISEPTIC DRUG PRODUCTS REVIEW

Office of Nonprescription Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

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I. Purpose

This review provides a summary and evaluation of data submitted by the Soap and Detergent Association and Cosmetic, Toiletry, and Fragrance Association Industry Coalition (Coalition) as a demonstration of the benefits of over-the-counter (OTC) antiseptics used by consumers as antiseptic bodywashes and handwashes. Submitted articles and technical reports pertaining to consumer products not previously reviewed are reviewed here. Food handler preparations will be considered at a later date.

II. Background

In response to the publication of FDA's Tentative Final Monograph (TFM) for OTC Healthcare Antiseptic Drug Products (59 FR 31402, June 17, 1994,), the Coalition proposed the Healthcare Continuum Model (HCCM). The HCCM extends the largely professional-use product categories proposed in the TFM, i.e., antiseptic handwashes/healthcare personnel handwashes, surgical hand scrubs, and patient preoperative skin preparations to include consumer antiseptic body washes and food handler handwashes. The model also proposes safe and effective active ingredients, labeling, testing, and effectiveness criteria for each product category.

The Coalition relies on the well-documented role of the hands in the transmission of infection and the benefits of hand hygiene to support the need for antiseptic handwashes in the home. The Coalition asserts that antiseptic handwashes produce larger reductions in the numbers of organisms on the skin than plain soap and that model systems have demonstrated the control of potentially pathogenic organisms on the skin. Further, antimicrobial ingredients, deposited on the skin, can also be of benefit when washing is perfunctory or inadequate, and leaves behind organisms that can cause infection or be transferred to other skin sites. The Coalition believes that the regular use of an antiseptic product in personal cleansing has a recognized role in the prevention of disease. However, as in the hospital setting, convincing studies demonstrating a clinical benefit from the use of these products in a nonclinical setting are lacking.

Bacteria are ubiquitous in the environment and are part of the normal flora of the skin. The Coalition asserts that antiseptic bodywashes help control the numbers of bacteria on the skin over the entire body. One of the benefits from this reduction suggested by the Coalition is a reduction in the risk of skin infections caused by gram-positive organisms. This benefit may be particularly important to segments of the population that are at increased risk for these infections, e.g., the elderly. The Coalition states that skin infections due gram-positive organisms are recognized as a common and significant public health problem for which antiseptic bodywashes may be beneficial. A second use for these products is the reduction of body odor.

In 1974, FDA's Advisory Review Panel on OTC Antimicrobial I Drug Products (Panel) evaluated the effectiveness of antimicrobial soaps for the prevention of skin infection. In its report to FDA published in the Federal Register of September 13, 1974⁴, the Panel concluded that the data were not sufficient to demonstrate that antimicrobial soaps are effective in the prevention of skin infection. Further, the Panel also voiced the concern that the routine use of topical antimicrobials may have a long-term harmful effect by reducing the protective effect of the normal skin flora thus leading to an increase in certain kinds of skin infections. The Panel also evaluated the use of antimicrobial soaps for the treatment of erythrasma, and concluded that while definite evidence of the effectiveness of antimicrobial soaps for this use had been provided, the condition required diagnosis by a doctor and was not a suitable OTC use. FDA agreed with the Panel's recommendations and did not propose to include claims relating to the prevention or treatment of skin infection for antimicrobial soaps in its TFM for OTC topical antimicrobials published in the Federal Register of January 6, 1978⁵. Labeling for antimicrobial soaps was limited to general claims such as "antibacterial soap" and deodorancy.

III. Review

Overview and Summary

Eleven articles not previously evaluated are reviewed below. The majority of the articles describe the use of antiseptics not currently marketed as consumer products, i.e., povidone iodine and chlorhexidine gluconate in the treatment of various skin conditions, e.g, atopic dermatitis (AD) and erythrasma. In most of the studies, the effectiveness of the antiseptic

was not the focus of the study. For example, in some studies the antiseptic was part of a treatment regimen that included other treatments such as antibiotics or corticosteroid creams, and the effectiveness of the treatment regimens were the primary focus of investigation. Thus, the studies were not adequately controlled to assess the contribution of the antiseptic. In others, treatment consisted of antibiotic therapy and the use of an antiseptic bodywash was not studied. These studies cannot be considered relevant to the proposed use of antiseptic bodywashes for the prevention of skin infection and were not designed to evaluate the contribution of any of the treatment components.

Of the remaining articles, one was an abstract, another was a microbiological risk assessment model for which the authors acknowledge that additional data are needed, and one was not able to demonstrate a benefit from the use of various handwashing regimens on the transfer of bacteria to sterile contact lenses. Thus, the data provided are not sufficient to demonstrate a benefit from the use of consumer antiseptic bodywashes in the prevention of skin infection.

