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August 19, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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Submission of comments and data in response to the re-opening of the Topical Antimicrobial Drug Products for Over-the-Counter Human Use: Health-Care Antiseptic Drug Products Tentative Final Monograph Docket No. 75N-183H

The Colgate-Palmolive Company ("Colgate") is submitting the following comments and data in response to the re-opening of the Topical Antimicrobial Drug Products for Over-the-Counter Human Use: Health-Care Antiseptic Drug Products Tentative Final Monograph (TFM) published June 17, 1994.

The objectives of this submission are to provide support for the efficacy of

- **triclosan as a Category I antimicrobial active ingredient for use in topical antimicrobial formulations, more specifically, consumer handwash, foodhandler handwash, and health-care personnel handwash products (CTFA/SDA Citizen Petition on Healthcare Continuum Model (HCCM), Vol. 1 submitted to Docket 75N-183H on June 15, 1995, CTFA/SDA Citizen Petition on Consumer and Foodhandler Products submitted to Docket 75N-183H on May 23, 2003), and**

- **triclocarban (TCC) as a Category I antimicrobial active ingredient for use in topical antimicrobial formulations, more specifically, consumer handwash, foodhandler handwash, and health-care personnel handwash products (CTFA/SDA Citizen Petition on Healthcare Continuum Model (HCCM), Vol. 1 submitted to Docket 75N-183H on June 15, 1995, CTFA/SDA Citizen Petition on Consumer and Foodhandler Products submitted to Docket 75N-183H on May 23, 2003).**

In addition, Colgate supports

- **the establishment of pre-determined performance criteria for final formulae to be set forth in the Final Monograph, in lieu of specific lower concentration limits of active ingredients, and**

75N-183H

C 82

- **the Agency's decision to bifurcate the Tentative Final Monograph and address topical antimicrobial consumer products in a separate rulemaking.**

Background:

Performance Criteria: Colgate supports past CTFA/SDA Industry Coalition proposals for performance criteria for consumer topical antimicrobial products (CTFA/SDA submission to FDA dated May 23, 2003) and topical antimicrobial health-care products (CTFA/SDA Citizen Petition on the Healthcare Professional Products submitted on August 6, 2001. Colgate is using these criteria as reference for the determination of product efficacy in this submission, and the data and comments that we are providing further supplement all of the above referenced submissions.

Triclosan: Triclosan is currently listed in the June 1994 Topical Antimicrobial TFM as a Category III active ingredient for efficacy as a patient pre-operative skin preparation and as a Category III active ingredient for safety and efficacy for use as an antiseptic handwash or health-care personnel handwash and as a surgical hand scrub at levels up to 1%. In previous submissions to the Agency, efficacy data have supported the use of triclosan at levels beginning at 0.2%. (Ciba-Geigy Corporation, Citizen's Petition dated December 14, 1995, CTFA/SDA Industry Coalition submission to FDA dated December 13, 1995).

Triclocarban: Triclocarban is currently listed in the June 1994 Topical Antimicrobial TFM as a Category I active ingredient for safety, and as a Category III active ingredient for efficacy at 1.5% in patient pre-operative skin preparations, antiseptic or health-care personnel handwashes, and surgical hand scrubs. Since the 1994 TFM, numerous Citizens Petitions have been submitted to the Agency supporting the efficacy of triclocarban beginning at 0.3% and 0.7% (Citizen Petition to Classify Triclocarban Category I for Efficacy in the Tentative Final Monograph for Health-Care Antiseptic Drug Products, Bayer Corporation, December 28, 2001, Dial Corporation submission to FDA dated December 13, 1995, and CTFA/SDA Industry Coalition submission to FDA dated December 13, 1995).

To further support previous submissions as noted above regarding the efficacy of triclosan and TCC, Colgate is submitting additional data to establish these active ingredients as Category I for efficacy in consumer handwash, foodhandler handwash, and health-care personnel handwash products.

I. Antibacterial Efficacy of Triclosan in Liquid Handwash Formulations:

In accordance with the CTFA/SDA Healthcare Continuum Model, Colgate has conducted the following *in-vivo* testing to support the efficacy of triclosan in liquid handwash formulations.

