Bayer

Industrial Chemicals Division

Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205

August 26, 2003

Dockets Management Branch (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.

RE: Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Health-Care Antiseptic Drug Products; Reopening of the Administrative Record -
Supplemental Data Related to Bayer's Citizen Petition Dated December 28, 2002 to Classify Triclocarban Category I for Efficacy
Docket 75N-183H

To Whom It May Concern:

In response to the above referenced reopening of the administrative record for rulemaking (Docket 75N-183H), enclosed are three (3) copies of supplemental product performance (efficacy) data. Subsequent to Bayer's December 28, 2002 Citizen's Petition, both a clinical hand wash study and a time-kill study were conducted to demonstrate the efficacy of a representative liquid soap containing 0.7% Triclocarban, which is the typical concentration of Triclocarban used in personal health care products. The clinical hand wash study employed *Staphylococcus aureus* as the indicator organism due to its frequent association with nosocomial infections.

The enclosed new data further support classification of the use of Triclocarban at 0.7% as a Category I ingredient for use as a health care personnel hand wash or an antiseptic hand wash. Specifically, the health care personnel hand wash test (ASTM E1174) demonstrated that a 0.7% Triclocarban containing product achieved a 2.82 $\log_{10}$ reduction following a single wash and a 3.09 $\log_{10}$ reduction following 10 subsequent washes. This compares to 1.84 and 1.99 $\log_{10}$ reductions for the placebo product, and 2.25 and 2.38 $\log_{10}$ reductions for a 4% chlorhexidine gluconate product. These data demonstrate the superiority of a Triclocarban containing hand wash product at clearing a Gram positive microorganism, *S. aureus*, from the hands.

The enclosed time kill study emphasizes determination of product performance against gram positive microorganisms and provides both confirmatory data and data on gram positive microorganisms not previously tested.

These studies were conducted with the following test articles:

3554-196 (TCC - 0.7%)
Active Ingredient: Triclocarban
Other Ingredients: Dipropylene Glycol, Water, Sodium Laureth Sulfate, Glycerin, Cocamidopropyl Betaine, Disodium Lauryl Sulfosuccinate, PEG-8, Ethoxydiglycol, Polyquaternium 10, Fragrance, Sodium Chloride, Citric Acid, DMDM Hydantoin & Iodopropynyl Butylcarbamate, Tetrasodium EDTA.

3554-194 (Placebo)
Active Ingredient: not applicable
Ingredients: Dipropylene Glycol, Water, Sodium Laureth Sulfate, Glycerin, Cocamidopropyl Betaine, Disodium Lauryl Sulfosuccinate, PEG-8, Ethoxydiglycol, Polyquaternium 10, Fragrance, Sodium Chloride, Citric Acid, DMDM Hydantoin & Iodopropynyl Butylcarbamate, Tetrasodium EDTA.

This submission consists of this letter and three (3) volumes:

- Volume 1 - Book I of "Efficacy Evaluation of Health Care Personnel Handwash Products," HTR Study No. 03-122085-106, Final Report dated August 21, 2003, by Hill Top Research, Inc. for Bayer Chemicals Corporation
- Volume 2 - Book II of "Efficacy Evaluation of Health Care Personnel Handwash Products, HTR Study No. 03-122085-106, Final Report dated August 21, 2003, by Hill Top Research, Inc. for Bayer Chemicals Corporation
- Volume 3 - "Assessment of Rapid Germicidal (Time Kill) Activity for Hand Product", HTP Study No. 03-122096-106, Final Report dated August 14, 2003, by Hill Top Research, Inc. for Bayer Chemicals Corporation

If you have any questions regarding this submission, please feel free to contact me by phone at (412) 777-3934 or by email at kevin.ajoku@bayerchemicals.com.

Sincerely,

JMelley for Kevin Ajoku

Kevin I. Ajoku
Market Segment Manager
Bayer Corporation

HILL TOP RESEARCH, INC.

VOLUME 1

REPORT FOR

EFFICACY EVALUATION OF HEALTH CARE PERSONNEL HANDWASH PRODUCTS

HTR STUDY NO. 03-122085-106

Final Report

August 21, 2003

FOR
BAYER CHEMICALS CORPORATION
100 Bayer Road, Building #14
Pittsburgh, PA 15205-9741

BY
HILL TOP RESEARCH, INC.
Main and Mill Sts.
Miamiville, OH 45147

BOOK I

1.0 SUMMARY

- The purpose of this study is to determine the ability of the test antimicrobial formulation to give reduction of transient microbial flora, *Staphylococcus aureus* ATCC 6538, when used in a hand washing procedure after a single treatment and after eleven treatments. *S. aureus* is not specified in the FDA Monograph as a test organism. Therefore, to properly control the study, a FDA approved positive control formulation, Hibiclens®, was tested against a Monograph prescribed standard test organism, *Serratia marcescens* ATCC 14756, as well as the *S. aureus* strain.

  Ninety subjects completed the study.

