

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-422 / S-032

STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIostatISTICS

Statistical Review and Evaluation CLINICAL STUDIES

sNDA: 19-422/S-032
Name of drug: Exidine (2% Chlorhexidine Gluconate Solution)
Applicant: Xttrium Laboratories, Inc.
Indication: Surgical Hand Scrub
Documents reviewed: Vol. I ~ III
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*Review's Note: Throughout the review, the following terms are abbreviated and referred to as:
CHG = Chlorhexidine Gluconate; Exidine = 2% CHG Solution (Dyna-Hex®); Hibiclens = 4%
CHG solution (Hibiclens®); MO = Medical Officer, TFM = Tentative Final Monograph).
Reviewer comments are given in italics throughout the review.*

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

The sponsor submits this supplemental NDA in order to obtain approval to market Exidine (2% CHG solution) used in a surgical hand scrub procedure without a scrub brush.

To support this indication, one pivotal phase III study was submitted for review. Study #010206-102 evaluated the antimicrobial efficacy of Exidine in a surgical hand scrub procedure without a scrub brush when Hibiclens (4% CHG solution) was used as a reference product in a surgical hand scrub procedure with a scrub brush. The immediate, the persistent, and the residual antimicrobial effects were measured in evaluation the products' effectiveness in reducing microorganism on hands after single and multiple hand scrubs. Of the sixty eligible subjects who completed the study, thirty subjects were utilized per test product configuration. Each subject performed eleven scrubs over a period of five days. Baseline sampling was on Days one, three, and five of the Baseline Week immediately following the fourteen-day pre-test period. The baseline counts were used to determine eligibility for continuing in the study, and to establish baseline values for each subject. The Test Week constituted the week immediately following the seven days Baseline Week. The products were used by the subjects once on Days one and five, and three times on Days two, three, and four of the Test Week. Approximately one hour was allowed to elapse between each of the three scrubs on Days two, three, and four. The hand-sampling of each subjects was randomized to two of three sampling times: immediately, three hours, or six hours following the first scrub. The Glove Juice Sampling Procedure was performed on Days one, two, and five of the Test Week. On these days, all subjects' hands not sampled immediately after the first scrub were protected by sterile powder-free surgical gloves until three or six hours had elapsed. The testing methods were based on the FDA's TFM for Effectiveness Testing of a Surgical Hand Scrub (FR 59:116, 17 June 94).

The evaluation of efficacy focused on the immediate, the persistent, and the residual antimicrobial effects of the product. The primary efficacy measure was the \log_{10} reduction from baseline at four designated sampling points. Demonstration of efficacy requires that all these four sampling points meet respective requirement of efficacy evaluation procedures specified by the TFM.

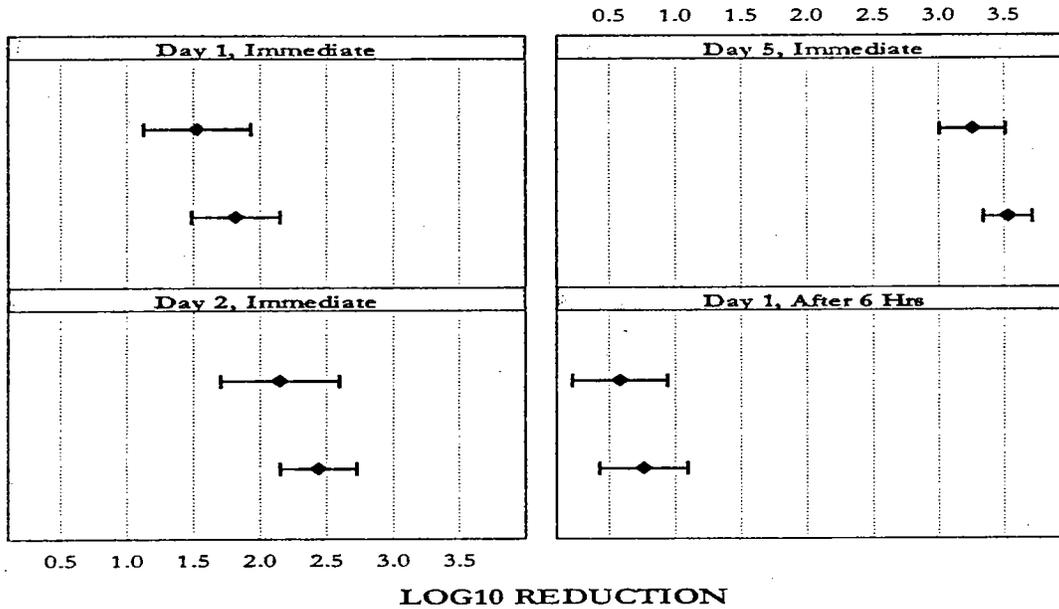
Statistical review and evaluation of this NDA has been based on the procedures specified in the TFM. The results showed that Exidine met the defined standards for product of this type, that is, reductions in bacterial counts at four primary endpoints, immediately after scrubbing, of at least 1 \log_{10} on Day one, 2 \log_{10} on Day two, and 3 \log_{10} on Day five; and maintenance of bacterial counts at six hours on Day one less than baseline counts.

