

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-524**

**MEDICAL REVIEW**

**CLINICAL TEAM LEADER MEMO**

<b>Application Type</b>	<b>NDA</b>
<b>Submission Number</b>	<b>21-524</b>
<b>Submission Code</b>	<b>N-000</b>
<b>Letter Date</b>	<b>July 26, 2004</b>
<b>Stamp Date</b>	<b>August 5, 2004</b>
<b>PDUFA Goal Date</b>	<b>June 5, 2005</b>
<b>Team Leader Name</b>	<b>Jean M. Mulinde, M.D.</b>
<b>Review Completion Date</b>	<b>March 31, 2005</b>
<b>Established Name</b>	<b>Chlorhexidine gluconate 3.15% and 70% (v/v) isopropyl alcohol</b>
<b>(Proposed) Trade Name</b>	<b>Chlorascrub™ Swabstick, Maxi Swabstick, and Swab</b>
<b>Applicant</b>	<b>Les Enterprises SoluMed Inc.</b>
<b>Therapeutic Class</b>	<b>Topical antiseptic</b>
<b>Priority Designation</b>	<b>S</b>
<b>Formulation</b>	<b>Swab impregnated with 3.15% chlorhexidine gluconate and 70% (v/v) isopropyl alcohol</b>
<b>Dosing Regimen</b>	<b>Single topical application</b>
<b>Indications</b>	<b>Patient Preoperative Skin Preparation and Preinjection Skin Preparation</b>
<b>Intended Population</b>	<b>Pediatric patients <math>\geq</math>2 months of age and adult patients</b>

**Recommendation  
on Approval**

From a clinical perspective, Chlorascrub™ Swabstick and Chlorascrub™ Maxi Swabstick may be approved for the patient preoperative skin preparation indication and Chlorascrub™ Swab, Chlorascrub™ Swabstick, and Chlorascrub™ Maxi Swabstick may be approved for the patient preinjection skin preparation indication.

**Relevant Product  
Development  
History**

Chlorascrub™ Swab, Chlorascrub™ Swabstick, and Chlorascrub™ Maxi Swabstick all contain a solution of 3.15% chlorhexidine gluconate and 70% (v/v) isopropyl alcohol. The Applicant originally filed a Pre-IND for this topical antiseptic product on August 12, 1998 and subsequently filed an IND for the product on December 5, 1999. After a number of discussions with the Agency regarding product development, the Applicant decided to pursue only claims for patient preoperative skin preparation (1.6 ml Chlorascrub™ Swabstick and 5.1 ml Chlorascrub™ Maxi Swabstick) and preinjection skin preparation (1.0 ml Chlorascrub™ Swab, 1.6 ml Chlorascrub™ Swabstick, and 5.1 ml Chlorascrub™ Maxi Swabstick). Notably, in a teleconference held November 19, 2003 between representatives of the Applicant and the Division of Anti-Infective Drug Products, the Applicant disclosed that one of their two pivotal efficacy studies did not provide satisfactory results at the groin site (see discussion of endpoints below). At that meeting the Applicant proposed that they would perform an additional study, looking at only the groin site, and Division of Anti-Infective Drug Product representatives agreed with the Applicant's plan.

**Discussion of  
Endpoints Used In  
Pivotal Studies**

Primary Endpoints

The study endpoints used in the Applicant's three pivotal *in vivo* efficacy studies were taken from those recommended in the FDA Proposed 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. For the patient preoperative skin preparation indication the TFM requires at least a mean 2 log<sub>10</sub> reduction in bacterial counts from baseline on abdominal sites (a "dry" site) and a mean 3 log<sub>10</sub> reduction in bacterial counts from baseline on inguinal sites (a "wet" site) 10 minutes after site preparation. In addition, the TFM also requires that the mean microbial counts on the abdominal and inguinal sites remain below baseline counts for six hours. For the patient preinjection skin preparation indication the TFM requires at least a mean 1 log<sub>10</sub> reduction in bacterial counts from baseline on a "dry" site (the forearm is most frequently used) within 30 seconds of product application.

It should be noted that these endpoints reflect only mean log<sub>10</sub> reductions of bacterial counts on the skin; an association with these endpoints and reduction in postoperative surgical site infection has not been demonstrated. It should also be noted that these endpoints are based on mean log

reductions, rather than individual subjects achieving specified reductions. Therefore, individual results may vary from increased to decreased counts on the skin for a given drug product, yet based on overall mean reductions the product could be considered efficacious. Further complicating the recent interpretation of studies relying on the TFM endpoints are reports by multiple FDA Stakeholders that the most frequently utilized positive control, Hibiclens (4% CHG), frequently is unable to achieve prescribed TFM bacterial log reductions, particularly on groin sites. In fact, within the last three NDA submissions (NDA \_\_\_\_\_, NDA 21-586, NDA 21-524), in which the Applicant performed *in vivo* efficacy studies to support the patient preoperative skin preparation, the Hibiclens positive control arm failed to meet the TFM mean 3 log<sub>10</sub> groin standard in six of eight studies. In only three of the same studies did the test product also fail to meet the standard. The findings for Hibiclens are unexpected and difficult to interpret; however, potential reasons for these findings include: (1) the positive control did not yield expected results because the study was not conducted according to protocol specified and accepted methods, (2) that the positive control product used was not in actuality 4% CHG, (3) current study designs and methods (study population utilized, method of application, method of dilution and neutralization, plating methods, etc.) differ substantially from those used in the original Application for Hibiclens (NDA 17-768) and Hibiclens can not reliably meet the groin standard using current designs/methods. Pending resolution of this issue it may be prudent to utilize an alternate positive control in studies of this type; addition of a negative control arm would also seem prudent.

#### Demonstration of Activity of Each Active Component in Combination Drug Products

Since Chlorascrub™ is a combination drug product (3.15% CHG and 70% isopropyl alcohol) it was necessary for the Applicant to demonstrate the contribution of both of the active components to the overall efficacy of the product. To fulfill this requirement a third study arm, 70% isopropyl alcohol, and an additional endpoint requirement, the demonstration that the Chlorascrub arm provided a statistically significant greater mean log reductions (at any timepoint) than the 70% isopropyl alcohol arm, was incorporated into each of the three pivotal *in vivo* efficacy studies. Of note, in the case of CHG and 70% isopropyl alcohol topical antiseptic products, a precedent to accept a successful demonstration of this endpoint as evidence of the contribution of each active ingredient was established by the approval of NDA 20-832, ChloroPrep (2% CHG and 70% isopropyl alcohol).

**Efficacy Results**

<b>Summary of Log Reduction of Bacterial Counts (CFU/cm<sup>2</sup>) For Chlorascrub, 70% Isopropyl Alcohol, and Hibiclens -Treated Sites (Efficacy-Evaluable Population)</b>			
	<b>Treatment Groups</b>		
	<b>Chlorascrub™</b>	<b>70% Isopropyl Alcohol</b>	<b>Hibiclens</b>
<b>SLM-SC-03</b>			
<b>Forearm (Swabs applied back and forth manner to 2.5 x 2.5 inch area)</b>			
Mean Log Reduction at 30 Seconds	2.64	2.65	2.69
<b>Abdomen (Maxi Swabstick applied back and forth manner to 7 x7 inch area)</b>			
Mean Log Reduction at 10 Minutes	2.72	2.44	2.08
Mean Log Reduction at 6 Hours	2.70	2.38	2.55
Mean Log Reduction at 24 Hours	2.96*	2.36*	2.47
<b>Groin (Swabstick applied back and forth manner to 4 x 4 inch area)</b>			
Mean Log Reduction at 10 Minutes	3.32	2.97	<del>2.46</del>
Mean Log Reduction at 6 Hours	3.01	2.66	2.70
Mean Log Reduction at 24 Hours	3.50*	1.78*	2.78
<b>SLM-SC-04</b>			
<b>Forearm (Swab applied back and forth manner to 2.5 x 2.5 inch area)</b>			
Mean Log Reduction at 30 Seconds	2.02	1.92	2.04
<b>Abdomen (Swabstick applied back and forth manner to 4 x 4 inch area)</b>			
Mean Log Reduction at 10 Minutes	2.22	2.29	1.99
Mean Log Reduction at 6 Hours	2.37	2.53	2.44
Mean Log Reduction at 24 Hours	2.53	2.17	2.13
<b>Groin (Maxi Swabstick applied back and forth manner to 7 x 7 inch area)</b>			
Mean Log Reduction at 10 Minutes	<del>2.28</del>	<del>2.18</del>	<del>2.46</del>
Mean Log Reduction at 6 Hours	2.68	2.61	2.70
Mean Log Reduction at 24 Hours	3.09*	1.75*	2.78
<b>SLM-SC-08</b>			
<b>Groin (Maxi Swabstick applied vigorously in a rapid back and forth manner to 3 x 7.5 inch area)</b>			
Mean Log Reduction at 10 Minutes	3.77	3.48	<del>2.89</del>
Mean Log Reduction at 6 Hours	4.01*	2.78*	3.34
Mean Log Reduction at 24 Hours	4.24*	2.57*	3.68

\* Statistically significant (p<0.05) difference between Chlorascrub and 70% Isopropyl Alcohol post- preparation log counts based on paired t-test (2-tailed).

Mean Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.

Shaded areas = those results that were considered by this Reviewer to not meet TFM requirements

## Safety Results

Chlorascrub™ has an irritancy potential equivalent to that of the positive control when applied repeatedly under occlusive dressings during irritancy testing. In the population tested, Chlorascrub™ did not demonstrate a significant sensitization potential. In the pivotal *in vivo* efficacy studies, at exposures which most closely mimic the exposure that is expected when used as a patient preoperative or preinjection skin preparation product, rates of skin reactions were similar to historical rates that were observed with ChloroPrep, NDA 20-832 (2% chlorhexidine gluconate, 70% v/v isopropyl alcohol). Rates of mild skin reactions in SLM-SC-08 were somewhat higher than those observed in SLM-SC-03 or SLM-SC-04, which the investigator attributed to the method of application (vigorous back and forth motion).

## Conclusions

### Patient Preinjection Skin Preparation Indication

The Applicant has provided data from two independent studies (SLM-SC-03, SLM-SC-04) that demonstrates that the Chlorascrub™ Swab provides a  $\geq$  mean 1 log<sub>10</sub> reduction in bacterial counts from baseline on a “dry” site of 2.5 x 2.5 inches within 30 seconds of product application. Given that larger volumes of the same product (3.15% chlorhexidine gluconate and 70% v/v isopropyl alcohol) are available in the Chlorascrub™ Swabstick and the Chlorascrub™ Maxi Swabstick it is reasonable to assume that they would also provide adequate reductions in bacterial counts on the skin for this indication.

### Patient Preoperative Skin Preparation Indication

The Applicant has provided data from two independent studies that demonstrates that the Chlorascrub™ Maxi Swabstick (SLM-SC-03) and the Chlorascrub™ Swabstick (SLM-SC-04) provide a  $\geq$  mean 2 log<sub>10</sub> reduction in bacterial counts from baseline on a “dry” site (abdomen) 10 minutes after site preparation. In addition, mean bacterial counts remained below baseline counts for six hours.