- The test articles evaluated in this study were identified as 3554-194 (HTR Code A), 3554-196 (HTR Code B) and Hibiclens®, Lot 4652F, Exp.: 01/2004 (HTR Code C).

- Test article 3554-194 HTR Code A achieved a 1.8422 $\log_{10}$ reduction of the marker organism *S. aureus A*TCC 6538 following a single 30-second handwashing procedure and 1.9873 $\log_{10}$ reduction after the eleventh wash in a series of eleven washes.

  Test article 3554-196 HTR Code B achieved a 2.2829 $\log_{10}$ reduction of the marker organism *S. aureus A*TCC 6538 following a single 30-second handwashing procedure and 3.0942 $\log_{10}$ reduction after the eleventh wash in a series of eleven washes.

  Test article Hibiclens®, Lot 4652F HTR Code C achieved a 2.2535 $\log_{10}$ reduction of the marker organism *S. aureus A*TCC 6538 following a single 15-second handwashing procedure and a 2.3844 $\log_{10}$ reduction after the eleventh wash in a series of eleven washes.

  Test article Hibiclens®, Lot 4652F HTR Code C achieved a 2.6808 $\log_{10}$ reduction of the marker organism *S. marcescens* ATCC 14756 following a single 15-second handwashing procedure and a 3.7287 $\log_{10}$ reduction after the eleventh wash in a series of eleven washes.

2.0 TABLE OF CONTENTS

3.0 SPONSOR PERSONNEL

Kevin Ike Ajoku
Bayer Chemical Corporation

4.0 INVESTIGATIVE PERSONNEL

Investigator:	E. Linn Jones, M.D., D.A.B.D.
Sub-Investigator:	Gayle K. Mulberry, B.S.
Sub-Investigator:	Ann R. Brady, B.A.G.S.
Biostatistician:	James P. Bowman, M.S.
Manager Biostatistics:	Barbara M. Fath

5.0 CLINICAL RESEARCH STANDARDS

The clinical investigation, including the informed consent, was reviewed by an Institutional Review Board in accordance with Title 21 of the Code of Federal Regulations, Parts 50 and 56. Approval by the Board was obtained on July 14, 2003, prior to initiation of the investigation (see Appendix I).

This study was conducted according to applicable Good Clinical Practices and the Standard Operating Procedures of Hill Top Research, Inc.

6.0 PROTOCOL

The study protocol was followed (see Appendix II) with the exception of the following deviation.

- The neutralization study was performed on August 4, 2003. The protocol stated that the neutralization study would be performed prior to the initation of the study on July 23, 2003.

In the opinion of the Investigator, the deviation did not compromise the integrity of the study.

The media, dilution fluid and other items used in the study but not defined in the protocol are shown in Appendix III, "Miscellaneous Procedural Information."

7.0 SUBJECTS

One hundred and seventy-four (174) subjects were enrolled in the pre-test conditioning phase. Ninety (90) subjects, twenty-five (25) males and sixty-five (65) females who met the study criteria were enrolled in the test phase and completed the study.

Eighty-four (84) subjects were excluded or withdrew from the study. The subject's screening number and reason each subject was excluded or withdrew are shown in Appendix IV.

8.0 STUDY SCHEDULE

Screening/Conditioning Dates:	July 15, 2003
Date Initiated:	July 23, 2003
Date Completed:	August 4, 2003

9.0 TEST ARTICLES

The test articles, HTR Code A and HTR Code B, were received by Hill Top Research, Inc. on July 9, 2003, for use in this study. Test article, HTR Code C, was purchased by Hill Top Research, Inc. on March 6, 2003.

HTR Code	Sponsor Code	Description	No. of Units
A	3354-194	Clear plastic bottle with white plastic pump nozzle containing clear colorless liquid and a 1 ½ gallon jug	7
B	3354-196	Clear plastic bottle with white plastic pump nozzle containing clear colorless liquid and a 1 ½ gallon jug	7
C	Hibiclens®, Lot 4652F, Exp.: 01/2004	Aqua plastic bottle with white cap, containing liquid	2

9.0 TEST ARTICLES (CONT.)

The test articles, HTR Code A and HTR Code B will be destroyed thirty days after the final report is issued.

Randomization of the assignment of test articles for subject treatment is shown in Appendix V.

10.0 ADVERSE EVENTS

There were thirty-four adverse events reported during the course of the study. Details of the Adverse Events are documented in the Adverse Event Reports found in Appendix VI. None of the Adverse Events are classified as related to the test articles.

11.0 TEST FOR ADEQUACY OF NEUTRALIZER

A report on testing performed to demonstrate the effectiveness of the antimicrobial neutralizers used in this study is shown in Appendix VII.

12.0 METHOD OF STATISTICAL ANALYSIS

The data were statistically analyzed using analysis of variance methods. The statistical methods are described below.

Bacterial counts recovered from the hands were transformed into $\log_{10}$ counts. The data used in the statistical analysis were the averages of each subject's right and left-hand $\log_{10}$ counts. The changes from baseline counts at each sampling interval were obtained for each test article.

