

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-669

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 21669 - Resubmission
Drug Name: SAGE's 2% Chlorhexidine Gluconate Antiseptic Solution
Indication(s): Pre-operative Skin Preparation
Applicant: Sage, Inc.
Date(s):
Date of Original Submission: 10/25/2004
Date of Deadline: 04/25/2005

Biometrics Division: Biometrics Division III
Statistical Reviewer: Thamban Valappil, Ph.D.
Statistical Team Leader: Daphne Lin, Ph.D.

Medical Division: HFD-520, Anti-Infective division
Clinical Team: Peter Kim, M.D., MS.
Project Manager: Maureen Dillon-Parker

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Drug Name: SAGE's 2% Chlorhexidine Gluconate Antiseptic Solution
Indication(s): Pre-operative Skin Preperation
Applicant: Sage, Inc.
Date(s):
Date of Original Submission: 09/04/03
Date of Deadline 07/04/04

Biometrics Division: Biometrics Division III
Statistical Reviewer: Thamban Valappil, Ph.D.
Concurring Reviewer: Daphne Lin, Ph.D.

Medical Division: HFD-520, Anti-Infective division
Clinical Team: Peter Kim, M.D., MS.
Project Manager: Maureen Dillon-Parker

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

From statistical perspective, there were several issues and limitations in this submission which were pointed out in this review. There were no major safety issues reported. However, based on collective evidence (although limited) and subsequent discussions with reviewers from other disciplines, it was concluded that the benefits of this product may outweigh the risks associated. Therefore, _____ (2% Chlorhexidine Gluconate Pre-op Prep), may be approvable for the indication of Patient Preoperative Skin Preparation and the product label should clearly reflect the limitations.

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1.2 Brief Overview of Clinical Studies

NDA 21,669 was submitted to evaluate the antimicrobial effectiveness of Sage's 2% CHG Pre-Op Prep product. The studies contained a positive control formulation (Hibiclens by Astrazeneca) previously approved by the Agency. A total of nine studies were submitted for this product and data from all nine studies were used to evaluate safety. In this submission, the efficacy review will be based on three pivotal trials, █ -01-109381-11, █ -020125-103, and █ -500-102. These studies were all Phase 3, studies comparing the proposed product, █ (2% Chlorhexidine Gluconate Pre-op Prep), with a positive control product approved by the FDA, Hibiclens® with 4% chlorhexidine gluconate.

Pivotal Clinical Studies

- █ -01-109381-11: █
- █ -020125-103: █
- █ -500-102: █

1.3 Statistical Issues and Findings

Based on evaluating the █ -01-109381-11 data, for the abdominal site, the Applicant's test product, █ met the required $2 \log_{10}$ mean reduction in bacterial counts. However, the approved positive control product, Hibiclens®, did not meet the Tentative Final Monograph (TFM) required $2 \log_{10}$ reduction for the abdominal site.

For the Inguinal site, the test product and the positive control product, Hibiclens®, failed to meet the required $3 \log_{10}$ mean reduction in bacterial counts. Also, the bacterial counts for both the test product and the positive control did not exceed the baseline counts at the six hour post-treatment sampling interval.

Based on evaluating the █ -020125-103 data, the test product met the required $2 \log_{10}$ reduction in bacterial counts at abdominal sites and a $3 \log_{10}$

reduction at the inguinal sites. However, the positive control product, Hibiclens®, met the required 2 log₁₀ reduction at the abdominal sites and failed to meet the required 3 log₁₀ reduction for the inguinal sites. This raises concern about the overall validity of the trial results for Inguinal and Abdominal site, although the test product met the 2 log₁₀ reduction in bacterial counts for the abdominal sites. The bacterial counts for both the test product and the positive control did not exceed the baseline counts at the six hour post-treatment sampling interval.

Based on evaluating the **■ -500-102** data, inguinal sites were tested. Based on the data provided, the Applicant's test product and the positive control met the efficacy requirement of 3 log₁₀ reduction in bacterial counts at the inguinal anatomical site. One observation to be noted that the results based on **■** was very different (the percentage above the threshold was higher) compared to the data from other two labs.

For the Abdominal and Inguinal sites, the positive control, Hibiclens®, did not perform as expected as an approved comparator except for the inguinal data submitted from **■**. The failure of the positive control to meet the TFM requirements raises concern regarding the validity of the trial(s).