The Applicant has provided data from two independent studies that demonstrates that the Chlorascrub™ Maxi Swabstick (SLM-SC-08) and the Chlorascrub™ Swabstick (SLM-SC-03) provide a  $\geq$  mean 3 log<sub>10</sub> reduction in bacterial counts from baseline on a “wet” site (groin) 10 minutes after site preparation. In addition, mean bacterial counts remained below baseline counts for six hours.

Of note the protocol specified positive control, Hibiclens, did not provide a  $\geq$  mean 3 log<sub>10</sub> reduction in bacterial counts from baseline on the “wet” site (groin) 10 minutes after site preparation in SLM-SC-03, SLM-SC-04, or SLM-SC-08. The incorporation of a third study arm, 70% isopropyl alcohol in these studies, however, provides additional important data (beyond that addressing the combination issue). Since 70% isopropyl alcohol is considered to be a Category I product (generally recognized as

safe and effective) for the patient preoperative skin preparation indication, it may also, in essence, be considered a second positive control arm in these studies. As both positive control arms (Hibiclens and 70% isopropyl alcohol) in SLM-SC-04 failed to achieve a  $\geq$  mean 3 log<sub>10</sub> reduction in bacterial counts from baseline on a “wet” site (groin) 10 minutes after site preparation, it is reasonable to consider data for the “wet” site portion of this study to be invalid. In studies SLM-SC-03 and SLM-SC-08, while Hibiclens failed to achieve a  $\geq$  mean 3 log<sub>10</sub> reduction in bacterial counts on a “wet” site (groin) 10 minutes after site preparation from baseline, 70% isopropyl alcohol did so; therefore, this Medical Officer considers these studies to be valid and to support the efficacy of the test product.

Demonstration of Contribution of Both Active Ingredients (3.15% chlorhexidine gluconate and 70% isopropyl alcohol)

The Applicant has provided data from multiple independent studies that demonstrates that at the 6 hour (SLM-SC-08) and/or 24 hour (SLM-SC-03, SLM-SC-08) time points that the Chlorasrub arm provides a statistically significant greater mean log reduction than the 70% isopropyl alcohol arm. This finding is consistent with what is believed about the mechanisms of action of the individual components; 70% isopropyl alcohol provides an immediate reduction in bacterial counts on the skin and chlorhexidine gluconate provides both an early reduction and more persistent effect. While the clinical utility of a persistently greater mean log reduction with this combination product or that of others that are similar has not been demonstrated, a precedent to accept a successful demonstration of this endpoint as evidence of the contribution of each active ingredient was established by the approval of NDA 20-832, ChloraPrep (2% CHG and 70% isopropyl alcohol).

Safety

The Applicant has demonstrated that Chlorasrub™ is safe for the intended single use indications that they seek. As efficacy appeared to be impacted by the method of application in at least one study (SLM-SC-08) it would seem reasonable to provide use instructions consistent with the method of application in this study (i.e., vigorous back and forth scrub technique); however, end users should be cautioned about use of excessive force during application that may result in damage to skin as the impact of such damage on rates of post-operative infection is unknown.

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/s/  
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## CLINICAL REVIEW

Application Type	NDA
Submission Number	21-524
Submission Code	N-000
Letter Date	July 26, 2004
Stamp Date	August 5, 2004
PDUFA Goal Date	June 5, 2005
Reviewer Name	David Bostwick
Review Completion Date	January 14, 2005
Established Name	Chlorhexidine gluconate 3.15% and 70% (v/v) isopropyl alcohol
(Proposed) Trade Name	Chlorascrub <sup>TM</sup> Swabstick, Maxi Swabstick and Swab
Therapeutic Class	Topical antiseptic
Applicant	Les Enterprises SoluMed Inc.
Priority Designation	S
Formulation	Swab impregnated with 3.15% chlorhexidine gluconate and 70% (V/V) isopropyl alcohol
Dosing Regimen	Topical
Indication	Patient preoperative and preinjection skin preparation
Intended Population	Pediatric $\geq 2$ months of age and adult patients



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## **1. EXECUTIVE SUMMARY**

### **1.1. Recommendation on Regulatory Action**

From a clinical perspective, this application may be approved for the single use indications patient preoperative skin preparation and patient preinjection skin preparation. The applicant has provided data that supports the conclusion that use of the product results in decreased bacterial counts on the skin, and that both active ingredients (chlorhexidine gluconate and isopropyl alcohol) make contributions to the antibacterial effect of the final dosage form. As is the case with other products of this type, there is no direct evidence that supports the conclusion that use of this product reduces the incidence of postoperative infection. This product should be distributed only to healthcare settings for use by healthcare professionals as inappropriate use may result in serious adverse events involving the skin, eyes, ears or mucous membranes.

### **1.2. Recommendation on Postmarketing Actions**

#### **1.2.1. Risk Management Activity**

No post-marketing risk management activities are indicated.

#### **1.2.2. Required Phase 4 Commitments**

From a clinical standpoint, no Phase 4 commitments are indicated.

#### **1.2.3. Other Phase 4 Requests**

From a clinical standpoint, no Phase 4 requests are indicated.

### **1.3. Summary of Clinical Findings**

#### **1.3.1. Brief Overview of Clinical Program**

Chlorascrub Swabsticks, Maxi Swabsticks and Swabs contain from 1.0 mL (Swabs) to 5.1 mL (Maxi Swabsticks) of a solution containing 3.15% chlorhexidine gluconate (CHG) and 70% v/v isopropyl alcohol (IPA). The Swabsticks and Maxi Swabsticks are intended for use as both patient preoperative skin preparations and patient preinjection skin preparations, while the Swabs are to be used for patient preinjection skin preparation only. The route of administration is topical. The proposed product was studied in adults aged 18 to 70 years.

A total of 574 subjects enrolled in eight trials were evaluated for safety. This included 256 subjects enrolled in the three pivotal efficacy trials, 241 patients enrolled in two safety trials, and 77 subjects enrolled in three pilot trials designed to evaluate the efficacy trial protocols. There were no other pertinent clinical data sources.

### 1.3.2. Efficacy

Protocols [redacted] 020509-103 [redacted] [redacted] 01-108607-11 [redacted] and 521-102 [redacted] are all Phase 3, pivotal efficacy studies comparing Chlorascrub, IPA alone and Hibiclens (4% CHG).

Chlorascrub fulfills the efficacy criteria outlined in the FDA Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products published in the June 17, 1994 Federal Register for patient preoperative skin preparations and patient preinjection skin preparations. Chlorascrub demonstrates reproducible mean 3 log<sub>10</sub> and 2 log<sub>10</sub> reductions in bacterial counts at inguinal and abdominal test sites, respectively, at 10 minutes after prepping with sustained responses below baseline bacterial counts at six hours. Two of the three efficacy studies performed at the inguinal anatomic site [redacted] met the TFM criteria for a patient preoperative skin preparation. Both of the efficacy studies performed at the abdominal anatomic site [redacted] and [redacted] met the TFM criteria for this indication.

Additionally, the data provide evidence that both active ingredients contributed to the overall effect of the product. In the [redacted] study, Chlorascrub suppressed regrowth of bacteria statistically significantly better than IPA alone at 24 hours. In the [redacted] study, Chlorascrub bacterial reductions were statistically significantly better than IPA alone 6 hours and 24 hours after prepping.

Finally, Chlorascrub fulfilled the requirements in the TFM for patient preinjection skin preparations by producing reproducible mean one log reductions at a forearm test site at 30 seconds after prepping. In the [redacted] study, Chlorascrub bacterial reductions were significantly better than 70% IPA alone at 24 hours, though this difference is not clinically meaningful in light of the intended preinjection usage.

The [redacted] studies have nearly identical study designs. They were intended to establish effectiveness for both the patient preoperative skin preparation and patient preinjection skin preparation indications. The products tested were Chlorascrub, 70% IPA and Hibiclens. The products were applied according to manufacturer's instructions. The study subjects were randomized. Neither the on-site investigators/technicians nor the study subjects were blinded to treatment during the course of these studies due to differences in the physical appearance and application procedures of treatments. The microbiologists and laboratory technicians who plated the site cultures and assessed for bacterial growth were blinded to treatment assignment. Bacterial samples were taken for counts 30 seconds, 10 minutes, 6 hours and 24 hours after prepping.

The [redacted] study differed in that only the groin test site (rather than abdomen, groin and forearm) was studied, and bacterial samples were not taken 10 seconds after prepping. In the [redacted] study, all 3 test preparations (Chlorascrub, 70% IPA, Hibiclens) met the TFM requirement of a mean 2 log reduction in bacteria at the abdominal site. Bacterial counts did not rise above baseline 6 hours after prepping. At the groin site, Chlorascrub and 70% IPA met the TFM standard of a mean 3 log reduction in bacteria with counts staying below baseline 6 hours after prepping. Hibiclens did not achieve the TFM standard at the groin site. Additionally, all 3 test preparations (Chlorascrub, 70% IPA, Hibiclens) met the TFM requirement for a patient preinjection skin preparation of a mean one log reduction in bacteria at the forearm site. Please see the tables below for details. The [redacted] study is also designated as Study SLM-SC-03 by the applicant.

Table 1. [redacted] Pivotal Efficacy Results: Forearm.  
[SLM-SC-03 [redacted] STUDY No. #020509-103]]  
Summary of Analysis on the Forearm

Test Article	Mean Log <sub>10</sub> Reductions from Baseline	
	30 Seconds	24 hours
Chlorascrub™	2.64 (N=41)	2.49 (N=41)
70% Isopropyl alcohol	2.65 (N=41)	2.32 (N=41)
Hibiclens®	2.69 (N=38)	2.35 (N=38)

N=Number of sites

Table 2. [redacted] Pivotal Efficacy Results: Abdomen  
[SLM-SC-03 [redacted] STUDY No. #020509-103]]  
Summary of Analysis on the Abdomen

Test Articles	Mean Log <sub>10</sub> Reductions from Baseline			
	30 seconds	10 minutes	6 hours	24 hours
Chlorascrub™	2.65 (N=40)	2.72 (N=40)	2.70 (N=40)	2.96 (N=40)*
70% Isopropyl alcohol	2.59 (N=42)	2.44 (N=42)	2.38 (N=42)	2.36 (N=42)
Hibiclens®	2.30 (N=40)	2.08 (N=40)	2.55 (N=40)	2.47 (N=40)

\*Reduction [from baseline] by Chlorascrub™ significantly greater than 70% IPA (p≤ 0.05)

Table 3. Pivotal Efficacy Results: Groin  
[SLM-SC-03 STUDY No. #020509-103]  
Summary of Analysis on the Groin

Test Articles	Mean Log <sub>10</sub> Reductions from Baseline			
	30 seconds	10 minutes	6 hours	24 hours
Chlorascrub™	2.89 (N=39)	3.32 (N=41)	3.01 (N=42)	3.50 (N=40)*
70% Isopropyl alcohol	2.71 (N=38)	2.97 (N=39)	2.66 (N=39)	1.78 (N=37)
Hibiclens®	2.33 (N=38)	2.46 (N=39)	2.70 (N=40)	2.78 (N=38)

\* Reduction [from baseline] by Chlorascrub™ significantly greater than 70% IPA (p≤ 0.05)

In the study, all 3 test preparations met the TFM requirement at the abdominal site. However, none of the test products met the TFM requirement of a mean 3 log reduction at the groin 10 minutes after prepping. The 3 test preparations did meet the requirement for a patient injection skin preparation. Please see the tables below for details. The study is also designated as Study SLM-SC-04 by the applicant.