A. Health-Care Personnel Hand Wash (HCPHW) Test Results

The formulation tested was a liquid handwash formulation containing 0.115% triclosan and was tested according to ASTM Test Method E1174-00 (Evaluation of Effectiveness of Health Care Personnel or Consumer Handwash Formulations). A reference control containing 4% chlorhexidine gluconate (Hibiclens®) was also included. The test method used to evaluate the efficacy of this formulation and the performance criteria are based on the recommendations described in the CTFA/SDA Citizen Petition on Consumer and Foodhandler Products submitted to Docket 75N-183H on May 23, 2003, the CTFA/SDA Citizen Petition on the Healthcare Professional Products submitted to Docket 75N -183H on August 6, 2001, and the two ASM posters on effective neutralization[1,2]. The result of this study (Hill Top Research Study Report 03-122055-106) is summarized in Table 1. After wash 1 and wash 11, the test formulation containing 0.115% triclosan effectively reduced the level of baseline bacteria (*S. marcescens* ATCC 14756) on the hands, consistent with the above recommendations. The full study report is included in Appendix 1.

Table 1. Summary of HCPHW Liquid Handwash Formulation (HTR 03-122055-106)

		Baseline Log_{10} Counts	Wash 1 Log_{10} Counts		Wash 11 Log_{10} Counts	
Treatment	Sample Size	Mean	Mean	Change from Baseline	Mean	Change from Baseline
A	16	9.11	7.09	2.02 [a]	7.17	1.92 [a]
B	8	9.12	6.70	2.42	5.27	3.85

[a] one-tailed t-test, p values < 0.0001. Only Treatment A was tested for statistical significance.

Test Product A (83185) Liquid Handwash containing 0.115% triclosan
Test Product B (83248) Hibiclens®, 4% chlorhexidine gluconate

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[1] Fischler G.E., *et al.* 2002. The Effect of Modifications to the ASTM E1174 Health-care Personnel Handwash Method on Evaluation of Antimicrobial Effectiveness. American Society for Microbiology 102nd Annual Meeting, Salt Lake City, Utah. Poster Q219.

[2] Jones, K., Morrison, B.M. 2002. Important Use of Neutralization in Evaluating Antimicrobial Efficacy. American Society for Microbiology 102nd Annual Meeting, Salt Lake City, Utah. Poster Q222.

B. Residual Antibacterial Efficacy – Agar Patch Test Results

Using a standard test method, ASTM E1882-00 (Evaluation of Antimicrobial Formulations by the Agar Patch Technique), multiple Agar Patch studies were conducted on liquid handwash formulations containing various levels of triclosan against both gram positive and gram negative bacteria. The test method used to evaluate the efficacy of these formulations and the performance criteria are based on the recommendations outlined in the CTFA/SDA Healthcare Continuum Model (HCCM) and the CTFA/SDA Proposal for Finished Product Efficacy Testing of Health Care Antiseptic Drug Products, September 29, 1999. Study results demonstrated that all formulations containing triclosan were significantly more effective than their respective placebos in inhibiting the growth of bacteria. Results also demonstrated that a liquid handwash formulation containing at least 0.1% triclosan exhibits efficacy against each strain of bacteria tested (Table 2 a, b, c).

Table 2. Summary of Residual Efficacy

(a) Organism: *S. aureus* (ATCC 6538)

Triclosan level	Log_{10} Reduction [b] (from placebo)
0.1%	1.86
0.115%	1.82
0.15%	1.64

[b] Mean log reductions calculated from multiple studies
(Colgate-Palmolive Co., Data and individual study statistics on file)

(b) Organism: *E. coli* (ATCC 11229)

Triclosan level	Log_{10} Reduction [b] (from placebo)
0.1%	1.31
0.15%	1.23

[b] Mean log reductions calculated from multiple studies
(Colgate-Palmolive Co., Data and individual study statistics on file)

(c) Organism: *K. pneumoniae* (ATCC 10031)

Triclosan level	Log_{10} Reduction [b] (from placebo)
0.1%	1.06
0.125%	1.46
0.175%	1.52
0.20%	1.87

[b] Mean log reductions calculated from multiple studies
(Colgate-Palmolive Co., Data and individual study statistics on file)

II. Antibacterial Efficacy of Triclocarban (TCC) in Liquid and Solid Handwash Formulations:

In accordance with the CTFA/SDA Healthcare Continuum Model, Colgate has conducted the following *in-vivo* testing to support the efficacy of triclocarban in liquid and solid handwash formulations.

