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September 7, 2001

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Documents Management Branch (HFA-306)
Food and Drug Administration, Room 1-23
12420 Parklawn Dr.
Rockville, MD 20857

Subject: Docket 75N-183H
Topical Antimicrobial Drug Products for Over-The-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products
59 Federal Register 31402-31452; June 17, 1994

Dear Madam/Sir:

Enclosed please find three sets of the appendices that correspond to the clinical studies submitted by ConvaTec on July 8, 1996. The current submission is in response to a request received from Dr. Walter Ellenberg on September 4, 2001. The letter from the original submission has also been included for reference.

The following outlines the enclosed appendices:

Report for an Evaluation of Alcare and an Iodine Scrub for Antimicrobial Effectiveness and Substantivity in the Surgical Scrub using Normal Skin Flora
Report 95-5307-11 – Appendix I through Appendix XI

An Evaluation of Two Alcohol No-Rinse Handwash Products and a Rinsable Iodine Handwash Product Under Two Different Regiments of Artificial Contamination using *Serratia marcescens* to Determine Antimicrobial Efficacy in the Healthcare Personnel Handwash
Report 951202 – Appendix I through Appendix XII

An Evaluation of a 1% Triclosan Handwash Product and its Placebo for Efficacy in a Healthcare Personnel Handwash using *Serratia marcescens*
Report 951203.01 – Appendix I through Appendix XI

If you have any specific questions regarding this submission, please contact Mike Ebers at (314)535-1390.

Best regards,

Kimberly Adams

Kimberly Adams
STERIS Corporation
Regulatory Affairs

RPT 5

75N-183H

ConvaTec
P. O. Box 147 St. Louis, MO 63166-0147 314-535-1810

July 8, 1996

Ms. Debbie Lumpkins
Office of Over-the-Counter Drug Evaluation (HFA-810)
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place Room 201
Rockville, Maryland 20855

Attention: Documents Management Branch (HFA-306)
Food and Drug Administration, Rm. 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Subject: Docket 75N-183H.
Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products.
59 Federal Register 31402-31452; June 17, 1994

Dear Ms. Lumpkins:

The enclosed submission provides supportive clinical data to ConvaTec comments previously submitted to the docket for the Tentative Final Monograph (TFM) for Over-the-Counter Topical Antimicrobial Drug Products (June 17, 1994). ConvaTec submitted comments to the FDA on June 15, 1995 and February 14, 1996. In our February 14, 1996 data submission protocols for the attached clinical studies were submitted for your review. This submission includes the final reports and for the identified studies listed below.

1. Surgical Scrub Study:

"Report For Evaluation of Alcare® And An Iodine Scrub For Antimicrobial Effectiveness And Substantivity In The Surgical Scrub Using Normal Skin Flora"

2. Health Care Personnel Handwash Study:

"An Evaluation Of Two Alcohol No-Rinse Handwash Products And A Rinsable Iodine Handwash Product Under Two Different Regiments Of Artificial Contamination Using *Serratia Marcescens* To Determine Antimicrobial Efficacy In The Health Care Personnel Handwash"

3. Health Care Personnel Handwash Study:

"An Evaluation Of A 1% Triclosan Handwash Product And Its Placebo For Efficacy In a Health Care Personnel Handwash Using *Serratia Marcescens*"

A final clinical study report for a surgical pre-operative skin preparation study will be filed under separate cover when the final report is received from our contract laboratory.

The results of the three completed clinical studies and the preliminary report for the surgical pre-operative skin preparation study are summarized in the attached tables (Tables 1-4). In addition to the study results, the tables include FDA's proposed pass/fail criteria, ConvaTec's June 1995 proposal and our current proposal for log reduction pass/fail criteria in each study category. The current ConvaTec proposals are based on the results obtained in the attached clinical studies. Based on the effectiveness and well established use history of these products, ConvaTec believes the currently proposed pass/fail criteria provide a reasonable and effective criteria for establishing antimicrobial activity of products in each of the referenced categories in the TFM.

The results of the submitted clinical studies support the following comments previously made by ConvaTec.

1. Isopropyl alcohol formulated at levels of 60-90% (v/v) as a Health Care Personnel Handwash is recommended for Category I as safe and effective.

2. Isopropyl alcohol formulated at levels between 60-70% (v/v) as a Surgical Pre-Operative Skin Preparation is recommended for inclusion into Category I as safe and effective.

3. Triclosan formulated at levels up to 1% (w/w) as a Health Care Personnel Handwash is recommended for Category I as safe and effective.

4. The pass/fail criteria currently published in the TFM for Health Care Antiseptic Drug Products is recommeded to be modified in consideration of ConvaTec's clinical test results. ConvaTec's proposed pass/fail recommendations are presented in the attached tables.