Table 4. Pivotal Efficacy Results: Forearm  
[SLM-SC-04 ( STUDY NO. 01-108607-11)]  
Summary of Analysis on the Forearm

Test Article	Mean Log <sub>10</sub> Reductions from Baseline	
	30 Seconds	24 hours
Chlorascrub™	2.02 (N=33)	2.23 (N=33)*
70% Isopropyl alcohol	1.92 (N=32)	1.76 (N=31)
Hibiclens®	2.04 (N=32)	2.33 (N=30)

\*Chlorascrub demonstrated significantly greater antimicrobial activity than 70% IPA (p≤ 0.05).

Table 5. Pivotal Efficacy Results: Abdomen  
[SLM-SC-04 STUDY NO. 01-108607-11)]  
Summary of Analysis on the Abdomen

Test Articles	Mean Log <sub>10</sub> Reductions from Baseline			
	30 seconds	10 minutes	6 hours	24 hours
Chlorascrub	2.37 (N=42)	2.22 (N=42)	2.37 (N=42)	2.53 (N=42)
70% Isopropyl alcohol	2.08 (N=40)	2.29 (N=40)	2.53 (N=40)	2.17 (N=39)
Hibiclens	1.98 (N=35)	1.99 (N=35)	2.44 (N=35)	2.13 (N=34)

Table 6. Pivotal Efficacy Results: Groin  
SLM-SC-04 (STUDY NO. 01-108607-11)]  
Summary of Analysis on the Groin

Test Articles	Mean Log <sub>10</sub> Reductions from Baseline			
	30 seconds	10 minutes	6 hours	24 hours
Chlorascrub	2.06 (N=36)	2.28 (N=38)	2.68 (N=39)	3.09 (N=39)
70% Isopropyl alcohol	2.35 (N=41)	2.18 (N=43)	2.61 (N=40)	1.75 (N=36)
Hibiclens	1.38 (N=42)	1.22 (N=39)	1.97 (N=38)	2.40 (N=29)

Following these results, some exploratory work was performed to determine whether the conditions of application should be varied. It was determined that the area of application used at the groin site in the study was 7x7 inches, which may have been larger than appropriate for the amount of product available. Therefore, when the third study was performed, a treatment area of 3x7.5 inches was used. In the study, both Chlorascrub and 70% IPA met the TFM requirement at the groin, though Hibiclens did not. Please see the table below for details. The study is also designated as Study SLM-SC-08 by the applicant. In all cases, N=41 for this study.

Table 7. Pivotal Efficacy Results: Groin  
SLM-SC-08 (STUDY NO. 521-102)]  
Summary of Analysis on the Groin

Product	Mean Log <sub>10</sub> Reductions from Baseline		
	10 Minutes	6 hours	24 hours
Chlorascrub™	3.77*	4.01**	4.24**
70% IPA	3.48	2.78	2.57
Hibiclens®	2.89	3.34	3.68

\*Reduction (from baseline) significantly greater than Hibiclens (p ≤0.05)

\*\*Reduction (from baseline) significantly greater than 70% IPA and Hibiclens (p ≤0.05)

The following table lists the efficacy studies (pivotal and exploratory) which were performed in support of this NDA.

Table 8. Table of Controlled Efficacy Studies

Protocol No.	Protocol Title	Subject			Demographics
		Planned	Enrolled	Withdraw	
020509-103 (SLM-SC-03)	Evaluation and Comparison of the Immediate and Persistent Antimicrobial Activity of One Test Product (CHG+IPA), The Active Vehicle (IPA), and a Reference Product (Hibiclens )	161	86	2	F – 19 M – 65 Median Age - 32
Study No. 01-108607-11 (SLM-SC-04)	Evaluating a Topical Antiseptic to be Used as a Patient Preinjection, and a Patient Preoperative Preparation	101	100	1	F - 72 M – 28 Median Age – 53
Study No. 521-102 (SLM-SC-08)	Evaluation of the Antimicrobial Efficacy of Maxi Swabsticks, Vehicle Maxi Swabsticks, and Hibiclens® Preoperative Skin Preparations	79	70	0	F – 44 M – 26 Median Age - 38
No. 03-121990-106 (SLM-SC-05)	Screening Study for Evaluating a Topical Antiseptic Formulation as a Patient Preoperative skin Preparation	32	32	9	Not available
Study # 020105-103	Evaluation and Comparison of Three Application Procedures Using Two Configurations of a Preoperative Skin Preparation	14	14	0	Not available

Project No. 521-101 SLM-SC-07	Evaluation of the Antimicrobial Efficacy of a 3.15% Chlorhexidine gluconate in 70% isopropyl alcohol Preoperative Skin Preparation	37	31	1	M-15 F-22 Median Age-43
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There was also one uncontrolled study in 6 subjects, — Study No. 020208-103, “R&D Evaluation and Comparison of the Antimicrobial Efficacy of a Preoperative Skin Preparation Applied in Three Different Configurations”.

### 1.3.3. Safety

Safety for the use of Chlorascrub as a single use preparation has been established by the following:

- A predictive irritancy study in humans
- A predictive sensitization study in humans
- Adverse event reports

There are no unresolved safety issues. The safety testing of Chlorascrub Swabsticks, Maxi Swabsticks and Swabs for the proposed indications of patient preoperative skin preparation and patient preinjection is adequate. There were no serious or severe adverse events attributed to study drug, deaths, or overdosage exposures.

In the predictive irritancy study, study products were applied continuously and repeatedly under occlusive and semi-occlusive dressings for 14 days. The results indicated that Chlorascrub has a high potential for irritation when tested under standard procedures. Since Chlorascrub is intended for one-time use only, its potential to produce cumulative irritation does not disqualify it from approval.

In the sensitization study, test products were applied intermittently for 3 weeks. A two week rest period (no drug application) was observed, followed by challenge of the subject at a naïve (previously unpatched) test site. The results indicate that Chlorascrub did not exhibit the potential to cause sensitization reactions.

In the safety studies described above, 35 subjects in the irritation study and 250 subjects in the sensitization study were enrolled. Of these, 241 received the study medications. In the irritation study, 8 subjects reported a total of 12 adverse events. None were evaluated as related to study medication by the investigator, though in the opinion of the reviewers, one of these events (ringworm-like rash) could possibly have been an allergic reaction.

In the sensitization study, 75 adverse events were reported in 57 patients, 14 of which were classified as severe. None of the events was evaluated as related to study medication by the

investigator, though one event was an anaphylactic event. The investigator stated that this reaction was caused by shellfish ingestion, though no evidence of this is presented.

There were no adverse events reported in 5 of the 7 controlled efficacy studies. There were 9 adverse events reported in the \_\_\_\_\_ pivotal efficacy study. Seven of the 9 events were erythema attributed to the dressing or tape used during the study. In the \_\_\_\_\_ pivotal efficacy study, mild skin irritation was seen on 22 occasions in 15 subjects. Since the irritation was seen with equal frequency in the Chlorascrub and IPA test areas, the sponsor attributes this to more vigorous scrubbing than was used in the other studies.

Currently, there is no evidence to suggest drug-demographic interactions, drug-disease interactions, drug-drug interactions, withdrawal phenomena or abuse potential with single use of the product.

Recommended warnings include the following:

- Avoid contact with eyes, ears, and mucous membranes, due to concerns with potential for development of corneal opacification, deafness, and severe irritation, respectively.
- Do not use in contact with meninges, due to concerns for potential nerve toxicity.
- Do not use in infants <2 months of age, due to concerns for increased absorption and severe irritation.

#### 1.3.4. Dosing Regimen and Administration

This product is intended for one time use only, which is consistent with the intended uses and safety profile seen in the human irritancy test. The use instructions for the three dosage forms are:

i. Swab



ii. Swabstick

- Prior to surgery, injection, \_\_\_\_\_ apply Chlorascrub Swabstick to the procedure site.
- Place one flat side of foam tip to the proposed skin site and prep the skin in vigorous back and forth repeated strokes for one minute.
- Turn the swabstick over (unused side of foam tip) and repeat the procedure by prepping for one minute.
- Allow the prepped area to air dry for one and one half minutes.
- Do not blot or wipe dry.
- Maximum area to be treated with one swabstick is approximately 4 x 4 inches (10 x 10 cm) for both wet and dry surgical sites.

- Discard after single use.

iii. Maxi Swabstick

The instructions for the Maxi Swabstick are the same as for the Swabstick with the exception that the maximum treatment areas are 7 x 7 inches (18 x 18 cm) for dry surgical sites and 3 x 7.5 inches (7.5 x 19 cm) for moist surgical sites.

These directions are the same instructions as were used in the pivotal studies.

### 1.3.5. Drug-Drug Interactions

There are no drug-drug interactions that affect the product's clinical use.

### 1.3.6. Special Populations

No special population studies were performed to support this NDA, nor are any necessary. The activity of the product (reduction of skin bacteria) is not affected by such variables as age, sex, ethnicity, etc. However, due to the high irritancy potential of the product, caution should be exercised in its use in infants. The applicant states in the labeling that the product may be used in children 2 months of age and older. A waiver for studies in children less than 2 months of age has been requested.

These actions are consistent with those taken for other products which contain CHG and 70% IPA in combination, and they are acceptable.

**APPEARS THIS WAY  
ON ORIGINAL**

## **2. INTRODUCTION AND BACKGROUND**

### **2.1. PRODUCT INFORMATION**

#### **2.1.1. Description of the Product**

The product is a topical liquid antiseptic containing 3.15% chlorhexidine gluconate (CHG) and 70% w/w isopropyl alcohol (IPA). It is packaged in three configurations: swabs containing 1.0 mL of the product, swabsticks containing 1.6 mL of the product, and “maxi” swabsticks containing 5.1 mL of the product.

#### **2.1.2. Established Drug Name**

Chlorhexidine gluconate 3.15% (w/v) with isopropyl alcohol 70% (v/v) solution.

#### **2.1.3. Proposed Trade Name**

Chlorascrub Swabs, Swabsticks and Maxi Swabsticks. The product was formerly named “SoluPrep” and that name appears in some summaries. Chlorascrub and SoluPrep are the same product.

#### **2.1.4. Chemical Class**

This is a combination of previously approved active ingredients. Other products containing this combination of active ingredients are available, but they do not contain this amount of CHG.