Based on this review and the discussions with the clinical reviewer, the benefits of this product may outweigh the risks associated. There were no major safety issues reported. Therefore, after evaluating the efficacy and safety, **■** **■** (2% Chlorhexidine Gluconate Pre-op Prep), may be approvable for the indication of Patient Preoperative Skin Preparation and the product label should reflect the limitations. A detailed safety review can be obtained from the clinical review of Dr. Peter Kim.

2. INTRODUCTION

2.1 Overview

NDA 21,669 was submitted to evaluate the antimicrobial effectiveness of Sage's 2% CHG Pre-Op Prep product. Chlorhexidine gluconate, CHG, was developed in the early 1950's in England and was introduced in the USA in the 1970's. The studies contained a positive control formulation (Hibiclens by Astrazeneca) previously approved by the agency and the studies were conducted at [REDACTED] and [REDACTED].

Based on the sponsor's submission, a total of nine studies for this product were documented and data from all nine studies were used to evaluate safety. Efficacy was evaluated based on the submitted three pivotal trials, to establish that 2% CHG Pre-OP Prep product meet the standard as described in the TFM. The efficacy review will be mainly based on the pivotal trials, [REDACTED]-01-109381-11, [REDACTED]-020125-103, and [REDACTED]-500-102. These studies were all Phase 3 studies comparing the proposed product, [REDACTED] (2% Chlorhexidine Gluconate Pre-op Prep), with Hibiclens® with 4% chlorhexidine gluconate, as Patient Preoperative Skin Preparations.

2.2 Data Sources

The data is available on EDR at \\CDSESUB1\N21669\N_000\2003-08-29

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design and Endpoints

In this submission, the efficacy review will be based on three pivotal trials, [REDACTED] -01-109381-11, [REDACTED] -020125-103, and [REDACTED] -500-102. These studies were all Phase 3, studies comparing the proposed product, [REDACTED] (2% Chlorhexidine Gluconate Pre-op Prep), with a positive control product approved by the FDA, Hibiclens® with 4% chlorhexidine gluconate.

Clinical Studies

Trial-1: [REDACTED] -01-109381-11 was performed at [REDACTED]
[REDACTED]

Trial-2: [REDACTED] -020125-103 was performed at [REDACTED]
[REDACTED]

Trial-3: [REDACTED] -500-102, was performed at [REDACTED]
[REDACTED]

Objectives: The objective of these studies were to evaluate the antimicrobial effectiveness of the test product, [REDACTED], against a positive control formulation approved by the FDA, Hibiclens®, as Patient Preoperative Skin Preparations.

The submitted studies were randomized and blinded. Each subject had both the test article and control applied contra laterally. Each subject had four (4) test sites (Abdomen and Inguinal –left and right) were tested at baseline, 10 minutes, 30 minutes, and 6-hour sampling intervals, and these sites were randomized. The laboratory personnel evaluating the samples were blinded as to whether the sample was the test product or the control.

Endpoints: The study endpoint was bacterial counts and was based on the Tentative Final Monograph (TFM) for Health Care Antiseptic Drug

Products, Effectiveness Testing of a Patient Preoperative Skin Preparation, published in the Federal Register on June 17, 1994.

Sponsor's Statistical Analysis:

Based on the sponsor's analysis, the original bacterial counts (CFU/mL) were converted to Log₁₀ scale. For each site, the Log reductions were calculated by subtracting the post-treatment log counts from the average of the two baseline counts (the screening and treatment day baselines) obtained. Based on meeting the inclusion criteria for baseline bacterial counts on the screening day and the treatment day of the study, subjects were included in the analysis.

The immediate and persistent antimicrobial effects of the test product, ~~_____~~ and positive control product, Hibiclens® were performed by the Sponsor and the mean log reductions (between baseline and 10 minutes and 6 hours post-application) of the test and control drug products as specified in the TFM, were submitted for FDA review.

Statistical Reviewer's Comments:

Based on these submitted studies, 2% Chlorhexidine Gluconate Pre-Op prep cloth were evaluated based on the standards as specified in the FDA proposed Tentative Final monograph for Health Care Antiseptic Drug Products.

According to the current TFM, the product, 2% Chlorhexidine Gluconate Pre-Op prep cloth should meet 2 log₁₀ and 3 log₁₀ reductions in bacterial counts at 10 minutes for abdominal and inguinal test sites and also, a sustained reduction below the baseline bacterial counts should be met in 6 hours respectively.

