Procter&Gamble

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Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Health Care Antiseptic Drug Products

Reopening of the Administrative Record; Docket No. 75N-183H

Dear Sir or Madam:

The Procter & Gamble Company is submitting the following comments in triplicate to support inclusion of triclocarban (TCC) at levels up to 1.5% in the rule-making for Topical Antimicrobial Drug Products for Over-the-Counter Human Use.

INTRODUCTION:

The Tentative Final Monograph for Health Care Antiseptic Drug Products (TFM), 59 Fed. Reg; 31401, June 17, 1994 for OTC Health Care Antiseptic Drug Products categorized triclocarban as Category III for efficacy for use in patient pre-operative skin preparations, surgical hand scrubs, and health care personnel handwash products. Subsequently, The Soap and Detergent and The Cosmetic, Toiletry and Fragrance Association Industry Coalition (SDA/CTFA Industry Coalition) has made a number of submissions to FDA providing data and comments relevant to this rule-making[1]. As a member of the SDA/CTFA Industry Coalition, The Procter & Gamble Company fully supports the recommendations of the Coalition and, additionally, requests that the following TCC efficacy data be taken into account in rule-making for health care personnel hand products, food handler products, consumer hand and consumer body products.

The Procter & Gamble Company has marketed a TCC-containing antibacterial bar soap since 1976 i.e. Safeguard® Antibacterial Deodorant Soap. Safeguard® containing 1.5% TCC was originally marketed under an NDA. In 1999 a new Safeguard® Antibacterial Deodorant Soap containing 1.2% TCC was introduced into the US market under the TFM, and sales of the NDA Safeguard® product were discontinued.

[1] These have included comments on the TFM and the proposal of the Health Care Continuum Model (June 15, 1995), compilations of efficacy data (December 13, 1995 & March 11, 1996), a detailed proposal on finished product testing methodology (September 29, 1999), a Citizen Petition for proposed labeling of HCCM product categories (April 2, 2001), a Citizen Petition addressing several OTC monograph flexibility issues (June 1, 2001), a Citizen Petition on surrogate end-point test methods (November 28, 2001), a Citizen Petition providing information in support of health care professional products (August 3, 2001), a Citizen Petition requesting anti-viral claims (January 17, 2003), and a Citizen Petition providing information in support of food handler, consumer hand and consumer body products (May 23, 2003).

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This submission includes the results of fourteen clinical studies that address the efficacy of TCC at levels up to 1.5% in Safeguard® Antimicrobial bar soap marketed in the United States. These studies have been conducted in the past 10 years; data from studies conducted earlier than 1993 have not been included. In some cases the studies include comparisons between the marketed Safeguard® bar and a matched placebo, without TCC. The placebo was prepared specifically for these studies as The Procter and Gamble Company does not commercialize a non-antibacterial variant of Safeguard® bar soap. In other cases, the studies include comparisons with marketed non-antibacterial brands, manufactured either by the Company or by other manufacturers.

Two of the clinical efficacy studies (BS# 591-CLC-9508 & CRB 96-05-005-PC) summarized here have been published in a peer-reviewed journal (Billhimer et al; 2001); the remainder are unpublished clinical efficacy studies. All studies measured the effects of washing with Safeguard® bars containing TCC at levels up to 1.5% on skin microflora. Qualitative formulation details for Safeguard® bars tested in the studies are provided in Table 1.

The data indicate reduction of resident skin bacteria, reduction of transient skin bacteria or the rate of growth of bacteria on occluded skin after washing, and support the SDA/CTFA Industry Coalition performance criteria proposals for bacterial log reductions for health care personnel hand product, food handler products, consumer hand and consumer body products.

This submission includes a description of the methods, a discussion of the results and conclusions, summary tables of the results, the formula of the marketed Safeguard® TCC-containing product and copies of each of the internal study reports. The study reports have been edited to remove confidential information and direct references to competitor products.

METHODS:

Since the benefits that result from washing with antibacterial soaps can not be easily measured under consumer use conditions, it is necessary to do controlled handwash clinical studies to demonstrate the reduction in the numbers of both resident and contaminating skin flora. The clinical testing that was conducted with Safeguard® bars containing TCC uses three standardized microbiological test procedures that are under consideration by the American Society for Testing of Materials (ASTM) for incorporation into their manuals. The SDA/CTFA Industry Coalition also recommends use of the ASTM methods as acceptable and standardized protocols for evaluating the antibacterial efficacy of liquid and bar soap products in the Final Monograph.