#### **2.1.5. Pharmacological Class**

This product is a topical antiseptic.

#### **2.1.6. Proposed Indications, Dosing Regimen, Age Groups**

The product is to be used as a patient preoperative skin preparation and/or patient preinjection skin preparation in patients 2 months of age or older. The dose will vary depending on the area of skin to be prepared.

## **2.2. Currently Available Treatment for Indications**

There are many preparations approved for the same indications as are proposed for Chlorascrub. A complete list will not be given here. Some representative information:

- isopropyl alcohol 70-91.3% by volume is classified as a Category I product (i.e., recognized as safe and effective) for both Chlorascrub indications in the Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products published June 17, 1994.
- 2% CHG plus 70% IPA are the active ingredients in ChloroPrep Antiseptic (NDA 20-832), which is also approved for the Chlorascrub indications.
- A number of products containing CHG alone have been approved through the NDA process as patient preoperative skin preparations, though none contain 3% CHG. Examples are NDA 17-768, Hibiclens (4% CHG) and NDA 19-422, Exidine (2% CHG).

### **2.3. Availability of Proposed Active Ingredient in the United States**

Both actives are freely available in this country.

### **2.4. Important Issues With Pharmacologically Related Products**

None.

### **2.5. Presubmission Regulatory Activity**

There has been extensive regulatory activity concerning this product. The following summary is not exhaustive, but does present the most relevant information concerning the product up to submission of the NDA.

- a. August 12, 1998. Pre-IND submission.
- b. October 27, 1998. Division response to Pre-IND submission.
- c. December 5, 1999. IND 59, 446 (subject of this NDA) submitted.
- d. January 11, 2000. Meeting between sponsor and representatives of the Division of Anti-infective Drug Products (HFD-520) and Division of Over-the-Counter Drug Products (HFD-560) to discuss development plans. At that time the sponsor was interested in pursuing a \_\_\_\_\_ indication.
- e. July 7 and August 1, 2000. Sponsor requested Fast Track designation for \_\_\_\_\_ indication on the basis that reduction of bacteria on the skin helps prevent \_\_\_\_\_ related \_\_\_\_\_ Submission also included numerous other questions.
- f. October 13, 2000. Division response to July and August questions. Fast Track designation not granted.
- g. March 11, 2002. Pre-NDA meeting with the sponsor and representatives of HFD-520 and HFD-560. The sponsor had dropped the \_\_\_\_\_ indication at this point.
- h. May 7, 2003. Meeting between sponsor and representatives of HFD-520 concerning chemistry.
- i. November 19, 2003. Teleconference between sponsor and representatives of HFD-520 concerning the fact that one of the two pivotal studies (\_\_\_\_\_) did not provide satisfactory results at the groin site. It was agreed that another study at the groin site only was necessary.

Clinical Review  
David Bostwick  
NDA 21-524  
Chlorax

j.



k. July 26, 2004. NDA 21-524 submitted.

## **2.6. Other Relevant Background Information**

None.

## **3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1. CMC (and Product Microbiology, if Applicable)**

The chemistry review is not yet available. In her preliminary review of the microbiology data, Dr. Connie Mahon finds that the applicant has submitted susceptibility results on some of the species listed in the TFM with fewer isolates than are normally required. However, the MIC results provided are comparable to those previously reported for this type of product.

### **3.2. Animal Pharmacology/Toxicology**

In her review dated March 16, 2005, Dr. Amy Ellis stated that she has no objection to the approval of this NDA.

## **4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1. Sources of Clinical Data**

The trials submitted with the NDA (see following table) were the principal data source for this review. The Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products was also consulted.

### **4.2. Tables of Clinical Studies**

The following tables are adapted from tables provided by the applicant.

Table 1. Required Human Safety Studies

Protocol No.	Principal Endpoint	Facility	Study Design	Comparators	No. Subjects	Duration
No. 01-108088-76 (SLM-SC-01)	Cumulative Irritancy	—	Double-blind, Randomized, occluded and semi occluded	Betadine, 70% IPA, Hibiclens, SLS, Saline	31	14 Days
No. 01-105168-76 (SLM-SC-02)	Sensitization	—	Double-blind, Randomized, occluded and semi occluded	Saline	210	3 week induction followed by challenge at 2 weeks

Table 2. Pivotal Efficacy Studies

Protocol No.	Indication Studied	Facility	Study Design	Comparators	No. Subjects	Duration
No. 020509-103 (SLM-SC-03)	Patient Preop, Preinjection	—	Block - randomized, laboratory blinded	70% IPA, Hibiclens	86	24 hrs.
No. 01-108607-11 (SLM-SC-04)	Patient Preop, Preinjection	—	Block - randomized, laboratory blinded	70% IPA, Hibiclens	100	24 hrs.
No. 521-102 (SLM-SC-08)	Patient Preop	—	Block - randomized, laboratory blinded	70% IPA, Hibiclens	70	24 hrs.

Table 3. Supportive and Pilot Studies

Protocol No.	Purpose	Facility	Study Design	Comparators	No. Subjects
No. 03-121990-106 (SLM-SC-05)	Definition of test area (pilot)	—	Laboratory blinded	ChloraPrep (2% CHG and 70% IPA)	23
No. 521-101 (SLM-SC-07)	Comparison of Chlorascrub and ChloraPrep	—	Laboratory blinded	ChloraPrep	31
No. 020105-103	Reduction of counts at groin	—	Laboratory blinded	ChloraPrep	14
No. 020208-103	Comparison of packaging configurations	—	Open	None	6

Two other studies were submitted with the NDA which will not be reviewed because they do not add any relevant information concerning the safety and efficacy of the drug. They are:

- a. Evaluation of Primary Irritation Potential in Humans (Three 24-Hour Applications). \_\_\_\_\_ Study No. 01-108751-76. The cumulative irritancy study (\_\_\_\_\_ No. 01-108088-76) is the standard protocol for human irritancy testing.
- b. Two-Phase Pilot Determination of the Antimicrobial Efficacy of One Alcohol /2% Chlorhexidine Gluconate Formulation. \_\_\_\_\_ Study No. 000619-103. This study concerns a formulation which is different from the Chlorascrub product.

### 4.3. Review Strategy

Data from nine studies were reviewed. As noted above, two studies primarily concerned safety, three pivotal studies were necessary, and four pilot studies were included. Literature was not relied upon for safety or efficacy evaluations.

### 4.4. Data Quality and Integrity

Division of Scientific Investigations audits were requested for \_\_\_\_\_  
\_\_\_\_\_ Results of these investigations are pending.

Because there were so few evaluable patients, the clinical source data for each evaluable patient in the pivotal studies was individually evaluated for outcome and accuracy.

### 4.5. Compliance with Good Clinical Practices

Informed consent was adequate for all submitted studies. Based on documentation submitted with the NDA, all studies were apparently congruent with good clinical practices.

#### 4.5.1. Protocol deviations noted in the pivotal studies

- a. \_\_\_\_\_ study.
  - i. There were 21 randomization deviations. Typically, this involved a switch of products. For example, product A was to be applied to the right side of the body, while product B was to be applied to the left side. The technician erred in switching body sides. Other errors occurred when designated time sampling sites were reversed (e.g, site 1 was designated as the baseline test and site 2 was for 24 hours, but they were reversed by the technician). The test facility states that all errors were accounted for in the data analysis.
  - ii. There was no incubator in/out log made for one of the test days.
  - iii. A technician error resulted in the listing of two diluents (rather than one) on the media tracking sheet.

- b.            Study
- i. There were 7 randomization deviations as described above for the            study.
  - ii. For 12 subjects, the 24 hour sample was taken later than recommended in the protocol (from 16-30 minutes late).
  - iii. For 7 subjects, plating time for one site or sampling time was not recorded.
  - iv. One subject showered 37½ hours prior to baseline sample, while the protocol prohibited showering for 48 hours prior to this sample.
- c.            study
- For one subject, the 6 hour samples were taken at 6 hours, 54 minutes.

**Reviewer's Comment:** The procedures used for handling the data errors were adequate. The minor errors in sampling times should not materially affect study outcomes.

#### **4.6. Financial Disclosures**

The Financial Disclosure form is adequate.

### **5. CLINICAL PHARMACOLOGY**

This review is not yet available.

#### **5.1. Pharmacokinetics**

Please see above.

#### **5.2. Pharmacodynamics**

Please see above.

#### **5.3. Exposure-Response Relationships**

Please see above.

### **6. INTEGRATED REVIEW OF EFFICACY**

#### **6.1. Indication**

The indications sought for this product are patient preoperative skin preparation (preop) and patient preinjection skin preparation (preinjection).

### 6.1.1. Methods

Three pivotal efficacy studies support the efficacy of Chlorascrub for these indications. They are:

- a. Study — no. 020509-103 (SLM-SC-03), performed by — (preop and preinjection).
- b. Study — no. 01-108607-11 (SLM-SC-04), performed by — (preop and preinjection).
- c. Study — no. 521-102 (SLM-SC-08), performed by — (preop at the groin test site).

### 6.1.2. General Discussion of Endpoints

The study endpoints were taken from the FDA Proposed 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. For a preop, the TFM requires a mean 2 log<sub>10</sub> reduction in bacterial counts from baseline on the abdominal sites and a mean 3 log<sub>10</sub> reduction in bacterial counts from baseline on the inguinal sites 10 minutes after preparation. In addition, the TFM also requires that the mean microbial counts on the abdominal and inguinal sites remain below baseline counts for six hours.

For preinjection, the TFM requires a mean one log<sub>10</sub> reduction in bacterial counts at a “dry” test site (in this case the forearm) within 30 seconds of product use. Additionally, it is necessary that the efficacy testing procedures demonstrate the contribution of both active ingredients (CHG and IPA) to the total effect of the product. In the case of CHG/IPA combination products, the precedent set during the review of NDA 20-832, ChloroPrep (2% CHG and 70% IPA) is relevant. In that case, it was necessary that at some point in the pivotal clinical studies (though not necessarily at the same point), the CHG/IPA combination should produce a statistically significant greater reduction in baseline bacteria than 70% IPA alone.

### 6.1.3. Study Design

Concerning the issue of adequate and well-controlled studies, the pivotal studies submitted for this NDA follow the outline set forth in the TFM. As is typically the case in studies of this type, the subjects and persons performing the studies are not blinded to the identity of the test products. However, the laboratory personnel who perform the microbial counts are blinded.

The matter of a control group for studies of this type is not as critical as in most studies because a “standard” of microbial reduction must be met, rather than equivalence or superiority to another drug product. In this NDA, as in most others of this type, Hibiclens (4% CHG) has been chosen as an internal control to validate the conduct of the study. It should also be noted that IPA 70-91.3% by volume is included in the TFM as safe and effective for both preop and preinjection



Efficacy

This study determined and compared the immediate and persistent antimicrobial activity of one (1) test product (SoluPrep 3.15% CHG with 70% IPA), its active vehicle (70% IPA), and a reference product (4% CHG Hibiclens®) when used as antimicrobial skin preparations for injections and as preoperative antimicrobial skin preparations.

