CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-832

STATISTICAL REVIEW(S)

JUL 5 2000

STATISTICAL REVIEW AND EVALUATION

NDA: 20-832
DRUG: ChloraPrep™ One-Step Antiseptic (2% Chlorhexidine Gluconate/ 70% Isopropyl Alcohol)
SPONSOR: Medi-Flex Hospital Products, Inc.
INDICATIONS: Patient Preoperative Skin Preparation

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***Review's Note**: Throughout the review, the following terms are abbreviated and referred to as: CFU = Colony Forming Units, CHG = 2% chlorhexidine gluconate, IPA = 70% isopropyl alcohol, Study HTR = Hill Top Research Study, No. 99-103691-11, Study MBT = MicroBioTest, Inc. Project, No. 371-104, TFM = Tentative Final Monograph. Reviewer comments are given in italics throughout the review.*

I. OVERVIEW

This NDA was originally submitted in 1997 and was made not approvable in February, 1998 for a variety of reasons, principally in the areas of microbiology and clinical studies. Please refer the not approvable letter for detailed deficiencies. Subsequently, the Sponsor designed a new clinical program to establish the effectiveness of the product as patient preoperative skin preparation, which is one of the standard uses for topical antiseptics. This resubmission included two pivotal phase III clinical studies to evaluate the immediate and persistent efficacy of the test article ChloraPrep for use as a patient preoperative skin preparation when compared with an active control article CHG and a reference article IPA, which are the active ingredients of ChloraPrep.

These two pivotal studies were single-center, randomized, paired-comparison trials in normal volunteers. ChloraPrep was compared to CHG and IPA, using methodology based upon TFM for evaluating patient pre-operative skin preparations. Test subjects were required to have sufficient numbers of resident bacterial flora to permit evaluation of TFM standards for microbial reduction. The so called "study criteria for inclusion" required subjects to have baseline counts for right and/or left abdomen site to be ≥ 2.2 $\log_{10}$ CFU/cm^2 of skin, and for right and/or left groin site to be ≥ 4.0 $\log_{10}$ CFU/cm^2 of skin.

According to TFM for Health-Care Antiseptic Drug Products published in the Federal Register on June 17, 1994, the drug product for patient preoperative skin preparation must meet the following criteria:

1. A 2.0 $\log_{10}$ reduction in CFU/cm^2 of skin on abdomen site within 10 minutes after product use.

2. A 3.0 $\log_{10}$ reduction in CFU/cm^2 of skin on groin site within 10 minutes after product use.

3. The CFU cell count of skin from both abdomen and groin sites must do not exceed the baseline within 6 hours after product use.

There is no TFM standard for bacterial counts at 24 hours after drug application.

Reviewer's Note: *Statistical review focuses on these two pivotal studies which formed the basis of this application. Statistical evaluation was conducted for data collected from abdomen and groin sites.*

The baseline $\log_{10}$ in CFU/cm^2 from the test day among the articles was compared using ANOVA.

Within-treatment analysis for $\log_{10}$ reductions from the test day baseline to the 10-minute, 6-hour, and 24-hour post-treatment samplings was conducted by paired t-test.

Between-treatment analysis for differences in $\log_{10}$ reductions among articles at 10 minute, 6 hours, and 24 hours was performed by ANCOVA with the test day baseline $\log_{10}$ in CFU/cm^2 as the covariate. The factors' mean square adjusted for the covariate was given by Type III mean square.

Least-squares mean $\log_{10}$ reductions between articles at three time points were compared likewise by t-test, where Bonferroni's adjustment was applied for the multiple comparison (two pairs of comparison), thus, the hypothesis testing was conducted at the level of significance 0.025.

II. RESULTS

II.A. STUDY HTR

One hundred six subjects, who had baseline counts (on the day treatment was applied) that met the "study criteria for inclusion" at abdomen and groin sites, completed the study.