Cade Handwash Test

The objective of these studies was to determine the effectiveness of Safeguard® antibacterial soap products to reduce the level of resident bacteria on the skin after exclusive use of these products for at least five days. The study consists of a wash-out period and a treatment period. During the wash-out period, the subjects agreed to refrain from using topical or systemic antibiotics, medicated lotions and creams, antibacterial soap products, anti-acne drugs, and dandruff shampoos. They also agreed to wear rubber gloves whenever necessary to protect their hands from exposure to chlorine, household cleaning products, solvents, and any other harsh chemicals or products which may adversely effect the bacterial flora on their hands.

At the beginning of the treatment period, before washing with the TCC Safeguard® bar, a baseline bacterial count, using a fifth basin bacterial sampling procedure, was done to determine the numbers of bacteria on the subjects' hands. This sampling procedure involved collecting the lather into a basin of sterile water after a series of five handwashes. Studies have shown that after four consecutive handwashes, the transient, contaminating bacteria were removed, but the bacteria that permanently colonize the skin remained and were relatively invariant on subsequent rinses. The lather collected from the fifth wash was representative of resident flora.

Following the base count, the subjects began the treatment period. During this period, they washed their hands with the TCC bar according to a prescribed wash procedure. The subjects did three washes per day, at least one hour apart, for four days, for a total of 12 washes. In addition to washing their hands at the test site, they were also given a bar of the test product to use at home for showering, bathing, and washing their hands. After the final wash, the subjects repeated the basin sampling procedure for determination of the test count. Aliquots of water, obtained from the basin washes during the baseline and test count procedures, were diluted in neutralizing phosphate buffer, plated on trypticase soy agar (TSA), and incubated for 36-48 hours at 35-37°C.

Efficacy was determined by comparing the numbers of bacteria on the hands before (baseline) and after (test) using the TCC-containing product. The number of organisms removed from the hands during the baseline and test count procedures were used to calculate the % reduction. The numbers of bacteria were converted to base 10 logarithms. The log difference between the average number of bacteria recovered at baseline and number of bacteria recovered after washing with Safeguard® was determined and the average % reduction was calculated.

Health Care Personnel Handwash Test (modified to a single use)

The objective of these studies was an evaluation the efficacy of TCC Safeguard® antibacterial soap products to reduce the numbers of transient bacterial flora on the hands after a single 30 second wash.

The studies consisted of a one week wash-out period and one day treatment period. During the wash-out period, subjects were asked to refrain from using medicated shampoos and antimicrobial soaps, lotions, or creams. During the treatment period, the subjects' hands were contaminated with cultured indicated species. The subjects' hands were contaminated and sampled two times. The first contamination and sampling was for the determination of the base count. The second contamination and sampling was for determination of the test count after washing with the test product.

For the baseline count, the bacteria on the subjects' hands were removed, immediately following the contamination step, using a plastic bag sampling procedure. For the test count, the subjects' hands were again contaminated with the test bacteria. However, before the sampling procedure was repeated, subjects washed their hands for 30 seconds with TCC-containing product. Aliquots of the sampling solutions were diluted, plated, and incubated. The numbers of colony forming units (CFU's) at the baseline and test sampling periods were enumerated. Bacterial removal/reduction was determined by comparing the number of bacteria removed from the hands after washing with Safeguard® to the number of bacteria removed from unwashed hands (baseline).

The number of surviving bacteria for each subject at each evaluation was determined. The numbers of bacteria were converted to base 10 logarithms. The log difference between the average number of bacteria recovered at baseline and the number of bacteria recovered after washing with the test product was determined and the average % reduction was calculated.

Residual Effectiveness Test

The objective of these studies was to evaluate the residual effectiveness of a TCC-containing Safeguard® antibacterial soap product versus a placebo soap against potentially pathogenic bacteria under simulated skin conditions that are considered optimal for bacterial growth, proliferation, and possible infection. They consisted of a washout period followed by a 3-day treatment period. Subjects, who were enrolled, were given a non-medicated personal cleansing bar to use in place of their regular personal cleansing product until the study was completed. They were also instructed to refrain from using any other antibacterial/antimicrobial soaps, medicated lotions and creams, and/or dandruff shampoos.