Analysis of variance techniques were used to evaluate the effectiveness of each treatment as a function of the number of treatments (within treatment analysis using $\log_{10}$ reductions) and to compare the baseline counts of different treatment groups (*S. aureus* only).

Hypothesis testing was performed at the α=0.05 level.

13.0 RESULTS OF STATISTICAL ANALYSIS

13.1 Baseline Bacterial Log Count Comparison

The source data for the baseline analysis were the average $\log_{10}$ values for the right and left hands of each subject. Potential differences between the treatment groups at baseline were examined using a one-factor analysis of variance procedure.

Mean Log_{10} Baseline Counts

HTR Code A	HTR Code B	HTR Code C	ANOVA p-value
9.1312	9.1551	9.1803	0.3742[1]

[1] **No significant difference among groups at baseline**

13.2 Comparison of the Effectiveness of the Test Article as a Function of Time

The data ($\log_{10}$ differences from baseline) were evaluated by analysis of variance techniques to determine the existence, if any, of significant differences among the $\log_{10}$ counts at Washes 1 and 11. The $\log_{10}$ average differences from baseline and the p-values from the ANOVA are shown below.

HTR Code	n	Wash 1	Wash 11	ANOVA p-value
		S. aureus		
A	30	1.8422	1.9873	**0.0005**[2]
B	30	2.2829	3.0942	**<0.0001**[2]
C	15	2.2535	2.3844	0.0524
		S. marcescens		
C	15	2.6808	3.7287	**<0.0001**[2]

[2] Significant difference in antimicrobial activity across washes. Conclusion: significantly better activity after Wash 11.

13.0 RESULTS OF STATISTICAL ANALYSIS (CONT.)

13.3 Log Reduction and Percent Reduction of Bacterial Counts

The log reductions and percent reductions of bacterial counts and associated confidence limits are presented below.

HTR Code	Log_{10} Reduction	95% Confidence Interval		Percent Reduction	95% Confidence Interval	
		Lower	Upper		Lower	Upper
S auerus						
Wash 1						
A	1.8422	1.7395	1.9450	98.56%	98.18%	98.86%
B	2.2829	2.1637	2.4020	99.48%	99.31%	99.60%
C	2.2535	2.0945	2.4126	99.44%	99.20%	99.61%
Wash 11						
A	1.9873	1.8800	2.0947	98.97%	98.68%	99.20%
B	3.0942	2.9365	3.2520	99.92%	99.88%	99.94%
C	2.3844	2.2040	2.5647	99.59%	99.37%	99.73%
S marcescens						
Wash 1						
C	2.6808	2.4979	2.8638	99.79%	99.68%	99.86%
Wash 11						
C	3.7287	3.4568	4.0007	99.98%	99.97%	99.99%

The Statistical Tables of Results are shown in Appendix VIII.

14.0 SUBJECTS COMPLETED DATA COLLECTION FORMS

Copies of the completed Data Collection Forms (DCF) for each subject participating in the study are shown as follows:

Appendix IX-A – DCFs for Subjects completing the study
Appendix IX-B – DCFs for Subjects excluded from the study

15.0 CONCLUSION

The test articles evaluated in this study were identified as 3554-194 (HTR Code A), 3554-196 (HTR Code B) and Hibiclens®, Lot 4652F, Exp.: 01/2004 (HTR Code C).

The $\log_{10}$ reductions achieved by each test article are shown in the following table.

HTR Code	n	Wash 1	Wash 11
S. aureus			
A	30	1.8422	1.9873
B	30	2.2829	3.0942
C	15	2.2535	2.3844
S. marcescens			
C	15	2.6808	3.7287

Test articles HTR Code A and B demonstrated significantly greater antimicrobial activity against *S. aureus* ATCC 6538 after Wash 11 than after the first wash. When tested against *S. marcescens* ATCC 14756, test article HTR Code C demonstrated significantly greater activity after Wash 11 than after the first wash.

16.0 SIGNATURE

HILL TOP RESEARCH, INC.

E. Linn Jones M.D. 8-21-2003

E. Linn Jones, M.D., D.A.B.D. Date
Investigator

HILL TOP RESEARCH, INC.

Ann R. Brady August 21, 2003

Ann R. Brady, B.A.G.S. Date
Sub-Investigator

17.0 QUALITY ASSURANCE STATEMENT

To assure compliance with the study protocol and standard operating procedures (SOPs) of Hill Top Research, Inc., the Quality Assurance Unit performed an in-phase audit during the conduct of the study on July 23, 2003, completed an audit of the study records on August 14, 2003 completed an audit of the draft report on August 15, 2003, and audited the final report on August 21, 2003.

Any observations found during the course of the audit were reported to (as pplicable) the Site Director, Study Director, Principal Investigator, Study Manager, Study Coordinator, Report Writer, and/or HTR Management.

Report reviewed by:

Nina Sullivan

Nina Sullivan, B.A.
Auditor, Quality Assurance

8/21/03
Date