A. Health-Care Personnel Handwash (HCPHW) Test Results

The antibacterial activity of TCC was tested using the standard method ASTM 1174-00. Test samples included one solid and one liquid handwash formulation each containing 0.1% TCC. A reference control containing 4% chlorhexidine gluconate (Hibiclens®) was also included. The test method used to evaluate the efficacy of these formulations and the performance criteria are based on the recommendations outlined in the CTFA/SDA Citizen Petition on Consumer and Foodhandler Products submitted to Docket 75N-183H on May 23, 2003, the CTFA/SDA Citizen Petition on Healthcare Professional Products submitted to Docket 75N-183H on August 6, 2001, and the two ASM posters (see footnotes page 3) on effective neutralization. Results of these studies (Hill Top Research Study Reports 03-122070-106 and 03-122071-106) are summarized in Tables 3 and 4. After wash 1 and wash 11, the test formulations containing 0.1% TCC effectively reduced the level of baseline bacteria (*S. marcescens* ATCC 14756) on the hands consistent with the above recommendations. The full study reports are included in Appendices 2 and 3.

Table 3. Summary of HCPHW Solid Handwash Formulation (HTR 03-122070-106)

		Baseline Log_{10} Counts	Wash 1 Log_{10} Counts		Wash 11 Log_{10} Counts	
Treatment	Sample Size	Mean	Mean	Change from Baseline	Mean	Change from Baseline
A	16	9.11	6.69	2.42[a]	6.58	2.53[a]
B	7	9.18	6.55	2.63	5.59	3.59

[a] one-tailed t-test, p values < 0.0001. Only Treatment A was tested for statistical significance.

Test Product A (83085) Solid Handwash containing 0.1% TCC
Test Product B (83245) Hibiclens®, 4% chlorhexidine gluconate

Table 4. Summary of HCPHW Liquid Handwash Formulation (HTR 03-122071-106)

		Baseline Log_{10} Counts	Wash 1 Log_{10} Counts		Wash 11 Log_{10} Counts	
Treatment	Sample Size	Mean	Mean	Change from Baseline	Mean	Change from Baseline
A	16	9.23	7.21	2.02[a]	7.05	2.18[a]
B	8	9.19	6.41	2.78	5.08	4.11

[a] one-tailed t-test, p values < 0.0001. Only Treatment A was tested for statistical significance.

Test Product A (83586) Liquid handwash containing 0.1% TCC
Test Product B (83246) Hibiclens®, 4% chlorhexidine gluconate

B. Residual Antibacterial Efficacy – Modified Cup Scrub Test Results

The residual efficacy of the test formulations were evaluated using a Modified Cup Scrub test (ASTM Test Method E1874-97, Evaluation of Antimicrobial Washes by Cup Scrub Technique). The test method used to evaluate the efficacy of these formulations and the performance criteria are based on the recommendations outlined in the CTFA/SDA Citizen Petition on Consumer and Foodhandler Products submitted to Docket 75N-183H on May 23, 2003.

- ***Summary of Residual Efficacy of Solid Handwash formulations containing TCC***

Modified Cup Scrub testing showed that a solid handwash formulation containing 0.1% solubilized TCC performed significantly better than a placebo formulation in lowering the levels of *S. aureus* on the skin immediately after washing (Table 5).

Table 5: Residual Efficacy of Solid Handwash Formulation Containing 0.1% TCC vs. Placebo

Test Product	Sample Size	Log_{10} Counts Recovered	Log Reduction (from placebo)
Solid Handwash (placebo)	8	5.64	-
Solid Handwash + 0.1% TCC	8	4.18	1.45

(Colgate-Palmolive Co., Data on file, one-tailed t-test, p-value = 0.0007)

An additional study investigated the residual efficacy of several solid handwash formulations containing different levels of TCC, 0.1% - 0.25%. An ANOVA showed that all solid handwash formulations were statistically more effective than the placebo in inhibiting the growth of *S. aureus* on the forearm several hours after washing (Table 6).