During the 3-day treatment period, the subjects were randomly assigned to wash one of their forearms with the antibacterial soap and the other forearm with placebo soap. On the first two days, the subjects did three washes at least one hour apart. On the third day, subjects did one additional wash, for a total of seven washes. Following the final wash, three test sites were marked off on both forearms. Each of the six test sites was inoculated with a known amount of test organism (*Staphylococcus aureus* strain 502A (ATCC 27217), or *Streptococcus pyogenes*). The sites were then occluded with a Hill Top Chamber® patch. At intervals of 30 minutes, 2 hours, and 5 hours, one of the patches on each arm was removed. Following removal of the patch, the bacteria on the skin were harvested using a scrub technique. Each sample of harvested bacteria was diluted, plated, and incubated. Following incubation, the number of surviving CFU's for each arm, at each time period, was determined and appropriately analyzed.

Using the above study design, the skin was inoculated immediately after the final (7th) wash. To evaluate if the residual antibacterial efficacy remained in effect 24 hours after the final wash, a second study was conducted with a slightly modified study design. This study consisted of a wash-out period followed by a 4-day treatment period. As in the first study, the subjects used a non-medicated soap and refrained from using other antibacterial/antimicrobial soaps, medicated lotions and creams, and/or dandruff shampoos until the study was completed.
During the 4-day treatment period, the subjects did a total of nine washes. They did three washes, at least one hour apart, for three consecutive days. On the fourth day, 24 hours after the final wash, test sites on the skin were inoculated with *S. aureus* as in the first study. The same procedures were also used for occluding, harvesting, and culturing of the test organisms. The $\log_{10}$ CFU counts were compared using a Wilcoxon Signed-Ranks Test (a nonparametric paired t-test) to estimate which of the test bars had the greatest antibacterial activity. In addition, a binomial (sign) test to determine any significant differences between the number of subjects experiencing a reduction in CFU's with the test bars was also performed on these data. P-values ≤ 0.05 were considered statistically significant.

RESULTS:

The results are summarized in Tables 2, 3, and 4, for the Cade Handwash Test studies, the Healthcare Personnel Handwash Test studies and the Residual Effectiveness Test studies, respectively.

Cade Handwash Studies:

There are two studies in this group. Handwashing with formulations containing 1.0%, 1.2% or 1.5% TCC resulted in the reduction of resident bacteria by greater than 90%. These studies contain additional data on bars with other antimicrobial ingredients, placebo, and an investigational TCC formula that was never marketed (designated B7S). In the case of the investigational TCC B7S formulation, the reduction was around 85%.

Healthcare Personnel Handwash Studies (HCPHWT):

There are five studies in this group. The results, show 97.4 % to 99.8% reduction of transient bacteria after a single 30-second washing with test product containing 0.9%, 1.2% or 1.5% TCC. The standard test organism in the HCPHWT is *Serratia marcesens.* In several of these studies, non-standard test organisms, *E. coli* and *S. aureus* were used. High reductions (99.7% and 99.8%) of these species were achieved with single 30-second washings, demonstrating the efficacy of TCC against bacterial species beyond the standard clinical test organism.

Residual Effectiveness Test:

There are seven studies in this group. These are paired studies in which the growth, over 30 minutes to 5 hours of occlusion of bacteria placed on the skin either immediately, 12 hours, or 24 hours after washing with Safeguard is measured and compared to growth of bacteria on skin after washing with a placebo or a non-antibacterial product. The results show consistently that the growth of *Staphylococcus aureus* on the skin after washing with TCC is significantly lower than after washing with non-antibacterial products. We believe this residual effectiveness of Safeguard® bar with TCC is important in lowering the rate of skin infections that can result from the uncontrolled growth of *Staphylococcus aureus* as demonstrated in a clinical study in atopic dermatitis subjects (Breneman et al; 2000).

In one study, *Staphylococcus aureus* was replaced by *Streptococcus pyogenes.* The 1.5% TCC product was not significantly more effective in controlling the growth of this test organism than placebo soap.