Safety

This study also evaluated and compared the safety of SoluPrep (3.15% CHG with 70% IPA), its active vehicle (70% IPA), and a reference product (4% CHG Hibiclens®).

Method:

1. Study design: This is a rather complex study design which compares Chlorascrub, 70% IPA (the product vehicle) and Hibiclens. Chlorascrub is packaged in 3 configurations: swabs, swabsticks and “maxi” swabsticks. The following is an outline of the dosage forms and test sites:
  - a. Swabs: forearm (median cubital site) – used for preinjection indication
  - b. Maxi swabsticks: abdominal site – used for preop indication.
  - c. Swabsticks: groin (inguinal site) – used for preop indication.
  - d. Hibiclens used at all 3 test sites.

Eighty-four subjects completed the study. The study employed methodology based on the TFM. Product applications were bilateral with two of the three test products used on each subject in random fashion.

2. Inclusion criteria: The following is taken directly from p. 33 of volume 11 of the NDA:

A sufficient number of overtly healthy human subjects of at least the age of eighteen (18) years, but not more than the age of seventy (70), will be recruited into the study to ensure that eighty-five (85) subjects complete the evaluation. All subjects will be free from dermatoses, inflammation, or injuries to the forearm, abdomen, or inguina. Insofar as possible, subjects will be of mixed age, sex, and race.

Additionally, subjects must have had the following baseline bacterial counts (at one or more of the test sites) to enter the study:

- forearm:  $\geq 2.0 \log_{10}/\text{cm}^2$
- abdomen:  $\geq 2.5 \log_{10}/\text{cm}^2$
- groin:  $\geq 4.5 \log_{10}/\text{cm}^2$

**Reviewer’s Comment: The TFM states that sites to be used for testing the preinjection indication should have baseline bacterial counts of at least 2.0  $\log_{10}/\text{cm}^2$ . There are no baseline requirements for the dry and moist sites for testing the preoperative indication, though they must obviously be high enough**

**to permit mean reductions at the 10 minute test period of 2 logs at the dry site and 3 logs at the moist site, as required by the TFM. See also section 6 below.**

3. Exclusion criteria: The following is also taken directly from p. 33 of volume 11 of the NDA:

Allergies or sensitivities to chlorhexidine gluconate or alcohols.  
Pregnant or nursing females.  
An active skin rash or break in the skin at the testing site regions.  
Contact dermatitis.  
Participation in a clinical trial within the past thirty (30) days.  
Use of any systemic or topical antibiotic medications, steroids, or any other product known to affect the normal microbial flora of the skin.  
Insulin-dependent diabetes or use of any medications that may interfere with the study.  
Compromised immunity or HIV positive.  
Mitral valve prolapse.  
Unwillingness to fulfill the requirements of the Protocol.

4. Dosage and duration of therapy:

This study was performed using a modified protocol for prep and preinjection products suggested in the TFM. Test subjects were screened for minimum bacterial counts as outlined in inclusion criteria, above. On the first test day, patients were evaluated for baseline skin irritation scores (see Safety evaluation below for scoring scales). Each test subject was assigned 2 of the 3 test materials. One material was applied to one side of the body at the selected test site and one to the other side in randomized fashion. Each treatment area (right or left) was divided into 3 or 4 subsites, 3x3 cm, for microbial sampling at baseline and 30 seconds, 10 minutes, 6 hours and 24 hours after drug application. The test sites were covered with a gauze bandage after the 10 minute sample to minimize contamination from external sources. Information concerning the microbial sampling procedure (cylinder sampling technique) may be found in the Microbiology Review for this NDA. Skin irritation was also scored at the various sampling times.

The prep procedures used were as follows (taken directly from the protocol):

**SWABS:** Remove swab from the container with sterile gloved hands, but do not unfold. Holding the swab between thumb and index finger, prep by applying the swab to the skin in a back and forth manner for 15 seconds. Allow the prepped area to air dry for 30 seconds. The total area covered should be approximately 2.5 x 2.5 inches. To assure that an area of sufficient size is available for post-treatment sampling, an adjacent area may be prepped using a second pad.

**SWABSTICKS:** Swabstick is a flat two sided device with a foam tip. Remove the Swabstick from the package wearing sterile gloved hands. Put one flat side of the foam tip onto the proposed site and prep the skin in a back and forth manner for one (1) minute, ensuring the size of the prepped area exceeds the size of the sample site and the dressing (approximately 4 x 4 inches). Turn the Swabstick over (unused side of the foam tip) and repeat the procedure by prepping for one (1) minute. Allow the prepped area to air-dry for one-and-one-half (1.5) minutes.

**MAXISWABSTICKS:** Swabstick is a flat two-sided device with a foam tip. Remove the Swabstick from the package wearing sterile gloved hands. Put one flat side of the foam tip onto the proposed site and prep the skin in a back and forth manner for one (1) minute, ensuring the size of the prepped area exceeds the size of the sample site and the dressing (approximately 7 x 7 inches). Turn the Swabsticks over (unused side of the foam tip) and repeat the procedure by prepping for one (1) minute. Allow the prepped area to air-dry for one-and-one-half (1.5) minutes.

**NOTE:** For the active vehicle (70% IPA), prep using same procedures as above. For control product (Hibiclens®), the prep procedure must follow the manufacturer's use-directions from the label.

There are no labeling instructions for Hibiclens as a preinjection preparation, since it is not approved for this use. For prep use, Hibiclens is to be applied to the surgical site and swabbed for 2 minutes. The site is to be dried with a sterile towel, and the procedure repeated.

5. Additional information: There was a 2 week washout period prior to the test during which no antimicrobial products were to be used by the test subjects. They were not to shave the test areas for 5 days prior to the test, and were not to bathe in the 48 hours before the test began.

All subjects were sampled for sufficient baseline bacteria 72 hours before the test began. A final baseline sample was taken on the day of testing. Subjects were admitted to the study only for those anatomical sites where sufficient baseline bacteria were present.

6. Effectiveness parameters: The TFM standard for preinjection preparations is a mean one  $\log_{10}$  reduction at a "dry" test site within 30 seconds of product use. The TFM standards for patient preoperative skin preparations are a mean decrease of 2 logs in the baseline microbial counts at a dry test site (abdomen) within 10 minutes of drug application, with the count not to exceed baseline for at least 6 hours. The requirement is similar for a wet test site (groin), though the 10 minute reduction is to be 3 logs, rather than 2. There is no TFM standard for microbial counts at 24 hours after drug application.
7. Safety: Adverse events were recorded and compared between the treatment groups. In addition, skin irritation was evaluated using the following scale:

Erythema	0	No reaction
	1	Mild and/or transient redness limited to sensitive area
	2	Moderate redness persisting over much of the product-exposed area
	3*	Severe redness extending over most or all of the product-exposed area
Edema	0	No reaction
	1	Mild and/or transient swelling limited to sensitive area
	2	Moderate swelling persisting over much of the product-exposed area
	3*	Severe swelling extending over most or all of the product-exposed area
Rash	0	No reaction
	1	Mild and/or transient rash limited to sensitive area
	2	Moderate rash persisting over much of the product exposed area

	3*	Severe rash extending over most or all of the product-exposed area
Dryness	0	No reaction
	1	Mild and/or transient dryness limited to sensitive area
	2	Moderate dryness persisting over much of the product-exposed area
	3*	Severe dryness extending over most or all of the product-exposed area

\* = Represents significant irritation and requires subject's removal from study.

Results:

1. Evaluability: 205 candidates were entered into the study. Of these, 161 met one or more of the baseline bacterial count screening requirements (forearm, abdomen, groin). The concept of evaluable subjects is somewhat difficult to apply to studies of this type. In general, a more relevant concept is evaluable test sites, since a subject may be evaluated at 1, 2 or 3 sites, depending on their baseline bacterial counts. Additionally, a certain number of subjects are held in reserve in case the screened subjects do not meet bacterial count requirements on the test day. These reserved subjects are used to replace the "failed" subjects. In this context, an "evaluable" subject or site is one who meets the baseline bacterial count requirement and progresses to the end of the study. Additionally, there are commonly a number of missed evaluations due to laboratory error. It is beyond the scope of this review to detail the fate of each patient/site individually, though the raw data has been checked to assure that the evaluability criteria have been met and that the data have been properly entered. The following table presents the number of test sites evaluated for each test article at each time point of the inguinal site.

Table 4. Sample Sizes by Product and Site  
Inguinal

Sample	Chlorascrub Sample Size	70% IPA Sample Size	Hibiclens Sample Size
Test Day Baseline	54	51	52
30 Seconds	39	38	38
10 Minutes	41	39	39
6 Hours	42	39	40
24 Hours	40	37	38

Sample sizes for the abdominal site at all time points were: Chlorascrub 40, 70% IPA 42, Hibiclens 40. Sample sizes for the forearm site at all time points were: Chlorascrub 41, 70% IPA 41, Hibiclens 38.

2. Demographics: There were 84 subjects who provided data from at least one test site in this study. They were 65 male and 19 female, aged 19-69 years. Eighty were Caucasian, 2 Hispanic, and 2 Native American.

3. Efficacy Results: In order to provide context for the summary data tables, this review will include the log reductions seen in individual subjects at the test sites. For this study, the log reductions at 10 minutes, 6 hours and 24 hours at the abdomen test site will be provided in this portion of the review. Reductions at the groin and forearm sites will be provided in Appendix I and II respectively. The 30 second time interval is omitted because the data are not necessary to comply with TFM requirements (the forearm site is used to support the preinjection indication). The reductions are calculated by subtracting the log count at the time point from the test day baseline count. Negative signs indicate that the log count at the time point was higher than baseline count.