Statistical results also showed that the lower bound of 95% confidence interval for Exidine in mean \log_{10} reductions from baseline sampled immediately after scrubbing on Days one, two, and five were 1.13, 1.71, and 3.01, respectively, and sampled at six hours on Day one

after scrubbing was 0.22.

When compared to the reference product Hibiclens at four primary sampling points, Exidine had less \log_{10} reductions in bacterial counts than its comparator, but their differences were not statistically significant.

Figure 1. depicts the efficacy results.



* Upper bar and lower bar represent Exidine and Hiberclens, respectively. Upper and lower bounds of 95% confidence intervals in mean \log_{10} reductions are described.

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2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

The Sponsor submitted one pivotal controlled study, #010206-102, as evidence to support that Exidine was antimicrobially efficacious in a surgical hand scrub procedure without a scrub brush when Hibiclens was used as a reference product in a surgical hand scrub procedure with a scrub brush. Statistical review focuses on this comparative clinical trial which formed the basis of this application.

2.2 STUDY DESIGN AND DATA ANALYSIS

Objectives

To determine the antimicrobial efficacy of Exidine for use as a surgical formulation without a scrub brush procedure, as per methodology specified by the TFM for surgical hand scrub products. The immediate, the persistent, and the residual antimicrobial effects were measured to evaluate its effectiveness in reducing microorganism on hands after single and multiple hand scrubs.

Study Design

This study evaluated the antimicrobial efficacy of Exidine used in a scrub procedure without a scrub brush. Hibiclens was used as the reference product, and a scrub brush was utilized in the scrub procedure. The test methods were based on the TFM for Effectiveness Testing of a Surgical Hand Scrub.

The study was conducted in normal volunteers, who met the inclusion criteria of baseline bacterial count. The subjects accepted into the study were assigned randomly to one of the two product groups. Subjects in each group were subdivided randomly into several block groups of six subjects each. Baseline sampling was on Days one, three, and five of the Baseline Week immediately following the fourteen-day pre-test period. During the Test Week, surgical scrubs were conducted on Day one through Day five immediately following the seven days Baseline Week. The subjects utilized their assigned product once on Days one and five, and three times on Days two, three, and four of the Test Week. Approximately one hour was allowed to elapse between each of the three scrubs on Days two, three, and four. The hand sampling of the subjects was randomized to two of three sampling times. This sampling was performed on Days one, two, and five of the Test Week.

Assessment of Efficacy

The evaluation of efficacy was focused on the immediate, the persistent, and the residual effectiveness of the products in reducing microorganism on hands after single and multiple hand scrubs. The primary efficacy measure was the \log_{10} reduction from baseline at four designated sampling points. Demonstration of efficacy requires that reductions in bacterial counts at these four primary endpoints all meet respective requirement specified by the TFM.

According to the TFM for Health Care Antiseptic Drug Product published in the Federal Register on June 17, 1994, the drug product for surgical hand scrub must meet the following criteria:

1. A 1.0 \log_{10} reduction from baseline in CFU/cm² of the microbial hand flora immediately after the 1st scrubbing on Day 1 with the count remaining below baseline 6 hours after scrubbing.
2. A 2.0 \log_{10} reduction from baseline at the immediate sampling after the 2nd scrubbing on Day 2.
3. A 3.0 \log_{10} reduction from baseline at the immediate sampling after the 10th scrubbing on Day 5.

Reviewer's Note: Although the test schedule included the sampling at 3 hours after scrubbing, there is no TFM criteria for efficacy evaluation at this sampling point. Hence, in this review, the sampling points at 3 hours were not evaluated.

Statistical Methods

Reviewer's Note: Statistical evaluation was conducted for data collected from hand sampling at four designated sampling points. The experiment unit was subject's hand.

The \log_{10} baseline count from the test day between the products was compared using t-test.

Within-treatment analysis for \log_{10} reductions from the test day baseline at four sampling points 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 \log_{10} baseline count as a covariate. The factors' mean square adjusted for the covariate was given by Type III mean square.

All tests were two-sided and used a 5% level of significance.