CONCLUSIONS:

The study data in this submission measure three important parameters for topical antimicrobial products: reduction in residual skin bacteria with continual use, rapid reduction in transient bacteria upon a single 30-second washing, and control of growth of potential skin pathogens for up to 5 hours after inoculation. TCC-containing formulations (Safeguard®) achieved greater than 1-log reductions in resident bacteria and greater than 2-log reductions in transient bacteria. Comparisons show superior growth control over non-antimicrobial bar-soap formulas including a matched placebo lacking TCC.

Taking these results together with those presented in the atopic dermatitis study (Breneman et al; 2000), it is reasonable to conclude that regular use of TCC-containing products can lower the incidence of skin infections by decreasing the number and growth of bacteria on the skin and lower the incidence of infections generally transmitted by hand by interrupting the transmission of pathogens (Rose and Haas, 1999).

We therefore recommend that FDA include TCC as a Category I ingredient, at levels up to 1.5%, in the Final Rule-making for health care personnel hand product, food handler products, consumer hand and consumer body products.

Sincerely,

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Table 1

Qualitative formulation details for Safeguard® Bar Soap tested in clinical studies (1993 – 2000)

Ingredients	Safeguard formulation 1993 – 1998	Safeguard formulation 1999 – 2000
Triclocarban	1.5%	1.2%
Water	x	x
Sodium tallowate &/or sodium palmate	x	x
Sodium cocoate or sodium palm kernelate	x	x
Coconut or palm kernel fatty acid	x	x
Sodium chloride	x	x
Tetrasodium EDTA	x	x
Glycerin	-	x
DMDM hydantoin	-	x
Fragrance	x	x
Color	x	x

x indicates ingredient present in formulation
- indicates ingredient absent in formulation

Table 2: Cade Handwash Studies of Reduction in Resident Bacteria

Study Number	Test Organism	Test Products	TCC Concentration	Base Size (n)	Results
BS#638-EXP-9602	Resident Bacteria	TCC bar vs placebo bar	1 0% TCC	46	92 6% reduction in resident bacteria Significantly more reduction vs placebo ($p \leq 0$ 05)
CRB-98-01-009-PC	Resident Bacteria	TCC bar	1.2% & 1 5% TCC	92	92 7% , 95 7%, and 85 6% reduction in resident flora

Table 3: Healthcare Personnel Handwash Tests of Reduction in Transient Bacteria

Study Number	Test Organism	Test Products	TCC Concentration	Base Size (n)	Results
BS#-410-CLS-9312	*Serratia marcesens*	TCC bar	1 5% TCC	15	97 4% reduction in transient bacteria after single 30 second wash
BS#505-CLS-9410	*Serratia marcesens*	TCC bar	1 5% TCC	16	99 8% reduction in transient bacteria after single 30 second wash
CRB-98-04-067-PC	*Serratia marcesens*	TCC bar	1 2% TCC	16	99 7% reduction in transient bacteria after a single 30-second wash
CRB-99-06-082-PC	*S aureus & E coli*	TCC bar	1 2% TCC	28	99 8% reduction of transient bacteria (*S aureus & E coli*) after single 30 second wash.
CRB-00-11-165-HB	*E coli & S aureus*	TCC bar	0 9% TCC	32	99 9% reduction of *E. coli* & 99 7% reduction of *S aureus* after a single 30-second wash