5. The statistical criteria currently published in the TFM for Health Care Antiseptic Drug Products is recommended to be modified to allow for alternative methods to establish a statistical basis for adequate subject numbers used in each study.

In addition to the comments impacted by the submitted clinical studies, ConvaTec strongly supports previously submitted comments to the docket as summarized below.

1. The clinical and *in vitro* methods used to establish the antimicrobial effectiveness of Health Care Antiseptic Drug Products must contain a neutralization validation procedure adequate to ensure the complete neutralization of the active ingredient in the subject tested products. In addition, it is imparative the data indicate neutralization is complete within the identified timing specified in the methodology for each product category.

2. As proposed in Convatec's June 15, 1995 comments, a reduction of the number of organisms for *in vitro* testing of a finished product to establish broad spectrum and fast acting activity.

3. *In vitro* testing of organisms in addition to the recommended list of organisms listed in the TFM may be allowed without consideration of an NDA submission for products that otherwise meet the requirements of the TFM.

4. The elimination of requirements for MIC *in vitro* testing of finished products.

5. The elimination of time kill testing requirements for active ingredients.

6. The modification of test sampling times for time kill studies based on proposed indications for the subject product.

ConvaTec would appreciate the inclusion of these items in the FDA's proposed industry workshop tentatively scheduled for the Fall of 1996. If you have specific questions related to the content of this submission, please contact me at 314-535-1390.

Sincerely,

Mike Ebers
Manager, Regulatory Affairs

REPORT FOR
AN EVALUATION OF ALCARE® AND AN IODINE SCRUB FOR ANTIMICROBIAL EFFECTIVENESS AND SUBSTANTIVITY IN THE SURGICAL SCRUB USING NORMAL SKIN FLORA
REF.: 95-5307-11

FOR

STL/95-1005.0

CONVATEC
P.O. BOX 147
ST. LOUIS, MO 63166

BY

HILL TOP BIOLABS, INC.
MAIN AND MILL STS.
MIAMIVILLE, OHIO 45147

SET 1 OF 3

1.0 SUMMARY

- The primary objective was to determine whether the Alcare® foamed formulation could achieve the log reductions identified in the tentative OTC Monograph (June, 1994) for a surgical scrub for immediate, persistent, and residual antimicrobial effects following single and multiple scrubs.

  The secondary objective was to determine whether the iodine scrub could achieve the log reductions identified in the tentative OTC monograph (June, 1994) for a surgical scrub for immediate, persistent, and residual antimicrobial effected following single and multiple scrubs.

  Both of the test articles, ALCARE® Lot 980 210F and the iodine scrub, Betadine® Surgical Scrub Lot 7VL, met the Monograph requirements for immediate, (0 hours) antimicrobial effect, greater than a 1 $\log_{10}$ reduction achieved immediately following a single scrub.

  Both of the test articles met the criteria for persistent activity, the bacteria counts of the hands did not exceed baseline within 6 hours following the first scrub.

  Neither of the test articles met the criteria required for residual antimicrobial effect, greater than or equal to a 2 $\log_{10}$ reduction of the hand immediately (0 hour) following the first wash on Day 2 or the required 3 $\log_{10}$ reduction immediately (0 hour) following the test scrub on Day 5.

- Thirty-four (34) subjects completed the study.

- Two subjects experienced adverse events during the course of the study, which in the Investigator's opinion were not related to the test articles.

2.0 SPONSOR STUDY MONITOR

Rita A. Brenden, Ph.D.
Manager, Clinical Research

This study was monitored by Rita Brenden and Irene Dorner on November 13 and 14, 1995.

3.0 INVESTIGATIVE PERSONNEL

Investigator:	Gayle K. Mulberry, M.S.
Project Supervisor:	Ann R. Brady, A.S.

4.0 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 October 19, 1995, prior to initiation of the investigation (See Appendix I).

5.0 PROTOCOL

The study protocol was followed (See Appendix II).

6.0 SUBJECTS

Sixty-nine (69) were enrolled in the pre-test conditioning phase of the study and thirty-four (34) subjects completed.

Thirty-five (35) subjects were excluded or dropped from the study. (See Appendix III)

A demographic profile of the subjects is presented in a table entitled, "Demographic Profile of Subjects."

7.0 TESTING SCHEDULE

Screening or Conditioning Date:	October 20, 1995
Date Initiated:	November 3, 1995
Date Completed:	November 20, 1995

8.0 TEST ARTICLES

The following articles were received on November 7, 1995 from ConvaTec, Inc. for evaluation in the study.

HTB Code	Sponsor Code	Description
A	ALCARE® Lot 980210F	72 white cans w/white plastic push button caps. The cans were labeled A-1 through A-72.
B	Betadine Surgical Scrub Lot 7VL Exp. 2/98	12 clear plastic bottles containing dark liquid. The bottles were labeled B-1 through B-72.