Table 1: Controlled Efficacy Studies: Pre-operative Skin Preparation

Protocol Number	Study Design	Formulation / Dosage	Number of Subjects
01-109381-11	<ul style="list-style-type: none"> ▪ Phase III ▪ Blinded ▪ Randomized 	Finished dosage form applied for 3 minutes	69 enrolled <u>Evaluable Subjects:</u> 31 inguinal 31 abdomen
020125-103	<ul style="list-style-type: none"> ▪ Phase III ▪ Blinded ▪ Randomized 	Finished dosage form applied for 3 minutes	88 enrolled <u>Evaluable Subjects:</u> 30 inguinal 30 abdomen
500-102	<ul style="list-style-type: none"> ▪ Phase III ▪ Blinded ▪ Randomized 	Finished dosage form applied for 3 minutes	43 enrolled <u>Evaluable Subjects:</u> 32 inguinal

PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Table 2: Demographic Characteristics (020125-103)		
Lab	Characteristics	Subjects
	Total	88
	Gender	
	Male	40
	Female	48
	Age	
	Median	29
Range	18 - 69	
Race		
Caucasian	81	
Hispanic	3	
Native American	4	
Other	0	

Reviewer's Table

Lab	Characteristics	Subjects
■■■■	Total	69
	Gender	
	Male	19
	Female	50
	Age	
Median	57	
Range	21- 69	
■■■■	Race	
	Caucasian	66
	African American	3
	Hispanic	0
	Native American	0
Other	0	

Reviewer's Table

Lab	Characteristics	Subjects
■■■■	Total	43
	Gender	
	Male	21
	Female	22
	Age	
Median	39	
Range	18 - 61	
■■■■	Race	
	Caucasian	29
	African American	3
	Asian	10
	Hispanic	1
	Native American	0
Other	0	

Reviewer's Table

Statistical Reviewer's Comments:

Based on the demographic data from ■■■■ (Protocol ■■■■-020125-103), there were 88 adult subjects enrolled between the ages of 18 and 69 years, of which 30 subjects provided evaluable data for analysis at the abdominal site and

30 subjects provided evaluable data for analysis at the inguinal site. The median age was 29 years. Enrolled subjects were predominantly Caucasians (92%).

Based on the demographic data from [REDACTED] -01-109381-11), there were 69 adult subjects enrolled, of which 31 subjects provided evaluable data for analysis at the abdominal site and 31 subjects provided evaluable data for analysis at the inguinal site. The age ranged between 21-69, with a median age of 57 years and 72% of the participants were females and among the total, 96% were Caucasians.

Based on the demographic data from [REDACTED] -500-102), there were no major differences evident with respect to gender. The participants were mostly Caucasians(90%). Among the enrolled 43 adult subjects, 32 subjects provided evaluable data for analysis at the inguinal site. The age ranged between 18-61 with a median age of 39 years.

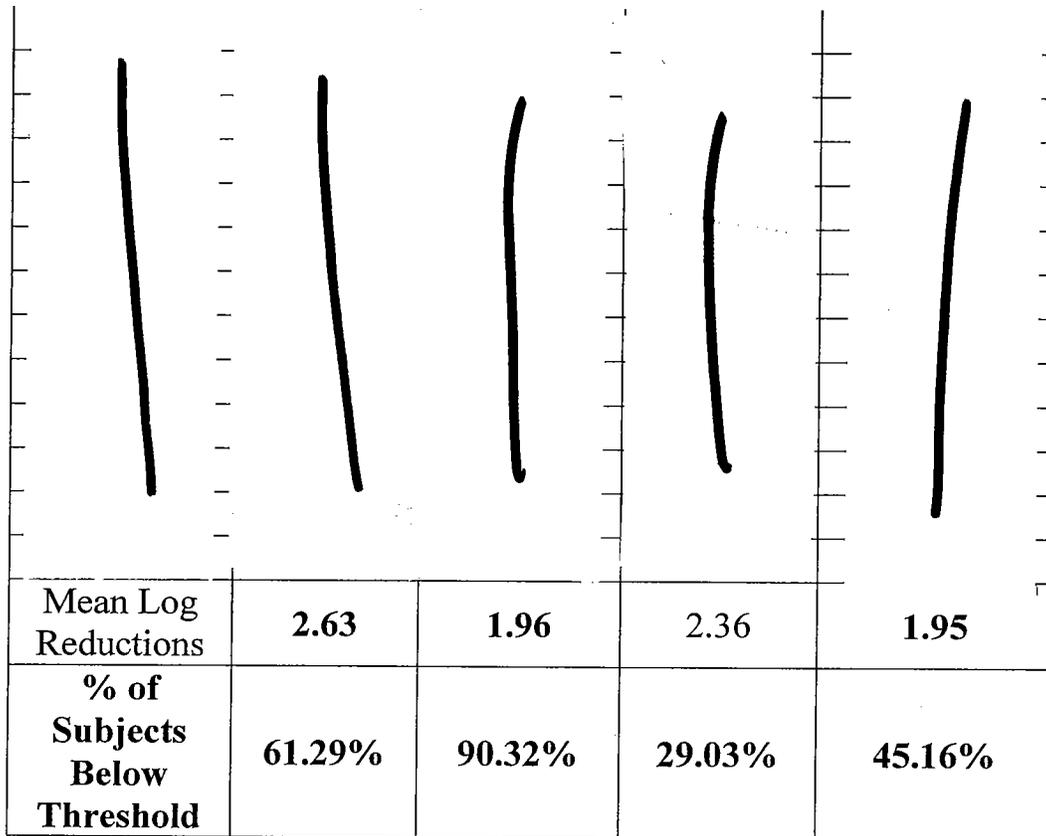
Comparing all the three studies across, [REDACTED] enrolled a lot more younger subjects while [REDACTED] enrolled less older subjects..