Study Evaluations

A. Topical antimicrobials in the treatment of skin conditions

Akiyama et al.¹ examined the effectiveness of a 10-percent povidone iodine solution (PI) in reducing the density of *Staphylococcus aureus* (*S. aureus*) on dermatitis lesions and reducing the severity of AD lesions. A total of 150 subjects who met the criteria of the Japanese Dermatological Association for AD were enrolled in the study, and were assigned to either PI or to non-PI treatment groups. Treatment in the PI group consisted of the application of PI followed 2 minutes later by cleansing with soap and water. An area less than 100 cm² was treated once daily for 14 days. Treatment for the non-PI group consisted of washing with soap and water for 14 days. No oral or topical antiseptics/antimicrobial agents or oral corticosteroids were used. However, approximately a third of the subjects in each group received topical corticosteroids. Topical corticosteroids were not applied to areas being used for bacterial sampling.

S. aureus density was assessed on a lesion area of 10 cm² once at the beginning and once after 14 days. Colonies from the sampling reacting positively to egg yolk were regarded as *S. aureus*. The *in vitro* activity of PI in the presence of human plasma against one of the isolated strains was also evaluated. Prior to sampling, lesions were evaluated for erythema, degree of exudation, and itching. Data were analyzed using the Mann-Whitney U-test and chi-square test (Yeat's correction). Treatment with PI resulted in a significant reduction in *S. aureus* density and lesion erythema and exudation when initial *S. aureus* counts were greater than 1,000 CFU per 10 cm². However, there were no significant differences in any of these when initial counts were below 1,000 CFU per 10 cm².

Besides the fact that the study assessed the use of PI in the treatment of AD lesions, a number of design flaws make interpretation of the study results problematic. The study was not randomized or blinded. Only a single site on each subject was sampled. Further, there is no evidence that disease severity was balanced between the groups.

Breneman and colleagues² evaluated the effectiveness of a soap containing 1.5 percent triclocarban when used in a daily bathing regimen in reducing the number of *S. aureus* on the skin and in improving the symptoms of atopic dermatitis. Fifty subjects with moderately severe AD according to the criteria of Rajka and Langeland were randomized to either an antimicrobial soap containing 1.5 percent triclocarban or placebo soap. Patients also used a nonmedicated moisturizer and a 0.025 percent triamcinolone acetonide cream as needed.

The study period consisted a 14-day standardization period, a 42-day treatment period, and a 21-day regression period. During the standardization period subjects were given a nonmedicated cleansing bar and moisturizing cream and were instructed to refrain from using systemic or topical antibiotics and antibacterial/antimicrobial soaps, lotions, or creams for the duration of the study. A corticosteroid cream was provided to replace other topical steroid medications that they may have been using. During the treatment phase of the study, subjects were required to wash their entire bodies with the assigned soap once daily and continued their use of the nonmedicated lotion and the corticosteroid cream as established during the standardization period. Subjects stopped using the topical corticosteroid cream during the regression period to determine the rate at which clinical symptoms returned.

The extent of the dermatitis was assessed and microbial specimens were taken at days 0 (before treatment), 14, 28, and 42. During the regression period, dermatologic evaluations were done on a weekly basis to ensure that subjects' conditions did not become extensively worse. Subjects were evaluated with regard to itching and percentage of body affected. A 3-point scale of -5 to 5 (-5 severe worsening, 0 no change, 5 total clearing) was used to evaluate the extent and severity of the dermatitis and symptomology. Microbiologic samples were taken from four to five skin sites using a swab-wash method. A circular area of 5 cm² was sampled, and a total of four specimens from the elbow- and knee-crease areas were taken. If a subject didn't have a lesion in either of these areas, a fifth specimen was taken from another site and sampling from this site was continued throughout the study. Specimens were plated on trypticase soy agar (TSA) with 5 percent sheep blood and on mannitol salt agar for the enumeration of total aerobic bacteria and *S. aureus*. Identification of *S. aureus* was verified using a Staphyloslide test.

Statistical comparisons were made using repeated measures analysis of variance or covariance over time. For primary and secondary dermatologic attributes, including total aerobic bacteria, *S. aureus*, itch, and changes from baseline were analyzed using baseline response as the covariant and body part as a factor when multiple samples were collected from different parts of the body. Repeated measures analysis was used to make statistical comparisons. Homogeneity at baseline was verified for all endpoints with an analysis of variance. P values ≤ 0.05 were considered significant.