Table 5. Log Reductions at Abdominal Site by Subject

Patient No.	10 Minute			6 Hours			24 Hours		
	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens
1	-	-	2.53	-	-	2.07	-	-	-1.03
13	-0.20	2.02	-	-0.37	3.68	-	1.34	3.68	-
14	2.65	-	0.89	2.65	-	2.64	2.81	-	2.04
23	2.75	-	2.90	2.75	-	2.90	2.75	-	2.90
24	-	1.81	-	-	1.40	-	-	1.95	-
25	-	3.00	3.90	-	4.35	2.92	-	2.04	3.03
26	3.57	-	1.41	3.57	-	3.40	3.23	-	3.06
29	-	2.03	0.26	-	2.51	2.79	-	2.67	-1.08
32	-	2.57	1.78	-	2.28	2.71	-	3.85	1.60
36	-	0.96	1.04	-	2.53	2.94	-	1.50	3.28
41	-	2.74	2.89	-	2.74	1.32	-	0.53	0.03
43	3.88	-	1.57	3.88	-	2.50	3.88	-	3.40
59	2.36	-	-	2.46	-	-	2.76	-	-
62	-	1.35	-	-	2.69	-	-	2.69	-
63	-	2.35	2.13	-	2.51	2.69	-	3.35	2.69
67	-	2.66	-	-	-1.04	-	-	2.02	-
76	-	0.18	-0.30	-	1.85	2.63	-	2.45	2.63
77	-	1.26	-	-	2.60	-	-	2.60	-
78	3.61	-	3.70	3.61	-	3.14	3.61	-	3.70
80	4.19	3.16	-	4.19	3.32	-	3.63	3.32	-
84	0.04	-	2.11	2.39	-	0.72	2.55	-	3.61
85	-	2.75	0.94	-	2.10	2.01	-	2.91	2.45
86	-	2.87	2.61	-	3.03	1.77	-	3.03	2.77
90	-	3.44	3.35	-	3.66	4.73	-	0.66	1.57
91	1.71	-	2.17	2.89	-	2.63	3.05	-	2.07
93	2.96	-	3.04	2.96	-	3.04	2.80	-	3.04
94	3.18	-	2.00	0.05	-	2.24	3.18	-	3.16
100	-	2.97	-	-	2.27	-	-	2.51	-

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102	-	0.10	2.56	-	1.60	2.68	-	2.61	0.22
107	-	-	-1.17	-	-	-1.09	-	-	3.11
109	-	-	3.27	-	-	2.63	-	-	3.11
111	-	0.59	2.58	-	2.01	1.77	-	0.92	2.58
113	4.07	2.61	-	3.17	2.55	-	3.91	1.96	-
115	2.76	2.95	-	2.76	3.29	-	2.60	3.29	-
117	2.51	-	-	2.51	-	-	2.35	-	-
118	3.46	-	3.49	3.46	-	2.85	2.02	-	0.73
119	4.19	-	3.56	2.52	-	3.40	3.22	-	3.56
120	2.80	-	0.53	1.77	-	1.74	2.80	-	2.80
121	3.03	2.95	-	3.03	3.29	-	3.03	3.29	-
124	4.11	3.25	-	4.11	3.25	-	3.95	0.08	-
126	3.00	-	3.24	2.12	-	3.65	3.38	-	2.68
130	2.51	2.10	-	1.08	2.45	-	2.51	3.26	-
137	3.00	3.29	-	3.00	0.25	-	0.72	3.13	-
138	3.04	2.60	-	2.48	2.14	-	3.04	2.60	-
141	-	2.17	2.95	-	0.93	2.95	-	0.65	2.95
142	2.45	2.39	-	3.09	1.37	-	3.09	-0.11	-
147	2.74	3.11	-	3.20	1.10	-	3.20	3.11	-
151	0.65	-	0.22	3.55	-	4.46	3.39	-	4.46
152	-	3.31	1.25	-	3.31	3.10	-	2.45	2.54
154	3.03	3.45	-	2.57	3.45	-	3.03	3.11	-
155	-	3.75	1.38	-	3.91	3.54	-	2.77	3.70
160	-	3.95	3.56	-	2.71	-0.04	-	3.95	3.56
161	1.12	-	1.20	2.82	-	0.93	2.34	-	1.68
162	3.39	-0.14	-	3.39	2.96	-	3.39	2.40	-
165	3.87	2.99	-	3.57	4.01	-	3.69	2.95	-
168	2.60	2.53	-	1.84	0.28	-	2.44	2.65	-
172	2.88	2.62	-	2.88	2.28	-	2.88	2.46	-
174	2.62	-	1.14	2.46	-	2.28	2.46	-	2.62
175	3.26	-	3.43	3.26	-	3.43	3.26	-	3.43
176	1.03	2.72	-	2.82	2.88	-	2.82	2.88	-
180	-	2.94	1.19	-	2.94	3.58	-	1.22	1.42
188	2.76	-	-	3.10	-	-	3.10	-	-
191	-	-	2.87	-	-	2.87	-	-	2.87
193	3.66	-	3.66	3.26	-	2.72	3.82	-	2.96
195	-	1.73	1.35	-	2.79	2.77	-	2.79	2.77
197	-	3.16	-	-	-0.44	-	-	3.16	-
205	-	3.11	-	-	2.95	-	-	1.73	-
209	0.15	-	-	-0.55	-	-	2.68	-	-
210	3.56	-	-	3.56	-	-	3.56	-	-

The following tables present the mean log reductions at the various test sites for the 3 test preparations. The reductions are calculated by subtracting the log counts found at the various time points from the test day baseline log counts.

Table 6: Mean Log Reductions at Inguinal Site

Sample	Chlorascrub	70% IPA	Hibiclens
	Mean (SD) (n)	Mean (SD) (n)	Mean (SD) (n)
Baseline Mean	5.95 (0.49) (54)	5.91 (0.53) (51)	5.91 (0.48) (52)
30 Seconds Post-Prep	2.89 (1.24) (39)	2.71 (0.89) (38)	2.33 (0.82) (38)
10 Minutes Post-Prep	3.32 (1.13) (41)	2.97 (1.04) (39)	2.46 (1.29) (39)
6 Hours Post-Prep	3.01 (1.13) (42)	2.66 (1.08) (39)	2.70 (0.85) (40)
24 Hours Post-Prep	3.50 (1.35)* (40)	1.78 (1.30)* (37)	2.78 (1.28) (38)

SD= Standard Deviation \* Significant difference between Chlorascrub and 70% IPA (p≤0.05)

Table 7: Mean Log Reductions at Abdominal Site

Sample	Chlorascrub	70% IPA	Hibiclens
	Mean (SD) (n=40)	Mean (SD) (n=42)	Mean (SD) (n=40)
Baseline Mean	3.23 (0.51)	3.14 (0.51)	3.33 (0.59)
30 Seconds Post-Prep	2.65 (1.08)	2.59 (0.99)	2.30 (1.25)
10 Minutes Post-Prep	2.72 (1.12)	2.44 (0.98)	2.08 (1.24)
6 Hours Post-Prep	2.70 (1.06)	2.38 (1.15)	2.55 (1.08)
24 Hours Post-Prep	2.96 (0.66)*	2.36 (0.98)*	2.47 (1.23)

SD= Standard Deviation \* Significant difference between Chlorascrub and 70% IPA (p≤0.05)

Table 8: Mean Log Reductions at Forearm Site

Sample	Chlorascrub	70% IPA	Hibiclens
	Mean (SD) (n=41)	Mean (SD) (n=41)	Mean (SD) (n=38)
Baseline Mean	3.22 (0.82)	3.13 (0.95)	3.21 (0.96)
30 Seconds Post-Prep	2.64 (1.17)	2.65 (1.00)	2.69 (1.03)
24 Hours Post-Prep	2.49 (1.33)	2.32 (1.21)	2.35 (1.34)

SD= Standard Deviation

**Reviewer's Comment:** This is a successful study in that it provides evidence that Chlorascrub meets the TFM requirements as a patient preoperative skin preparation and as a preinjection skin preparation. Evidence of the utility of both ingredients is provided by the greater ability of the combination to suppress bacterial growth at 24 hours.

At the inguinal site, Chlorascrub met the TFM requirement of a mean 3 log reduction in baseline bacterial counts at 10 minutes post-prep. 70% IPA alone nearly met the TFM standard, while Hibiclens failed. There was a statistically significant greater log reduction with Chlorascrub vs. 70% IPA alone in bacterial counts at 24 hours.

At the abdominal site, all 3 products met the TFM requirement of a mean 2 log reduction at 10 minutes post-prep. Again, Chlorascrub was able to suppress bacterial regrowth statistically significantly better than 70% IPA alone at 24 hours.



Are in good health, based on medical history collected on the Screening, Inclusion/Exclusion Form and Treatment Inclusion/Exclusion Form (Exhibits B1 and B2).

The same baseline bacterial counts that were necessary to enter the \_\_\_\_\_ study were necessary to enter this one.

3. Exclusion criteria: The following is taken directly from p. 90 of vol. 17 of the NDA:

An individual cannot be enrolled in the study if they:

Have been exposed to topical or systemic antimicrobials during the two-week pretest conditioning period. This restriction includes, but is not limited to, shampoos, lotions, soaps, body powders, and materials such as solvents, acids or alkalis.

Have been medically diagnosed as having a medical condition, which would preclude participation such as: diabetes, hepatitis, an organ transplant, a medical surgical implant, or an immune compromised system.

Have any medical condition, which in the opinion of the Investigator would preclude participation.

Have bathed in chemically treated pools or hot tubs two weeks prior to any microbial sampling.

Have used UV tanning lamps two weeks prior to any microbial sampling.

Have tattoos, dermatoses, abrasions, cuts, lesions, or other skin disorders on the test site.

Have bathed or showered less than 48 hours prior to any microbial sampling.

Have a known sensitivity to adhesive products, i.e., tape.

Have a known sensitivity to chlorhexidine gluconate (CHG).

Have a known sensitivity to latex products.

Have a known sensitivity to fragrances.

Are not willing to fulfill the requirements of the protocol.

4. Dosage and duration of therapy: These were the same as for the \_\_\_\_\_ study, above.

5. Additional information: This is the same as for the \_\_\_\_\_ study.

6. Effectiveness parameters: These are the same as for the \_\_\_\_\_ study.

7. Safety: Same as for the \_\_\_\_\_ study.

Results:

1. Evaluability: 137 candidates were entered into the study. Of these, 101 met one or more of the baseline bacterial count screening requirements. Please see the "Evaluability" section of the review of the \_\_\_\_\_ study for further discussion of evaluable patients and evaluable test sites.

Sample sizes for the forearm site at all time points were: Chlorascrub 33, IPA 32, and Hibiclens 32. The following table present the number of test sites evaluated for each test article at the inguinal site.

Table 9. Sample Size by Product and Site

Inguinal			
Sample	Chlorascrub Sample Size	70% IPA Sample Size	Hibiclens Sample Size
Test Day Baseline	52	55	55
30 seconds	36	41	42
10 minutes	38	43	39
6 hours	39	40	38
24 hours	39	36	29

At the abdomen site, the number of samples at all time points for Chlorascrub was 42. For 70% IPA, all sample sizes were 40, with the exception of 24 hours, where the number was 39. For Hibiclens, all sample numbers were 35, except for 24 hours, where the number was 34.

2. Demographics: There were 100 subjects who provided data from at least one test site in this study. There were 28 males and 72 females, aged 21-69 years. Thirteen were black and the remainder Caucasian.
3. Efficacy Results: For this study, the data gathered at the forearm site will be presented by subject. The 24 hour data will not be presented, as it is not relevant to the preinjection indication. The data for the abdomen and groin will be presented in Appendices III and IV, respectively..