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RESULTS AND CONCLUSIONS

Table 5: Study **01-109381-11**

Log ₁₀ Reductions (10 minute bacterial count subtracted from baseline)		
ID#	<u>INGUINAL</u>	<u>ABDOMINAL</u>
1		
2		
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Dr. Peter Kim's Table

Statistical Reviewer's Comments:

In Study -01-109381-11, based on the log reductions at 10 minutes, 61.29% and 29.03% of the subjects treated with the _____, did not meet the TFM requirement of a 5 log₁₀ reduction for the Inguinal and 2 log₁₀ reduction for the Abdominal site.

It is important to note that subjects treated with the positive control product, Hibiclens®, 90.32% of the subjects did not meet the 3 log₁₀ reduction at the inguinal sites and 45.16% did not meet a 2 log₁₀ reduction at the abdominal anatomical sites. Based on the data, it was concluded that a large number of the subjects treated with both the test product, _____, and the control product, Hibiclens®, failed to meet the 10-minute TFM requirements at both Abdominal and Inguinal sites.

Table 6: Study — -01-109381-11 (Abdomen Site)

	Mean Log Reductions from baseline	
	—	Hibiclens® (positive Control)
10 minutes	2.37	1.95
6 hours	2.41	2.29

Table 7: Study — -01-109381-11 (Inguinal Site)

	Mean Log Reductions from baseline	
	—	Hibiclens® (positive Control)
10 minutes	2.63	1.96
6 hours	3.18	2.46

Statistical Reviewer's Comments:

Based on the — data (tables 6-7), for the abdominal site, the Applicant's test product met the required $2 \log_{10}$ mean reduction in bacterial counts. It should be noted that the positive control (approved) product, Hibiclens®, did not meet the TFM required $2 \log_{10}$ reductions for the abdominal site. However, the Division felt that the result was close enough to the $2 \log_{10}$ reduction (1.95) that the Hibiclens®-

treated abdominal site data was deemed acceptable. Also, the bacterial cell counts for each test site did not exceed the baseline counts at the six hour post-treatment sampling interval.

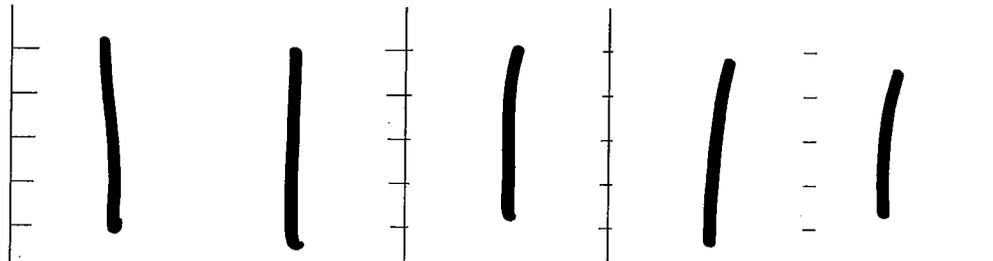
Based on the data for Inguinal site, the test product failed to meet the required 3 log₁₀ mean reduction in bacterial counts for the inguinal sites. It should also be noted that the positive control product, Hibiclens®, failed to meet the TFM required 3 log₁₀ reduction for the Inguinal sites.