2.3 STATISTICAL EVALUATION ON EFFICACY

Ninety healthy subjects at least the age of eighteen years, but not older than seventy years, were admitted into the study. All enrolled subjects met the study criteria for inclusion. After admission into the study, subjects could withdraw at any time for any reason. Fifteen subjects withdrew per treatment arm. The most common reason for dropped subjects was voluntary withdrawal from study by not showing up for one of their assigned test dates. Sixty subjects completed the study with thirty subjects in each product group.

Reviewer's Note: Analysis of baseline data is presented in Table 1, which indicated that the log₁₀ bacterial counts of the subjects assigned to the two products did not differ significantly at baseline. There were 60 experiment units (hands) per arm.

TABLE 1: MEAN LOG ₁₀ BASELINE COUNTS (WITH THREE COUNTS AVERAGED)			
	Exidine (N=60)	Hibiclens (N=60)	P-value
Mean ± SD	5.90 ± 0.43	5.96 ± 0.35	0.0853

Reviewer's Note: Table 2 displays the results of within treatment analysis. For the two products, the mean log₁₀ reduction from baseline at four sampling points all satisfied the standards specified by TFM, and they significantly decreased bacterial counts from the test day baseline at four sampling points. The lower bound of 95% confidence interval for Exidine in mean log₁₀ reductions from baseline sampled immediately after scrubbing at Days one, two, and five were 1.13, 1.71, and 3.01, respectively, and sampled at six hours on Day one after scrubbing was 0.22.

TABLE 2: MEAN LOG ₁₀ REDUCTION FROM BASELINE				
Product	Mean Log ₁₀ Reduction From Baseline			
	Day 1 Immediate	Day 1 6-Hour	Day 2 Immediate	Day 5 Immediate
Exidine (N=20)				
Mean ± SD	1.53 ± 0.86	0.58 ± 0.77	2.15 ± 0.95	3.26 ± 0.54
95% C.I.	(1.13, 1.93)	(0.22, 0.94)	(1.71, 2.59)	(3.01, 3.51)
P-value	<0.0001	0.0035	<0.0001	<0.0001
Hibiclens (N=20)				
Mean ± SD	1.82 ± 0.71	0.76 ± 0.71	2.44 ± 0.61	3.53 ± 0.40
95% C.I.	(1.49, 2.15)	(0.43, 1.09)	(2.15, 2.73)	(3.34, 3.72)
P-value	<0.0001	0.0001	<0.0001	<0.0001

Reviewer's Note: Between treatment analysis is showed in Table 3, where ANCOVA with the test day baseline as the covariate was performed to evaluate the difference between the two products at the four sampling points. The adjusted mean \log_{10} reduction difference represented the difference adjusted for baseline \log_{10} counts between the \log_{10} reduction by Exidine and that by Hibiclens at indicated sampling points. A negative figure implies that Exidine had less \log_{10} reduction in bacterial counts than Hibiclens at that sampling point. The results showed Hibiclens was numerically better than Exidine in this efficacy measurement, but not so significantly different. Adjusted mean \log_{10} reduction turned out to be very closed to mean \log_{10} reduction in Table 2.

Sampling Point	Adjusted Mean Log ₁₀ Reduction			P-value
	Exidine (N=20)	Hibiclens (N=20)	Difference	
Day 1, Immediate	1.53	1.83	-0.30	0.2478
Day 1, 6-Hour	0.58	0.75	-0.17	0.4223
Day 2, Immediate	2.15	2.44	-0.29	0.2748
Day 5, Immediate	3.28	3.50	-0.22	0.1070

2.4 SUMMARIES AND CONCLUSIONS

This NDA submission was supported by one study (#010206-102) to demonstrate the antimicrobial efficacy of Exidine in a surgical hand scrub procedure without a scrub brush. Statistical evaluation of efficacy is summarized below.

- *Mean reductions in bacterial counts of Exidine met the standards required by the TFM, that is, immediately after scrubbing, of at least 1 \log_{10} on Day one, 2 \log_{10} on Day two, and 3 \log_{10} on Day five; and maintenance of bacterial counts at sampling point of six hours on Day one less than baseline counts. Hibiclens also satisfied the criteria.*
- *The lower bound of 95% confidence interval for Exidine in mean \log_{10} reductions from baseline sampled immediately after scrubbing at Days one, two, and five were 1.13, 1.71, and 3.01, respectively, and sampled at six hours after scrubbing was 0.22.*
- *When compared to Hibiclens at four primary sampling points, Exidine had less \log_{10} reduction in bacterial counts than its comparator, but they were not significantly different.*

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