Table 10. Log Reductions at Forearm Site by Subject- 30 second time point

Patient No.	Chlorascrub	IPA	Hibiclens
1	-	0.26	2.35
2	0.31	2.78	-
3	-	3.43	-
4	2.12	-	2.46
5	1.34	2.30	-
6	2.05	2.21	-
10	-0.73	-0.73	-
12	1.81	1.84	-
13	-	2.23	-
14	1.93	-	-
16	-	2.06	2.69
17	-	3.05	4.00
18	-	0.89	1.66
20	2.87	-	1.81
21	-	0.97	-
22	2.81	3.89	-
23	-	2.32	2.50
24	1.23	0.57	3.95

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25	-	2.17	-
26	1.77	3.04	-
37	3.62	-	-
39	0.81	-	3.04
40	3.27	-0.02	-
42	-	3.72	0.49
44	-	1.81	3.62
45	-	-1.08	2.61
46	2.53	2.82	-
49	-	1.27	-0.20
50	3.34	-	1.40
51	1.91	-	-
52	-	-	0.37
54	2.54	-	1.30
57	2.24	-	0.14
58	-	2.32	1.97
61	-	-0.67	2.23
62	1.14	-	2.69
63	-	2.32	-
64	1.30	2.53	-
67	2.23	-	2.38
68	1.42	-	0.18
70	-	2.80	1.21
71	1.24	-	1.03
73	-	-	1.18
76	-	-	3.90
77	2.11	1.58	-
78	2.30	2.25	-
83	4.04	4.11	-
88	1.39	-	-
89	2.62	-	2.00
91	-	2.21	2.97
96	3.32	-	4.61
97	1.38	-	2.08
99	3.90	-	0.78
101	0.31	-	1.79

The following tables present the mean log reductions at the various test sites for the 3 test preparations. The reductions are calculated by subtracting the log counts found at the various time points from the test day baseline log counts.

Table 11: Mean Log Reductions at Inguinal Site

Sample	Chlorascrub	70% IPA	Hibiclens
	Mean (SD) (n)	Mean (SD) (n)	Mean (SD) (n)
Baseline Mean	5.67 (0.56) (52)	5.66 (0.61) (55)	5.70 (0.61) (55)
30 Seconds Post-Prep	2.06 (1.19) (36)	2.35 (1.17) (41)	1.38 (1.02) (42)
10 Minutes Post-Prep	2.28 (0.93) (38)	2.18 (1.19) (43)	2.46 (1.03) (39)
6 Hours Post-Prep	2.68 (1.37) (39)	2.61 (1.32) (40)	2.70 (0.92) (38)
24 Hours Post-Prep	3.09 (1.11) (39)	1.75 (1.21) (36)	2.78 (1.23) (29)

SD= Standard Deviation

Note: Since this portion of the study did not succeed, significant differences between test articles were not considered.

Table 12: Log Reductions at Abdominal Site

Sample	Chlorascrub	70% IPA	Hibiclens
	Mean (SD) (n=42)	Mean (SD) (n=40)	Mean (SD) (n=35)
Baseline Mean	3.23 (0.63)	3.38 (0.61) (n=40)	3.23 (0.59) (n=35)
30 Seconds Post-Prep	2.37 (1.05)	2.08 (1.12) (n=40)	1.98 (0.87) (n=35)
10 Minutes Post-Prep	2.22 (1.18)	2.29 (1.07) (n=40)	1.99 (0.81) (n=35)
6 Hours Post-Prep	2.37 (1.15)	2.53 (1.05) (n=40)	2.44 (0.90) (n=35)
24 Hours Post-Prep	2.53 (0.84)	2.17 (1.24) (n=39)	2.13 (1.27) (n=34)

SD= Standard Deviation

Note: The p-value for the difference between the Chlorascrub and 70% IPA reductions at 24 hours is 0.19.

Table 13: Log Reductions at Forearm Site

Sample	Chlorascrub	70% IPA	Hibiclens
	Mean (SD) (n=33)	Mean (SD) (n=32)	Mean (SD) (n=32)
Baseline Mean	3.21 (0.88)	3.27 (0.88)	3.21 (0.98)
30 Seconds Post-Prep	2.02 (1.07)	1.92 (1.32)	2.04 (1.22)
24 Hours Post-Prep	2.23 (1.13)*	1.76 (1.38)*	2.33 (1.09)

SD= Standard Deviation \*Significant difference between Chlorascrub and 70% IPA (p≤ 0.05)

**Reviewer's Comment:** This study failed at the inguinal site in that none of the test products met the TFM requirement of a mean 3 log reduction at 10 minutes after prepping. For this reason, the sponsor performed another study at the inguinal site ( ) which is described later in this review. The reason for this failure is not immediately clear. Possibilities include:

- a. The ( ) study used a 4 x 4 sq. inch treatment area at the groin (with the Swabstick) while this study used a 7 x 7 sq. inch treatment area (with the Maxi

Swabstick). It may have been that the 7 x 7 sq. inch site did not receive a sufficient amount of the drug.

b. The \_\_\_\_\_ study (in addition to a smaller test area), used “vigorous” pressure while applying the test products. This may have increased the number of bacteria removed. It will be necessary to use the term “vigorous” in the labeling to describe the proper application technique at the groin (or “wet”) sites. Additionally, while mean baseline counts were slightly lower in the \_\_\_\_\_ study, some subjects had unusually high baselines in that study, which permitted large reductions (a few of more than 5 logs) in some cases.

c. There may have been difficulty in harvesting, neutralizing, or counting the bacteria.

In any event, this study was successful in some respects. All products met TFM requirements at the forearm site. Therefore, the \_\_\_\_\_ studies provide sufficient effectiveness of Chlorascrub as a patient preinjection preparation. It is noted that there were no significant differences between Chlorascrub and 70% IPA alone at the 30 second time interval required by the TFM for the preinjection indication. This is acceptable because CHG is a slower-acting antiseptic than 70% IPA alone is and would not be expected to contribute antimicrobial activity until later. There were significant differences between Chlorascrub and 70% IPA at 24 hours. No significance should be assigned to this information because the injection will be performed immediately after skin disinfection.

The \_\_\_\_\_ studies also provide adequate evidence of the effectiveness of Chlorascrub at “dry” surgical sites as required by the TFM. The Swabstick was used in the \_\_\_\_\_ study and the Maxi Swabstick was used in the \_\_\_\_\_, so both dosage forms were successful at this site. Chlorascrub achieved a statistically significant greater log reduction than 70% IPA alone in the \_\_\_\_\_ study at 24 hours.

#### 6.1.4.3. \_\_\_\_\_ Study

Study Title: Evaluation of the Antimicrobial Efficacy of Maxi Swabsticks, Maxi Swabsticks Vehicle, and Hibiclens Preoperative Skin Preparation (Protocol No. 521-102, also SLM-SC-08).

Investigator:



Study Dates: January 23- March 8, 2004

Study Objectives: The following is taken directly from p. 119 of vol. 22 of the NDA:

To evaluate and compare the immediate and persistent antimicrobial activity of Maxi Swabsticks, Maxi Swabsticks Vehicle, and Hibiclens and to evaluate and compare the safety of all three test articles.

Method:

1. Study design: This study compared Chlorascrub, 70% IPA alone and Hibiclens at the groin site, using the "maxi" swabstick. Seventy subjects completed the study. The study used methodology based on the TFM. Product applications were bilateral with two of the three test products used on each subject in random fashion.

2. Inclusion criteria: The following is taken directly from p. 152 of vol. 22 of the NDA:

Potential subjects may be included in this study if they meet the following requirements:

Male or females,  $\geq 18$  years of age and  $\leq 64$  years of age.

Are cooperative and willing to answer questionnaires and sign a consent form (to be provided prior to study initiation).

Are in general good health.

Have skin within 6 inches of the test site that is free of tattoos, dermatoses, abrasions, cuts, lesions or other skin disorders.

The subjects must have had a baseline bacterial count of at least  $4.5 \log_{10}/\text{cm}^2$  at the groin site to enter the study.

3. Exclusion criteria: These are the same as for the \_\_\_\_\_ study above, with two exceptions:

- a. The exclusion for subjects with tattoos, dermatoses, abrasions, etc. which is in the \_\_\_\_\_ protocol is not included here.

- b. An exclusion for pregnant or nursing women has been added.

4. Dosage and duration of therapy: This study was performed using the protocol suggested in the TFM. Test subjects were screened for minimum bacterial counts as outlined in the inclusion criteria, above. On the first test day, patients were evaluated for baseline skin irritation scores (see Safety evaluation below). Each test subject was assigned 2 of the 3 test materials. One material was applied to the inguinal area on one side of the body and one to the other side in randomized fashion. Each treatment area was divided into subsites for microbial sampling at 10 minutes, 6 hours, and 24 hours after drug application. The test sites were covered with a gauze bandage after the 10 minute sample to minimize contamination from external sources. Skin irritation was also scored at the various sampling times.

The prep procedures used were as follows (taken directly from the protocol):

A. Test Product: Maxi Swabstick

1. The test product, a flat two-sided device with a foam tip, will be removed from the package with sterile gloves.
2. One of the flat sides of the foam tip of Maxi swabstick will be placed in the center of 3 x 7.5 inch prep area.

3. An initial spread of the product will be performed over the prep site assuring that product stays within the prep area.
4. After spreading, the skin will be held taut and prepped vigorously in a rapid back and forth manner for one minute. (Note – this one minute application will include the initial spread over the prep area).
5. The test product will be turned over and the unused side of the foam tip will be used to prep the same area. The skin will be held taut and prepped vigorously in a rapid back and forth manner for one minute.
6. The prepped area will be aired dry for 1.5 minutes prior to the initiation of the contact time.

B. Vehicle Product: Maxi Swabsticks Vehicle

The Vehicle product will be applied in the same manner as the test product.

C. Reference Product: Hibiclens

1. Based on the manufacturer's instructions, 5 mL of the reference product will be applied onto a sterile gauze pad.
2. The product will be applied to the treatment area using the same area used for the test and vehicle products (3" x 7.5") for 2 minutes. The area will be dried with a sterile towel or sterile gauze.
3. Steps 1-2 will be repeated.
4. Contact time will begin after the site is dried a second time.

5. Additional information: This is the same as for the \_\_\_\_\_

6. Effectiveness parameters: These are the same as for the \_\_\_\_\_ though no 30 second reading was done.

7. Safety: This is the same as for the \_\_\_\_\_

Results:

1. Evaluability: Eighty-one candidates were entered into the study. Of these, 70 met the baseline bacterial count screening requirement. The sample sizes for the test products were 41 in all cases.
2. Demographics: There were 44 male and 26 female subjects aged 18-63 years. There were 45 Caucasian, 13 Asian, 7 Black, and 5 Hispanic subjects.
3. Efficacy results: The following tables present the log reductions seen for each evaluable subject. The reductions are calculated by subtracting the log count at the time point from the test day baseline count.