Table 8:  : Mean Log Reduction and 95% CIs

Study Center, Anatomical Site, and Test Product	Mean Log Reduction at 10 minutes	95% CI	Standard Deviation	No. Subjects (%) below threshold
Abdominal - 	2.37	(2.01, 2.73)	0.983	9 (29%)
Abdominal - Hibiclens®	1.95	(1.62, 2.28)	0.9043	14 (45.2%)
Inguinal - 	2.63	(2.26, 3.00)	1.0145	19 (61.3%)
Inguinal - Hibiclens®	1.96	(1.63, 2.30)	0.9146	28 (90.3%)

Statistical Reviewer’s Comments:

The 95% confidence interval limits around the mean log₁₀ reductions for the abdominal and inguinal anatomical sites for both the test and positive control products are given in the above table. The confidence limits are wide reflecting the variability and the lack of precision in the mean log reductions. Also, the



Mean Log Reductions	3.45	2.78	2.50	2.18
% of Subjects Below Threshold	33.33%	63.33%	30%	36.67%

Dr. Peter Kim's Table

Statistical Reviewer's Comments:

In Study 020125-103, based on the log reductions at 10 minutes, 33.33% and 30% of the subjects treated with the _____ did not meet the TFM requirement of a 3 log₁₀ reduction for the Inguinal and 2 log₁₀ reduction for the Abdominal site.

It is important to note that subjects treated with the positive control product, Hibiclens®, 63.33% of the subjects did not meet the 3log₁₀ reduction at the inguinal sites and 36.67% did not meet a 2 log₁₀ reduction at the abdominal anatomical sites. From the above, it can be concluded that among the subjects treated with the control product, Hibiclens®, there were 30% more subjects, failed to meet the 10-minute TFM requirements at the Inguinal site. This raises concern about the validity of the trial results for Abdominal as well as Inguinal sites.

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Table 10: Study ~~001~~-020125-103 (Abdomen Site)

	Mean Log Reductions from baseline	
	001	Hibiclens® (positive Control)
10 minutes	2.50	2.18
6 hours	2.54	2.19

Table 11: Study ~~001~~-020125-103 (Inguinal Site)

	Mean Log Reductions from baseline	
	001	Hibiclens® (positive Control)
10 minutes	3.45	2.78
6 hours	3.64	3.15

Statistical Reviewer's Comments

The Applicant's test product met the required 2 log₁₀ reduction in bacterial counts at abdominal sites and a 3 log₁₀ reduction at the inguinal sites (tables 10-11). However, it should be noted that the positive control product, Hibiclens®, met the required 2 log₁₀ reduction at the abdominal sites and failed to meet the required 3 log₁₀ reduction for the inguinal sites. The bacterial counts for both the test product and the positive control did not exceed the baseline counts at the six hour post-treatment sampling interval.

Table 12: _____ : Mean Log Reduction and 95% CIs

Study Center, Anatomical Site, and Test Product	Mean Log Reduction at 10 minutes	95% CI	Standard Deviation	No. Subjects (%) below threshold
Abdominal - _____	2.51	(2.20, 2.82)	0.8273	9 (30%)
Abdominal - Hibiclens®	2.18	(1.77, 2.59)	1.094	11 (36.7%)
Inguinal - _____	3.46	(3.10, 3.82)	0.9581	10 (33.3%)
Inguinal - Hibiclens ®	2.78	(2.40, 3.17)	1.0381	19 (63.3%)

Statistical Reviewer's Comments:

The 95% confidence interval limits around the mean log₁₀ reductions for the abdominal and inguinal anatomical sites for both the test and positive control products are given in table 12. The width of the confidence interval reflects on the lack of precision in the mean log reduction.

Table 13: Study -500-102

Log ₁₀ Reductions (10 minute bacterial count subtracted from baseline)	
ID#	<u>INGUINAL ONLY</u>
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In the trial **500-102**, only inguinal sites were tested. Based on the data provided, the Applicant's test product and the positive control met the efficacy requirement of 3 log₁₀ reduction in bacterial counts at the inguinal anatomical site (table 14).