Reviewer's Note: *The mean log_{10} reductions from baseline in CFU/cm^2 of skin achieved at abdomen and groin sites are tabulated in Tables 1 and 2, respectively. For all three articles at abdomen and groin sites, the mean log_{10} reductions achieved at the 10-minute sampling exceeded 2 log_{10} criteria for abdomen site and 3 log_{10} criteria for groin site, and populations remained below baseline at both the 6-hour and 24-hour post treatment samplings, with one exception that CHG did not achieve a 3 log_{10} reduction at groin site at 10 minutes. Based on the results of the within-treatment t-test, it was concluded that all three articles significantly decreased bacterial counts from the test day baseline at three time points.*

TABLE 1: STUDY HTR: MEAN LOG_{10} REDUCTION FROM BASELINE IN CFU/CM^2 AT ABDOMEN SITE

Article	Mean Log_{10} Reduction From Baseline		
	10 Minutes	6 Hours	24 Hours
ChloraPrep (N=42) Mean ± SD P-value	2.5196 ± 0.80 0.0001	2.3693 ± 0.84 0.0001	2.6935 ± 0.72 0.0001
CHG (N=43) Mean ± SD P-value	2.3017 ± 0.92 0.0001	2.3993 ± 0.63 0.0001	2.1188 ± 1.11 0.0001
IPA (N=42) Mean ± SD P-value	2.5378 ± 0.66 0.0001	2.2338 ± 1.04 0.0001	1.7911 ± 1.59 0.0001

P-value from paired t-test for log_{10} reduction from the test day baseline to post-treatment sampling

TABLE 2: STUDY HTR: MEAN LOG_{10} REDUCTION FROM BASELINE IN CFU/CM^2 AT GROIN SITE

Article	Mean Log_{10} Reduction From Baseline		
	10 Minutes	6 Hours	24 Hours
ChloraPrep (N=26) Mean ± SD	3.5381 ± 1.10 0.0001	3.7390 ± 1.28 0.0001	3.8166 ± 1.22 0.0001
CHG (N=20) Mean ± SD	2.7314 ± 1.18 0.0001	3.6693 ± 1.67 0.0001	3.6523 ± 1.70 0.0001
IPA (N=28) Mean ± SD	3.2618 ± 1.37 0.0001	2.2972 ± 1.57 0.0001	2.6138 ± 2.35 0.0001

P-value from paired t-test for log_{10} reduction from the test day baseline to post-treatment sampling

***Reviewer's Note**: The analyses of baseline data from the test day are shown for abdomen and groin sites in Table 3. The results illustrated that the log_{10} bacterial counts of the subjects assigned to three articles did not differ significantly at baseline at both abdomen and groin sites.*

TABLE 3: STUDY HTR: MEAN LOG_{10} BASELINE COUNTS FROM THE TEST DAY				
At Abdomen Site				
	ChloraPrep N=42	CHG N=43	IPA N=42	ANOVA P-value
Mean ± SD	3.0597 ± 0.56	2.9429 ± 0.41	2.9194 ± 0.57	0.4155
At Groin Site				
	ChloraPrep N=26	CHG N=20	IPA N=28	ANOVA P-value
Mean ± SD	5.0388 ± 0.77	4.9531 ± 0.75	4.9611± 0.68	0.9007

***Reviewer's Note**: ANCOVA with the test day baseline log_{10} CFU as the covariate was performed to evaluate the difference between articles at the 10-minute, 6-hour, and 24-hour time points correspondingly, which was presented for abdomen and groin sites in Tables 4 and 5, respectively. The results demonstrated for groin site, no significant differences among articles at the 10-minute, 6-hour, and 24-hour samplings adjusted for the test day baseline. For abdomen site, no significant differences were detected among articles at the 10-minute and 6-hour sampling, but significantly greater decrease was observed in bacterial count with ChloraPrep at 24-hours sampling. The significant baseline effects for abdomen site were observed at the 10-minute, 6-hour, and 24-hour samplings adjusted for the test day baseline.*