The scores for both groups improved during the treatment period and worsened during the regression period. However, global improvement was significantly greater than in the placebo group. Analysis of the combined three primary attributes, and the combined six dermatologic endpoints indicated that the change from the baseline scores was significantly greater in the antibacterial soap regimen when compared to the placebo regimen. The results of the analyses of the individual primary and secondary attributes except for

oozing/weeping/crusting also indicted a significant difference in favor of the antibacterial regimen. The greatest improvement was for excoriation. The antibacterial group regressed more slowly than the placebo group during the regression period. There was also a significant reduction in the percentage of the body surface area affected in the antibacterial group. The reduction of aerobic bacterial counts was greater than in the antibacterial group. There was also a significant reduction in the numbers of *S. aureus* in subjects infected with the organism. However, there was no significant difference between the regimens when subjects without *S. aureus* were included in the analysis. The authors concluded that the study results suggest that even a small decrease in the numbers of *S. aureus* can result in improvement in AD. However, there was approximately a 1-log₁₀ reduction in *S. aureus* isolated from the lesions during the regression period (no topical steroid use with continued treatment soap use) for both the antibacterial and placebo groups. This suggests that the reductions in the organism may not have been solely due to the use of the antibacterial soap.

Breuer et al³, investigated the colonizing features of *S. aureus* in adult subjects with AD and in their contacts and the effect of antimicrobial treatment of the subjects and their partners. The study included a multifaceted treatment regimen of cefalexin, topical chlorhexidine gluconate, as well as treatment of the anterior nares with mupirocin and daily baths with potassium permanganate. The study did not include an antibacterial soap, and even if it had, the study was not designed to assess the contribution of each of the components of the regimen.

Sugimoto et al.¹³, describe their treatment of AD. The treatment consisted of the use of 10-percent povidone iodine applied for 2 minutes on lesions of the face and 3 minutes elsewhere on the body followed by thorough rinsing 2 to 4 times a day. In addition to use of povidone iodine, an undisclosed steroid cream was used once a day and a moisturizing Vaseline ointment was used on an as-needed basis. Data were collected using a patient questionnaire. There was no control population, and the study was not blinded.

A study by **Leigh and Joy**⁶ evaluated the effectiveness of the use of 2-percent mupirocin nasal ointment or 1-percent chlorhexidine and 5-percent neomycin cream in eradicating *S. aureus* from the anterior nares, axillae, groin, and perianal areas of subjects with AD and their families. In addition to either of these treatments, subjects in both treatment groups were given a 4-percent chlorhexidine gluconate solution for washing and a 1-percent chlorhexidine powder for application to the axillae, groin, and perianal regions twice daily. Thus, as with the study by Breuer et al., the study was not designed to assess the contribution of the use of an antimicrobial wash product.

Leyden⁷ and colleagues evaluated the effectiveness of a 1-percent neomycin cream and oral erythromycin 250 mg daily in eliminating *S. aureus* from AD lesions and unaffected skin. The use of an antimicrobial wash product was not included in the study design.

A study by **Somerville**¹¹ and colleagues compared the effectiveness of a nonantimicrobial soap with a pink antimicrobial soap containing triclocarban (triclocarban), 2-hydroxy-2',4',4'-trichlorodiphenyl ether (triclosan), and 3-trifluoromethyl-4-dichlorocarbanilide (cloflucarban) in reducing the incidence of erythrasma in patients in a mental hospital. The

study was not blinded, and the authors found that both the placebo soap and the antimicrobial soap reduced the incidence of erythrasma in this setting. The study provided no details of the soap use or whether or not the extent of the infection was balanced between the groups. However, the study investigators suggested that the groups may not have been balanced with regard to IQ. In previous study, they had determined that patients with lower IQs had more intensive nursing care and better hygiene that they believe translated into a lower incidence of erythrasma.

Stoughton and Leyden¹² conducted three controlled comparative studies to assess the effectiveness of 4-percent chlorhexidine gluconate in the treatment of acne lesions. One study compared chlorhexidine gluconate with 5-percent benzoyl peroxide. Two studies evaluated the chlorhexidine gluconate solution with its vehicle formulation. The treatment period in each study was 12 weeks. Fifty healthy subjects with a minimum of 10 erythematous facial papules and pustules were entered into the active control study, and 110 were entered into the vehicle control studies. Subjects with chronic illness or skin diseases (other than acne), severe acne requiring more than topical therapy, or who were using systemic antibiotics or other therapy for acne were excluded from the study. Subjects applied the appropriate treatment twice a day. Use of concomitant topical or systemic drugs, the use of harsh or abrasive detergents, alcoholic cleansers, or ultraviolet treatments were prohibited during the studies. The treatment groups at baseline were balanced with regard to demographics. However, it is not clear that they were balanced with regard to severity. P values of ≤ 0.05 were considered significant.