Table 15: **500-102**: Mean Log Reduction and 95% CIs

Anatomical Site, and Test Product	Mean Log Reduction at 10 minutes	95% CI	Standard Deviation	No. Subjects (%) below threshold
Inguinal - 500-102	4.19	(3.87, 4.50)	0.8697	2 (6.3%)
Inguinal - Hibiclens®	3.84	(3.48, 4.19)	0.9833	4 (12.5%)

Statistical Reviewer's Comments:

The 95% confidence interval limits around the mean log₁₀ reductions for the abdominal and inguinal anatomical sites for both the test and positive control products are given in table 15.

3.2 Evaluation of Safety

There were no major safety issues. Please refer to the clinical review for more details on the related safety issues.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The demographic data from all the three labs _____ are given in Tables 2, 3 and 4. The participants were predominantly Caucasians (92%, 96% and 90%) in labs _____

Protocol -020125-103 enrolled 88 adult subjects between the ages of 18 and 69 years, out of which 30 subjects provided evaluable data for analysis at the abdominal site and 30 subjects provided evaluable data for analysis at the inguinal site. The median age was 29 years.

Protocol -01-109381-11 enrolled 69 adult subjects, out of which 31 subjects provided evaluable data for analysis at the abdominal site and 31 subjects provided evaluable data for analysis at the inguinal site. The age ranged between 21-69 with a median age of 57 years.

Protocol -500-102 enrolled 43 adult subjects, out of which 32 subjects provided evaluable data for analysis at the inguinal site. The age ranged between 18-61, with a median age of 39 years.

This is a topical product and based on the discussions with the clinical reviewer, the findings of efficacy based on gender, age and race was not that relevant. However, findings based on these subgroup populations were evaluated for safety and no significant differences were noticed. Also, for _____, the distribution of gender is almost the same. Based on the data submitted from _____ there were 72% of women enrolled.

4.2 Other Special /Subgroup Populations

No other special or subgroup populations were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

— -01-109381-11:

For the abdominal site, based on evaluating the data, the Applicant's test product, — met the required 2 log₁₀ mean reduction in bacterial counts. The approved positive control product, Hibiclens®, did not meet the TFM required 2 log₁₀ reduction for the abdominal site. However, based on the earlier discussions with the sponsor, the Hibiclens®-treated abdominal site data was deemed acceptable.

For the Inguinal site, the test product and the positive control product, Hibiclens®, failed to meet the required 3 log₁₀ mean reduction in bacterial counts. Also, the bacterial counts for both the test product and the positive control did not exceed the baseline counts at the six hour post-treatment sampling interval.

— -020125-103:

Based on evaluating the data, the test product met the required 2 log₁₀ reduction in bacterial counts at abdominal sites and a 3 log₁₀ reduction at the inguinal sites. However, the positive control product, Hibiclens®, met the required 2 log₁₀ reduction at the abdominal sites and failed to meet the required 3 log₁₀ reduction for the inguinal sites. This raises concern about the overall validity of the trial results for Inguinal and Abdominal site, although the test product met the 2 log₁₀ reduction in bacterial counts for the abdominal sites. The bacterial counts for both the test product and the positive control did not exceed the baseline counts at the six hour post-treatment sampling interval.

— -500-102:

Based on evaluating the data for the inguinal sites, the Applicant's test product and the positive control met the efficacy requirement of 3 log₁₀ reduction in bacterial counts at the inguinal anatomical site. One observation to be noted that the results based on — was different compared to the results from the other two labs.

Overall, for the Abdominal and Inguinal sites, the positive control, Hibiclens®, did not perform as expected as an approved comparator except for the inguinal data submitted from [REDACTED]. The failure of the positive control to meet the TFM requirements in some trials raises concern regarding the validity of the whole trial(s).

5.2 Conclusions and Recommendations

From statistical perspective, there were several issues and limitations in this submission which were pointed out in this review. There were no major safety issues reported. However, based on collective evidence (although limited) and subsequent discussions with reviewers from other disciplines, it was concluded that the benefits of this product may outweigh the risks associated. Therefore, [REDACTED]; (2% Chlorhexidine Gluconate Pre-op Prep), may be approvable for the indication of Patient Preoperative Skin Preparation and the product label should clearly reflect the limitations.

For future studies, a negative control should be included in the trial design. In the absence of a negative control, one cannot effectively assess the efficacy of these types of products.

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Daphne Lin
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