TABLE 4: STUDY HTR: BETWEEN TREATMENT ANALYSIS FOR BACTERIAL COUNTS BY ANCOVA ON ABDOMEN SITE				
Effect	df	Mean Squares	F-statistic	P-value
10 Minutes Sampling				
Baseline	1	8.9583	29.12	0.0001
Subject	66	0.4241	1.38	0.1081
Article	2	0.7788	2.53	0.0885
Error	57	0.3077		
6 Hour Sampling				
Baseline	1	8.1575	21.60	0.0001
Subject	66	0.7927	2.10	0.0024
Article	2	0.0554	0.15	0.8640
Error	57	0.3777		
24 Hour Sampling				
Baseline	1	8.6730	7.85	0.0069
Subject	66	1.4086	1.27	0.1752
Article	2	5.7736	5.22	0.0083
Error	57	1.1055		
Mean squares here are type III MS adjusted for the covariate.				

TABLE 5: STUDY HTR: BETWEEN TREATMENT ANALYSIS FOR BACTERIAL COUNTS BY ANCOVA ON GROIN SITE				
Effect	df	Mean Squares	F-statistic	P-value
10 Minutes Sampling				
Baseline	1	3.1987	3.17	0.0871
Subject	45	1.7222	1.71	0.0768
Article	2	0.6398	0.63	0.5386
Error	25	1.0087		
6 Hour Sampling				
Baseline	1	3.0309	3.01	0.0951
Subject	45	2.1019	2.09	0.0257
Article	2	2.6606	2.64	0.0910
Error	25	1.0070		
24 Hour Sampling				
Baseline	1	2.4201	1.68	0.2063
Subject	45	3.8518	2.68	0.0050
Article	2	4.2644	2.97	0.0698
Error	25	1.4378		

***Reviewer's Note**: Tables 6 and 7 present the comparison results of ChloraPrep versus CHG or IPA at the designated time intervals for abdomen and groin sites, respectively. The adjusted mean log_{10} reduction difference represents the difference adjusted for baseline log_{10} CFU between the log_{10} reduction by ChloraPrep and that by the other two articles at indicated time point. A negative figure indicates that CHG or IPA was superior to ChloraPrep at that time point. The results showed that at abdomen site at the 24-hour observation, ChloraPrep was significantly better than IPA.*

TABLE 6: STUDY HTR: BETWEEN TREATMENT DIFFERENCE IN MEAN LOG_{10} REDUCTION FROM BASELINE AFTER ADJUSTED FOR BASELINE AT ABDOMEN SITE		
Time Point	Adjusted Mean Reduction Differece	P-value
ChloraPrep – CHG		
10 minute	0.2396	0.0920
6 hours	0.0837	0.5912
24 hours	0.5979	0.0280
ChloraPrep – IPA		
10 minute	-0.0749	0.6090
6 hours	0.0343	0.8323
24 hours	0.8432	0.0031

TABLE 7: STUDY HTR: BETWEEN TREATMENT DIFFERENCE IN MEAN LOG_{10} REDUCTION FROM BASELINE AFTER ADJUSTED FOR BASELINE AT GROIN SITE		
Time Point	Adjusted Mean Reduction Differece	P-value
ChloraPrep – CHG		
10 minute	0.4860	0.2716
6 hours	0.0935	0.8303
24 hours	0.2369	0.6501
ChloraPrep – IPA		
10 minute	0.1600	0.6455
6 hours	0.7292	0.0438
24 hours	0.9554	0.0283

II.B. STUDY MBT

Sixty eight subjects, who had baseline counts (on the day treatment was applied) that met the "study criteria for inclusion" at abdomen and groin sites, completed the study.