Table 4: Residual Effectiveness Tests of Bacterial Growth Rate Control

Study Number	Test Organism	Test Products	TCC Concentration	Base Size (n)	Results
BS# 477-EXP-9406	*Staphylococcus aureus*	TCC bar vs placebo bar	1 5% TCC	10	Significant reduction in growth rate of *S aureus* on skin of test subjects compared to placebo following 2 & 5 hrs occlusion immediately after washing ($p \leq 0$ 10)
BS# 591-CLC-9508	*Staphylococcus aureus*	TCC bar vs placebo bar	1 5% TCC	20	Significant reduction in growth of *S aureus* on skin of test subjects compared to placebo following 30 mins, 2 & 3 hrs occlusion immediately after washing ($p \leq 0$ 05)
CRB-96-05-005-PC	*Staphylococcus aureus*	TCC bar vs non-antibacterial brand bar	1 5% TCC	22	Significant reduction in growth of *S aureus* on skin of test subjects compared to placebo following 30 mins, 2 & 3 hrs occlusion immediately after washing ($p \leq 0$ 05)
CRB-96-06-015-PC	*Streptococcus pyogenes*	TCC bar vs non-antibacterial brand bar	1 5% TCC	22	Safeguard bar did not control *S pyogenes* growth sign better than placebo soap at any of the occlusion intervals (30 mins , 2 & 5 hrs) immediately after washing ($p \leq 0$ 05)
CRB-98-05-068-PC	*Staphylococcus aureus*	TCC bar vs placebo bar	1 2% TCC	18	Significant reduction in growth of *S aureus* on skin of test subjects compared to placebo following 30 mins, 2 & 5 hrs occlusion immediately after washing ($p \leq 0$ 05)
CRB-99-09-116-PC	*Staphylococcus aureus*	TCC bar vs placebo bar	1 2% TCC	14	Significant reduction in growth of *S aureus* on skin of test subjects compared to placebo following 2 & 5 hrs occlusion immediately after washing ($p \leq 0$ 10)
CRB-99-12-156-PC	*Staphylococcus aureus*	Safeguard bar vs placebo bar	1 2% TCC	13	Significant reduction in growth of *S aureus* on skin of test subjects compared to placebo following 2 & 5 hrs occlusion immediately after washing ($p \leq 0$ 10)

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CUTIS Vol 66, Oct. 2000, pp.296-300.

Rose, J.B., and C.N. Haas.
A Risk Assessment Framework for the Evaluation of Skin Infections and the Potential Impact of Antibacterial Soap Washing.
AJIC Vol. 27 (6), pp.S26-S33.

CLINICAL STUDY REPORTS:

BS# 638-EXP-9602
Cade handwash test results on antibacterial bar soap formulations containing triclocarban, chloroxylenol, or thymol, and a placebo bar soap.
April 26, 1996

CRB-98-01-009-PC
Cade handwash test results on B28 bar with 1.2% TCC, B28 bar with 1.5% TCC, and B7S bar with 1.5% TCC.
March 30, 1998

BS# 410-CLS-9312
Health care personnel hand wash test results on Safeguard bar with 1.5% TCC.
January 10, 1994

BS# 505-CLS-9410
Health care personnel hand wash test results on Safeguard bar with 1.5% TCC.
September 10, 1995

CRB-98-04-067-PC
Health care personnel hand wash test results on B-28 bar with 1.2% TCC.
July 24, 1998

CRB-99-06-082-PC
Efficacy evaluation of an antibacterial bar soap in a health care personnel hand wash study versus *E. coli* & *S. aureus*.
June 30, 1999

CRB-00-11-165-HBT
Efficacy evaluation of an antibacterial bar soap in a health care personnel hand wash study versus *E. coli* & *S. aureus*.
November 10, 2000

BS# 477-EXP-9406
Evaluation of residual effectiveness of antibacterial bar soaps.
February 12, 1995

BS# 591-CLS-9508 (published, Billhimer et al; 2001)
Residual effectiveness (cup scrub) test results on Safeguard Bar with 1.5% TCC versus a placebo bar.
September 20, 1995

CRB-96-05-005-PC (published, Billhimer et al; 2001)
24-hour residual effectiveness (cup scrub) test results on Safeguard Bar with 1.5% TCC versus non-antibacterial bar soap.
July 26, 1996

CRB-96-06-015-PC
Residual effectiveness (cup scrub) test results on Safeguard Bar with 1.5% TCC versus non-antibacterial bar soap against *Streptococcus pyogenes*.
October 15, 1996

CRB-98-05-068-PC
24-hour residual effectiveness (cup scrub) test results on B-28 bar with 1.2% TCC versus B-28 placebo bar.
July 24, 1998

CRB-99-09-116-PC
Evaluation of the 24-hour residual effectiveness of an antibacterial bar versus a placebo bar soap.
September 30, 1999

CRB-99-12-156-PC
Evaluation of the 24-hour residual effectiveness of an antibacterial bar soap versus a placebo bar soap.
December 23, 1999