Randomization of the assignment of test articles for subject treatment can be found in Appendix IV.

The test articles, used or unused, were returned to the Sponsor on December 12, 1995. Copies of the Sample Record Sheets are shown in Appendix V.

9.0 DEVIATIONS

See Appendix VI.

10.0 ADVERSE EVENTS

There were three adverse events reported during the course of the study.

Subject No. 032 was observed as having two (2) pustules surrounded by moderate erythema on the right forearm on November 14, 1995. Both areas of erythema equaled 1 cm each.

10.0 ADVERSE EVENTS (CONT.)

Subject thought they were bug bites and denied itching or burning. Subject was checked on November 15, 17 and December 1, 1995. No new pustules and erythema was decreased. Subject indicated the skin cleared by November 20, 1995. This subject completed the study.

Subject #11 withdrew from the study after a scheduled visit on November 16, 1995. Several hours after leaving the laboratory on November 16, 1995, the subject experienced pain in his chest and arms and immediately went to the hospital. Quadruple by-pass surgery was performed on November 17, 1995.

The right hand of Subject #19 became irritated after being gloved for approximately 6 hours on November 13, 1995. Subject completed the study.

In the Investigator's opinion, neither of these events were related to the test article. Copies of the Adverse Event Forms completed for these subjects are shown in Appendix VII.

11.0 PROCEDURAL INFORMATION

Appendix VIII-A, Miscellaneous Procedural Information, list media, reagents and materials used to recover organisms used in this study.

The source of media ingredients, is shown in Appendix VIII-B, Media Preparation Record Sheets.

Copies of Project Equipment Records, which identify the source of other study related commodities, are shown in Appendix VIII-C.

12.0 TEST FOR ADEQUACY OF NEUTRALIZER

Prior to initiation of the study, the adequacy of the neutralizer system used was demonstrated (see Appendix IX). The neutralizer validated consisted of: Azolectin, polysorbate 80, and sodium thiosulfate in purified water. This was incorporated into the dilution blanks and the solid agar.

13.0 RESULTS

Copies of completed Protocol Appendices, 3, 4, 5a, 5b, 6, 7a, 7b, 8, and 10 are attached in the following Report Appendices: Appendix X-A contains forms for subjects entered into the treatment phase of the study.

Appendix X-B contains those applicable forms for subjects who withdrew, dropped or were not entered into treatment phase of the study.

The statistical analysis of the hand wash microbiological data and a summary of the results comparing the test and the control formulations are presented in Appendix XI.

14.0 DATA RETENTION

The raw data and the original of the final report will be on file at the testing facility for a period of five years. After two years, the paper study file will be shipped to the Sponsor. Permanent records will be filed at Hill Top in the form of microfilm.

15.0 CONCLUSIONS

Thirty-four (34) subjects completed this evaluation of two surgical scrub articles, ALCARE® and Betadine® Surgical Scrub.

15.0 CONCLUSIONS (CONT.)

Both of the test articles met the June 17, 1994, FDA Proposed Monograph requirements for immediate antimicrobial effect, greater than 1 $\log_{10}$ reduction achieved immediately following a single scrub. ALCARE® provided a 1.8349 ± 0.5956 $\log_{10}$ reduction and Betadine® Surgical Scrub a 1.1858 ± 0.2607 $\log_{10}$ reduction.

Also, the test articles met the criteria for persistent activity, the bacteria counts of the hands did not exceed baseline within 6 hours of the first scrub counts.

Hands sampled 6 hours after scrubbing with ALCARE® yielded bacteria counts of 0.3275 $\log_{10}$ below the baseline counts while those scrubbed with Betadine® Surgical Scrub Solution were 0.1500 $\log_{10}$ below baseline.

Both articles, following repetitive usages, continued to suppress the 6 hour post usage counts below baseline. After completing eleven scrubs, it was found that ALCARE® suppressed the flora over a 6 hour period post scrub significantly more than Betadine®. Reduction of 1.1881 $\log_{10}$ for ALCARE® vs. 0.6393 $\log_{10}$ reduction for Betadine®.

Neither of the test articles met the criteria required for residual antimicrobial effect, greater than or equal to a 2 $\log_{10}$ reduction of the hand population immediately (0 hour) following the first scrub on Day 2, nor did either of the test articles meet the immediate reduction required following the eleventh and final wash scheduled on Day 5, greater than or equal to a 3 $\log_{10}$ reduction.