***Reviewer's Note**: The mean log_{10} reductions from baseline in CFU/cm^2 of skin achieved at abdomen and groin sites are tabulated in Tables 8 and 9, respectively. For all three articles at abdomen and groin sites, the log_{10} reduction achieved at the 10-minute sampling exceeded 2 log_{10} criteria for abdomen site and 3 log_{10} criteria for groin site, and populations remained below baseline at both the 6-hour and 24-hour post treatment samplings. Based on the results of the within-treatment t-test, it was concluded that all three articles significantly decreased bacterial counts from the test day baseline at three time points.*

TABLE 8: STUDY MBT: MEAN LOG_{10} REDUCTION FROM BASELINE IN CFU/CM^2 AT ABDOMEN SITE			
Article	Mean Log_{10} Reduction From Baseline		
	10 Minutes	6 Hours	24 Hours
ChloraPrep (N=39) Mean ± SD P-value	2.5616 ± 0.99 0.0001	2.1503 ± 1.29 0.0001	2.1807 ± 1.15 0.0001
CHG (N=40) Mean ± SD P-value	2.3723 ± 1.16 0.0001	1.8032 ± 1.31 0.0001	2.1045 ± 1.41 0.0001
IPA (N=41) Mean ± SD P-value	2.8382 ± 0.78 0.0001	2.0764 ± 1.29 0.0001	1.8622 ± 1.26 0.0001
P-value from paired t-test for log_{10} reduction from the test day baseline to post-treatment sampling			

TABLE 9: STUDY MBT: MEAN LOG_{10} REDUCTION FROM BASELINE IN CFU/CM^2 AT GROIN SITE			
Article	Mean Log_{10} Reduction From Baseline		
	10 Minutes	6 Hours	24 Hours
ChloraPrep (N=36) Mean ± SD P-value	4.1999 ± 1.30 0.0001	3.4952 ± 1.45 0.0001	2.6685 ± 1.56 0.0001
CHG (N=45) Mean ± SD P-value	3.8635 ± 1.29 0.0001	3.3459 ± 1.66 0.0001	2.8583 ± 1.84 0.0001
IPA (N=39) Mean ± SD P-value	3.9601 ± 1.24 0.0001	3.1376 ± 1.53 0.0001	2.5358 ± 1.82 0.0001
P-value from paired t-test for log_{10} reduction from the test day baseline to post-treatment sampling			

Reviewer's Note: *The analyses of baseline data form the test day are shown for abdomen and groin sites in Table 10. The results illustrated that the log_{10} bacterial counts of the subjects assigned to three articles did not differ significantly at baseline at both abdomen and groin sites.*

TABLE 10: STUDY MBT: MEAN LOG_{10} BASELINE COUNTS FROM THE TEST DAY				
At Abdomen Site				
	ChloraPrep N=39	CHG N=40	IPA N=41	ANOVA P-value
Mean ± SD	3.2426 ± 0.80	3.3080 ± 0.74	3.2342 ± 0.68	0.8874
At Groin Site				
	ChloraPrep N=36	CHG N=45	IPA N=39	ANOVA P-value
Mean ± SD	4.9409 ± 0.70	4.8167 ± 0.62	4.8137 ± 0.63	0.6258

Reviewer's Note: *ANCOVA with the test day baseline log_{10} CFU as the covariate was performed to evaluate the difference between articles at the 10-minute, 6-hour, and 24-hour time points correspondingly, which was presented for abdomen and groin sites in Tables 11 and 12, respectively. The results demonstrated for abdomen site, no significant differences among articles at the 10-minute, 6-hour, and 24-hour samplings adjusted for the test day baseline, and only significant baseline effects at the 24-hour evaluation. For groin site, significant differences were detected among articles at the 10-minute sampling, and significant baseline effects were also observed at the 10-minute, 6-hour, and 24-hour samplings adjusted for the test day baseline.*

TABLE 11: STUDY MBT: BETWEEN TREATMENT ANALYSIS FOR BACTERIAL COUNTS BY ANCOVA ON ABDOMEN SITE				
Effect	df	Mean Squares	F-statistic	P-value
10 Minutes Sampling				
Baseline	1	0.6813	1.25	0.2688
Subject	59	0.8586	1.57	0.0443
Article	2	1.0669	1.95	0.1513
Error	57	0.5464		
6 Hour Sampling				
Baseline	1	1.4234	1.72	0.1951
Subject	59	1.6967	2.05	0.0036
Article	2	0.7920	0.96	0.3903
Error	57	0.8280		
24 Hour Sampling				
Baseline	1	5.6487	11.34	0.0014
Subject	59	1.9908	4.00	0.0001
Article	2	0.1841	0.37	0.6927
Error	57	0.4983		