A blinded observer evaluated treatment response. The observer counted the total number of papules, pustules, comedones, and macules on the subject's face (bounded by the mandible inferiorly, by the hairline superiorly, and by the ears laterally), and this was compared to baseline. Within the treatment group, the mean reduction at each visit was evaluated using a paired t-test. Between treatment groups, the mean reduction at each observation was compared by an analysis of covariance using baseline values as the covariant. The investigators concluded that only assessments made at 8 weeks and beyond were valid indications of effectiveness. Thus, only week 8 and 12 data were presented in detail.

In the active control study, both the chlorhexidine gluconate and benzoyl peroxide formulations achieved a significant reduction of the mean papules and pustules at weeks 8 and 12 ($P < 0.001$ to 0.01). Only the chlorhexidine gluconate achieved a significant reduction of the mean comedone count at both time points ($P < 0.05$). In the vehicle studies, chlorhexidine gluconate achieved a significant reduction in mean papules and pustules at all time points ($P < 0.001$). These reductions were greater than those of the vehicle at week 8 ($P < 0.1$) and at week 12 ($P < 0.001$). Chlorhexidine gluconate also produced a significant reduction in the mean comedone count at week 12 ($P < 0.01$; $P < 0.05$, versus the solution).

B. Other antimicrobial studies

Ly et al.⁸ compared the effect of five different hand washing regimens on the transfer of bacterial contaminants from the hands to sterile hydrogel contact lenses. Forty-seven

subjects were randomly assigned to one of five handwashing regimens for each weekly visit. All subjects performed each of the handwashing regimens or no handwashing once. The handwashing regimens consisted of the following:

- handwashing with tap water for 15 seconds (no drying)
- handwashing with Ivory Liquid Soap (a nonantimicrobial soap) for 15 seconds followed by rinsing with tap water and no drying
- handwashing with Ivory Liquid Soap for 15 seconds followed by rinsing with tap water and paper towel drying
- handwashing with Ivory Liquid Soap for 15 seconds followed by rinsing with tap water followed by paper drying then wiping with an alcohol pad and air drying before lens handling.

Subjects enrolled in the study also filled out questionnaire about their handwashing habits.

Following each of the handwashing or no washing regimens subjects were given a new sterile soft contact lens to handle for 20 to 30 seconds. After handling, the lenses were placed in sterile 0.1-percent peptone water and vortexed vigorously for 10 seconds. The peptone extract was serially diluted and cultured on TSA and chocolate agar (CA). In some cases, the lens itself was cultured. A sample of positive plates was cultured further for identification.

The data were analyzed using nonparametric methods because the sample distributions indicated a non-Gaussian distribution. The TSA and CA data sets were analyzed using the Friedman two-way analysis of variance of ranks to test the hypothesis that the bacterial count medians for the five handwashing methods were equal. In each case, the observed sample medians were found to be significantly different (TSA: $S=57.55$, $df=4$, $P<0.0005$, CA: $S=46.82$, $df=4$, $P<0.0005$). A *post hoc* Wilcoxon paired sample rank test in combination with a Bonferoni procedure was also conducted. Based on a Spearman rank correlation coefficient there was high correlation between the TSA and CA data ($r_s > 0.88$).

Median colony forming units (CFU) on lenses handled after washing with water, nonantimicrobial soap and water, or nonantimicrobial soap and water followed by towel drying were higher than the median CFUs for lenses handled after no handwashing. The median CFUs for lenses handled after nonantimicrobial soap and water washing followed by an alcohol wipe was not different from the no washing group. In both groups, the median CFUs were below 1,000.

Rose and Haas¹⁰ developed a quantitative microbial risk assessment to estimate the reduction in risk of skin infection with *S. aureus* resulting from the use of antibacterial soaps. The model is based on existing data on the growth kinetics of the organism on skin and dose data based on the inoculation of the skin on the forearm of volunteers. From these data a predictive relationship was developed. The authors acknowledge that the data on which the model is based is limited and conclude that more studies on exposure, contact times, growth, and infection outcomes are needed. Nevertheless, the authors predict based on the model that a significant reduction in the risk of infection of *S. aureus* could be achieved by using antimicrobial soaps.

Peters and Flick-Fillies⁹ prospectively evaluated the incidence of puerperal mastitis during two 12-month periods with and without additional hand disinfection at bedside. However, the study is presented as an abstract with insufficient detail to permit evaluation.

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Appendix – Acronyms and Abbreviations

AD	atopic dermatitis
CA	chocolate agar
cm ²	square centimeter
CFU	colony forming unit
HCCM	Healthcare Continuum Model
OTC	over-the-counter
TSA	trypticase soy agar
TFM	Tentative Final Monograph