15.0 CONCLUSIONS (CONT.)

The log_{10} reduction from baseline, obtained immediately following the first scrub on Day 2 and immediately following the eleventh scrub on Day 5, were as follows:

Product	Day 2	Day 5
ALCARE®	1.9772 ± 0.5088	2.0050 ± 0.5925
Betadine®	1.8913 ± 0.2635	2.0440 ± 0.4423

In summary, there were no statistically significant differences in the log_{10} reductions from baseline achieved by ALCARE® and Betadine® at 0, 3 or 6 hours on Day 1 or 0 and 6 hours on Day 2 or 0 hour on Day 5.

On Day 2 at the 3 hour sampling interval and Day 5 at the 3 hour and 6 hour sampling interval ALCARE® showed statistically significantly greater reduction from baseline than Betadine® Surgical Scrub Solution.

16.0 SIGNATURES

HILL TOP BIOLABS, INC.

Ann R. Brady 3.26.96

Ann R. Brady, A.S. — Date
Project Supervisor

Gayle K. Mulberry 3-26-96

Gayle K. Mulberry, M.S. — Date
Investigator

17.0 QUALITY ASSURANCE STATEMENT

This study was inspected in accordance with the Standard Operating Procedures of the Hill Top Companies. To assure compliance with the study protocol, the Quality Assurance Unit performed an inspection during the conduct of this study and completed an audit of the study records and final report.

Report Reviewed by:

Terrence L Boos 3/26/96

Terrence Boos, B.S. — Date
Auditor, Quality Assurance

HTB REF.: 95-5307-11
STL/95-1005.0
CONVATEC

TABLE

DEMOGRAPHIC PROFILE OF SUBJECTS

Subj. Test No.	Subj. Baseline No.	Age	Sex		Race		Status
			Male	Female	Caucasian	Black	
1	1020	66		x	x		C
2	1006	65		x	x		C
3	1024	53		x	x		C
4	1017	57		x	x		C
5	1025	52		x	x		C
6	1046	55	x		x		C
7	1018	54	x		x		C
8		# not used					
9	1039	25		x	x		C
10	1012	43		x	x		C
11	1048	61	x		x		D
12	1001	61		x	x		C
13	1015	65		x		x	C
14	1003	65		x	x		C
15	1041	66		x	x		C
16	1067	24		x	x		C
17	1031	37	x		x		C
18	1033	66		x	x		C
19	1023	52		x	x		C
20	1002	67		x	x		C

C = Completed
D = Dropped

TABLE (CONT.)

DEMOGRAPHIC PROFILE OF SUBJECTS

Subj. Test No.	Subj. Baseline No.	Age	Sex		Race		Status
			Male	Female	Caucasian	Black	
21	1016	65	x			x	C
22	1005	58		x	x		C
23	1056	44		x	x		C
24	1054	37	x			x	C
25	1042	42		x	x		C
26		# not used					
27	1032	38		x	x		C
28	1007	36	x		x		C
29		# not used					
30	1030	53	x		x		C
31		# not used					
32	1028	36		x	x		C
33		# not used					
34	1055	55	x		x		C
35		# not used					
36	1036	51	x		x		C
37	1009	30		x	x		C
38	1008	28	x		x		C
39	1011	30		x	x		C
40	1045	39		x		x	C
41		# not used					
42	1038	48		x	x		C

C = Completed
D = Dropped

TABLE (CONT.)

DEMOGRAPHIC PROFILE OF SUBJECTS

Subj. Test No.	Subj. Baseline No.	Age	Sex		Race		Status
			Male	Female	Caucasian	Black	
NA	1004	No paper work - Subject was on another study					D
NA	1010	59		x	x		D
NA	1013	52		x	x		D
NA	1014	53		x	x		D
NA	1019	43		x	x		D
NA	1021	39		x	x		D
NA	1022	39		x	x		D
NA	1026	24		x	x		D
NA	1027	34		x	x		D
NA	1029	56	x		x		D
NA	1034	28		x	x		D
NA	1035	24	x		x		D
NA	1037	39		x	x		D
NA	1040	50		x	x		D
NA	1043	35		x	x		D
NA	1044	42		x	x		D
NA	1047	60		x	x		D
NA	1049	38		x	x		D
NA	1050	38		x	x		D
NA	1051	40		x	x		D
NA	1052	25		x	x		D

C = Completed
D = Dropped

TABLE (CONT.)

DEMOGRAPHIC PROFILE OF SUBJECTS

Subj. Test No.	Subj. Baseline No.	Age	Sex		Race		Status
			Male	Female	Caucasian	Black	
NA	1053	34		x	x		D
NA	1057	18		x	x		D
NA	1058	54		x	x		D
NA	1059	34		x	x		D
NA	1060	18	x			x	D
NA	1061	54		x	x		D
NA	1062	65		x	x		D
NA	1063	26		x	x		D
NA	1064	55		x	x		D
NA	1065	35		x	x		D
NA	1066	27		x	x		D
NA	1068	21		x	x		D
NA	1069	21		x	x		D

C = Completed
D = Dropped