TABLE 12: STUDY MBT: BETWEEN TREATMENT ANALYSIS FOR BACTERIAL COUNTS BY ANCOVA ON GROIN SITE				
Effect	df	Mean Squares	F-Statistic	P-value
10 Minutes Sampling				
Baseline	1	4.0726	5.92	0.0181
Subject	59	1.7909	2.61	0.0002
Article	2	3.3707	4.90	0.0108
Error	57	0.6875		
6 Hour Sampling				
Baseline	1	6.7725	6.20	0.0157
Subject	59	2.4211	2.22	0.0015
Article	2	1.3760	1.26	0.2915
Error	57	1.0924		
24 Hour Sampling				
Baseline	1	84.8294	73.20	0.0603
Subject	59	3.5719	3.08	0.0001
Article	2	0.2638	0.23	0.7971
Error	57	1.1589		

***Reviewer's Note**: Tables 13 and 14 present the multiple comparison results of ChloraPrep versus CHG or IPA at the designated time intervals for abdomen and groin sites, respectively. The adjusted mean log_{10} reduction difference represents the difference adjusted for baseline log_{10} CFU between the log_{10} reduction by ChloraPrep and that by the other two articles at indicated time point. A negative figure indicates that CHG or IPA was superior to ChloraPrep at that time point. The results showed that at groin site at the 10-minute observation, ChloraPrep was significantly better than both its ingredients.*

TABLE 13: STUDY MBT: BETWEEN TREATMENT DIFFERENCE IN MEAN LOG_{10} REDUCTION FROM BASELINE AFTER ADJUSTED FOR BASELINE AT ABDOMEN SITE		
Time Point	Adjusted Mean Reduction Differece	P-value
ChloraPrep – CHG		
10 minute	0.2534	0.1953
6 hours	0.2947	0.2209
24 hours	0.0703	0.7050
ChloraPrep – IPA		
10 minute	-0.1204	0.5387
6 hours	0.2772	0.2523
24 hours	0.1595	0.3947

TABLE 14: STUDY MBT: BETWEEN TREATMENT DIFFERENCE IN MEAN LOG_{10} REDUCTION FROM BASELINE AFTER ADJUSTED FOR BASELINE AT GROIN SITE		
Time Point	Adjusted Mean Reduction Differece	P-value
ChloraPrep – CHG		
10 minute	0.6168	0.0057
6 hours	0.2414	0.3762
24 hours	0.0418	0.8812
ChloraPrep – IPA		
10 minute	0.6171	0.0096
6 hours	0.4609	0.1181
24 hours	0.1865	0.5354

III. CONCLUSIONS

The Sponsor submitted two pivotal studies which contained adequate evidence to support the approval of ChloraPrep used as a patient preoperative skin preparation. Statistical evaluation of efficacy is summarized below.

- *According to TFM, ChloraPrep met the standards for product of this type, that is, log_{10} reductions achieved at the 10-minute sampling exceeded 2 log_{10} criteria at abdomen site and 3 log_{10} criteria at groin site, and populations remained below baseline at the 6-hour sampling at both sites.*
- *Furthermore, ChloraPrep kept bacterial counts well below baseline for 24 hours.*
- *When compared to its ingredients, ChloraPrep was superior to IPA at 10 minutes at groin site in Study MBT and at 24 hours at abdomen site in Study HTR. Also, ChloraPrep was superior to CHG at 10 minutes at groin site in Study MBT.*
- *Although the results from the two studies were not always consistent, they demonstrated that ChloraPrep behaved at least as effective as its ingredients in efficacy of patient preoperative skin preparation, and at some time and at some test sites, it was shown to be superior to its ingredients in both studies. It is noteworthy that the performance of its two ingredients satisfied the standards of TFM, only with one exception that CHG did not achieve a 3 log_{10} reduction at groin site at 10 minutes in Study HTR.*

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This review contains 10 pages and 14 tables.

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