Table 6. Residual Efficacy of Solid Handwash Formulations Containing TCC Several Hours After Washing

TCC level	Sample Size	Log_{10} Counts Recovered	Log Reduction (from placebo)
0.1%	12	3.12	0.48
0.15%	12	2.85	0.75
0.25%	12	2.65	0.95
0% (placebo)	12	3.60	-

(Colgate-Palmolive Co., Data on file, ANOVA p-value = 0.0001)

Several studies were conducted to compare the efficacy of solid handwash formulations in which the active ingredient, TCC, was either solubilized or micronized in the formulation. Statistical results using ANOVA showed (Table 7) that the solid handwash formulations containing levels of 0.3% or 0.7% solubilized TCC were parity in efficacy to the solid handwash formulation containing 1.5% of unsolubilized (micronized) TCC in lowering the levels of *S. aureus* on the skin. A further study showed that the solid handwash formulation containing 0.3% solubilized TCC was statistically more effective than the solid handwash formulation containing 0.3% micronized TCC in inhibiting the growth of bacteria (Table 8). These data show that by solubilizing TCC in handwash formulations, products with low levels of TCC meet the proposed performance criteria.

Table 7. Micronized vs. Solubilized TCC in Solid Handwash Formulations

TCC level	Sample Size	Solubilized vs. Micronized	Log_{10} Reduction (from placebo)
0.3%	24	Solublized	2.46
0.7%	24	Solublized	2.63
1.5%	24	Micronized	2.32

(Colgate-Palmolive Co., Data and statistics on file)

Table 8. Micronized vs. Solubilized TCC in Solid Handwash Formulations

TCC level	Sample Size	Solubilized vs. Micronized	Log_{10}Reduction (from placebo)
0.3%	7	Solublized	1.27
0.3%	7	Micronized	0.75

(Colgate-Palmolive Co., Data on file, p-value < 0.05)

- ***Summary of Residual Efficacy of Liquid Handwash formulations with TCC***

Several Modified Cup Scrub tests showed that liquid handwash formulations containing at least 0.1% solubilized TCC performed significantly better than a placebo formulation at lowering the levels of *S. aureus* on the skin immediately after washing. The data from these studies were combined, and an ANOVA was performed to test the significance on the mean log reduction data from the placebo using TCC as the test factor. All tested formulations were statistically equivalent to each other in efficacy (Table 9).

Table 9. Liquid Handwash Formulations Containing TCC vs. Placebo

Organism: *S. aureus* (ATCC 6538)

TCC level	Log Reduction [b] (from placebo)
0.1%	1.79
0.12 %	2.12
0.15%	2.17

[b] Mean log reductions calculated from multiple studies (Colgate-Palmolive Co., Data on file, ANOVA p-value = 0.457)

Conclusions:

- This submission supports the Category I Efficacy of triclosan in consumer handwash, foodhandler handwash, and health-care personnel handwash formulations. This is supported by HCPHW and Agar Patch studies. Also, the data show that triclosan provides residual efficacy in liquid handwash formulations.

- This submission supports the Category I Efficacy of triclocarban (TCC) in consumer handwash, foodhandler handwash, and health-care personnel handwash formulations. This is supported by HCPHW and Modified Cup Scrub studies. Also, the data show that TCC provides residual efficacy in both liquid and solid handwash formulations.

- The data provided in this submission further show that the efficacy of TCC formulations can be enhanced by formula/process modifications, such as solubilization of TCC.

- Colgate supports the performance criteria as proposed by the CTFA/SDA Industry Coalition and considers these criteria appropriate for assessing efficacy in consumer handwash, foodhandler handwash, and health-care personnel handwash formulations.

- Colgate believes the Agency should base the efficacy of topical antimicrobial formulations on their ability to meet set performance criteria for finished formulations to be specified in the Final Monograph. Therefore, it is not necessary for the Agency to adopt lower limits or concentration ranges for active ingredients in the Final Monograph given that the antimicrobial active ingredients may exhibit efficacy at levels lower than what is demonstrated in this Docket.

In closing, Colgate would like to thank the Agency for this opportunity to provide comments and additional data to support the Category I rating and inclusion of triclosan and triclocarban in the Final Monographs for Topical Antimicrobial Drug Products for OTC Human Use.

Respectfully,

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