Table 14. Log Reductions at Inguinal Site by Subject

Patient No.	10 Minute			6 Hours			24 Hours		
	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens
1	-	4.61	1.97	-	2.08	3.88	-	1.82	3.61
2	3.53	-	3.15	4.56	-	3.42	4.56	-	4.66
3	3.16	3.18	-	3.02	3.00	-	3.38	2.56	-

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4	-	3.76	2.02	-	3.13	2.89	-	3.48	4.60
5	3.48	-	2.10	3.55	-	3.27	4.24	-	3.49
6	5.53	1.93	-	5.53	2.29	-	3.59	2.14	-
7	-	4.62	4.63	-	3.28	4.63	-	3.67	4.63
8	5.14	-	3.88	3.20	-	2.57	3.46	-	4.67
9	4.74	3.86	-	4.09	3.48	-	4.74	4.60	-
10	-	7.00	5.79	-	3.03	5.79	-	3.93	5.79
12	3.10	3.38	-	3.48	2.97	-	4.66	1.84	-
13	-	3.94	3.41	-	1.98	2.73	-	2.49	3.05
14	4.91	-	2.40	4.91	-	4.37	4.07	-	4.31
15	3.39	3.04	-	2.82	3.07	-	3.22	2.20	-
17	4.59	-	1.31	4.59	-	4.61	4.59	-	4.61
18	3.23	2.91	-	4.29	3.87	-	5.67	4.36	-
19	-	4.97	4.53	-	4.19	5.00	-	3.45	1.86
20	4.61	-	2.91	3.67	-	4.61	2.31	-	2.65
22	-	-	2.75	-	-	1.66	-	-	3.51
23	4.61	-	2.54	4.31	-	3.54	3.64	-	3.70
24	4.59	5.16	-	6.56	6.16	-	6.56	4.88	-
25	-	4.88	2.99	-	2.04	4.42	-	1.57	5.56
26	2.87	-	3.92	1.84	-	3.22	3.82	-	1.92
27	3.30	2.94	-	3.67	3.15	-	4.61	3.09	-
29	2.88	-	4.09	4.41	-	2.88	5.54	-	4.40
31	-	2.83	2.96	-	4.28	4.93	-	5.03	5.63
33	4.42	4.25	-	4.54	2.92	-	4.40	2.12	-
34	-	1.18	1.41	-	1.40	2.03	-	2.94	3.46
35	4.01	-	1.77	3.67	-	2.01	4.61	-	3.92
36	3.24	3.09	-	3.10	2.87	-	4.71	2.30	-
37	-	2.85	3.00	-	3.13	3.97	-	3.00	3.97
38	4.20	-	5.80	6.30	-	4.43	7.44	-	4.07
39	3.15	3.31	-	3.00	3.46	-	3.85	2.57	-
40	-	4.63	3.11	-	1.66	3.22	-	2.06	5.34
42	3.44	3.04	-	4.62	2.63	-	4.62	2.21	-
43	-	3.02	2.46	-	1.85	2.38	-	1.85	4.36
44	3.37	-	-	4.71	-	-	4.71	-	-
45	4.62	-	-	4.62	-	-	3.84	-	-
46	-	2.07	2.81	-	1.23	2.75	-	1.05	2.99
47	3.33	-	2.39	5.81	-	4.88	6.84	-	3.84
48	3.66	3.06	-	3.49	2.78	-	4.45	2.55	-
49	-	3.09	3.28	-	2.35	4.60	-	1.91	4.60
50	2.96	-	1.76	3.13	-	3.00	2.50	-	3.14
51	3.74	3.72	-	3.90	3.07	-	4.18	2.38	-
52	-	4.76	0.93	-	3.20	3.10	-	2.96	4.37
56	4.33	-	2.95	4.80	-	2.83	4.24	-	3.00

58	-	3.44	2.30	-	1.47	1.45	-	1.28	1.61
59	3.08	-	2.75	3.26	-	2.69	3.06	-	2.86
60	2.07	1.94	-	3.29	1.87	-	3.17	1.94	-
61	-	3.15	2.90	-	3.05	2.74	-	2.64	3.37
63	3.46	2.84	-	4.05	2.70	-	5.54	1.65	-
64	-	2.80	2.07	-	1.69	2.27	-	1.57	2.55
65	3.25	-	-	3.04	-	-	3.19	-	-
66	3.27	3.33	-	2.94	2.33	-	3.43	2.14	-
67	-	3.08	2.90	-	2.93	2.96	-	4.74	3.23
68	4.15	-	2.93	3.06	-	3.02	4.07	-	2.50
69	2.61	2.05	-	3.30	1.91	-	2.90	0.63	-
70	-	3.06	2.93	-	2.76	2.96	-	2.35	3.61
74	-	-	2.57	-	-	2.91	-	-	3.15
75	5.76	5.68	-	5.76	2.74	-	4.46	2.68	-
77	2.77	-	-2.02	3.11	-	1.91	3.26	-	2.18
78	3.40	3.19	-	3.40	3.51	-	2.63	2.68	-
80	4.70	-	3.16	5.00	-	3.49	5.00	-	3.22
81	-	3.21	3.03	-	2.61	2.82	-	2.24	3.00

The following table presents the mean log reductions at the test sites for the 3 test preparations. The reductions are calculated by subtracting the log counts found at the various time points from the test day baseline counts.

Table 15: Log Reductions at Inguinal Site

Sample	Chlorascrub	70% IPA	Hibiclens
	Mean (SD) (n=41)	Mean (SD) (n=41)	Mean (SD) (n=41)
Baseline Mean	5.28 (0.67)	5.26 (0.60)	5.26 (0.63)
10 Minutes Post-Prep	3.77* (0.83)	3.48 (1.11)	2.89 (1.04)*
6 Hours Post-Prep	4.01** (1.03)	2.78 (0.91)**	3.34 (1.03)**
24 Hours Post-Prep	4.24** (1.12)	2.57 (0.98)**	3.68 (1.03)**

SD= Standard Deviation

\* Significant difference between Chlorascrub and Hibiclens ( $p \leq 0.05$ )

\*\* Significant difference between Chlorascrub and both comparators ( $p \leq 0.05$ )

**Reviewer's Comment:** This is a successful study in that Chlorascrub met the TFM requirements for a patient preoperative skin preparation at the inguinal site. IPA alone also met the TFM requirement, while Hibiclens did not. Mean log reductions were statistically significantly greater for Chlorascrub compared to 70% IPA at the 6 hour and 24 hour timepoints.

It is noted from the individual subject data that this laboratory was able to achieve high baselines (7 logs) in some patients. The Chlorascrub and IPA preps were applied "vigorously," while Hibiclens was not. This may explain some of the difference in results.

It is noted that this study used Maxi Swabsticks, while the study used Swabsticks at the groin site. Thus, both applicators were successful at this site.

#### 6.1.4.4. Exploratory Studies

Reviewer's Note: The studies described below were exploratory in nature and are included here for informational purposes. The data was not verified by the reviewers, and the descriptions of the studies are not meant to be exhaustive, but rather are intended as summaries.

##### a. [redacted] Screening Study

Study Title: Screening Study for Evaluating a Topical Antiseptic Formulation as a Patient Preoperative Skin Preparation (Protocol No. 03-121990-106, also SLM-SC-05).

Investigator: [redacted]

Study Objective: Not formally stated. This study explored various application procedures and test sites within the groin area. The study was undertaken because the earlier [redacted] study failed at the groin area.

Method: This study initially compared Chlorascrub to Chloraprep in their ability to reduce bacterial counts at the groin. Three different test strategies were used. In the first group using the Maxi Swabstick, Chlorascrub was applied to 14 test sites using the same method as described above for the [redacted] Study. In the second group, Chlorascrub was compared to ChloraPrep using a test site area of 5 x 6 inches rather than 7 x 7 inches. In the third group, the 5 x 6 inch area was tested and ChloraPrep was not used. Log reductions from baseline were calculated at 10 minutes after prepping. ChloraPrep contains 2% CHG and 70% IPA (NDA 20-832).

Results: In the first portion of the study, 14 sites at the groin were tested for microbial reduction with Chlorascrub using essentially the same methodology as was described for the pivotal [redacted] Study. The mean log reduction seen was 2.29 log<sub>10</sub> (less than the 3 log TFM standard for this site).

In the second portion of the study, 7 groin test sites were prepped with Chlorascrub and 7 with ChloraPrep. The test site area used was 5 x 6 inches (not the 7 x 7 inch size used previously). This resulted in a 2.91 log<sub>10</sub> reduction in counts for Chlorascrub and a 3.34 log<sub>10</sub> reduction for ChloraPrep.

In the final portion, 18 groin sites were sampled using Chlorascrub only and the 5 x 6 inch site. The results were a 2.56 log<sub>10</sub> reduction. However, when test sites with less than 4.5 log<sub>10</sub> organisms at baseline were excluded, Chlorascrub achieved a 3.9 log<sub>10</sub> reduction (in 6 samples).

##### b. [redacted] Comparison of Chlorascrub and ChloraPrep

Study Title: Evaluation of the Antimicrobial Efficacy of a 3.15% Chlorhexidine Gluconate in 70% Isopropyl Alcohol Preoperative Skin Preparation (Protocol No. 521-101, also SLM-SC-07).

Clinical Review  
David Bostwick  
NDA 21-524  
Chlorascrub

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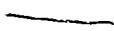
Investigator: 

Study Objectives: The following is taken directly from p. 3 of vol. 23 of the NDA:

To evaluate the antimicrobial activity of Maxi Swabsticks. Two groups of subjects were evaluated. One group contained at least twenty (20) subjects and compared the effectiveness of the test article; Maxi Swabsticks (Primary lot) and a marketed product article; ChloroPrep for a total of at least twenty completed sites each. The second group contained at least five (5) subjects and evaluated the effectiveness of the test article; Maxi Swabsticks (Secondary lot) only for a total of at least ten completed sites. The efficacy is demonstrated by the reduction in the number of viable bacteria recovered from intact skin.

Method: This study compared Chlorascrub Maxi Swabsticks to ChloroPrep at the groin test site, using a test area of 3 x 7.5 inches. Chlorascrub and ChloroPrep were applied to opposite sides of the body in 21 subjects. Log reductions from baseline were calculated at 10 minutes after prepping. In this study, all subjects had baseline microbial counts of at least 4.5 log<sub>10</sub>.

Results: The results were a 3.88 log<sub>10</sub> reduction for Chlorascrub vs. a 3.74 log<sub>10</sub> reduction for ChloroPrep at 10 minutes. In a secondary group of 5 subjects tested with Chlorascrub only, the log reduction at 10 minutes was 4.29 log<sub>10</sub>.

c.  Pilot Study of Application Techniques

Study Title: Evaluation and Comparison of Three Application Procedures using Two Configurations of a Preoperative Skin Preparation (Protocol No. 020105-103).

Investigator: 

Study Objectives: The following is taken directly from p. 96 of vol. 23 of the NDA:

The purpose of this study is to evaluate and compare three (3) application procedures using two (2) configurations of a Preoperative Skin Preparation applied to the femoral vein site (inguinal). A reference product will also be evaluated.

Method: This study compared Chlorascrub Maxi Swabsticks and Swabsticks to ChloroPrep at the groin test site, using a test area of 3 x 5 inches. Each product was tested on a minimum of 4 sites. Though the study objectives speak of 3 application procedures, the results are presented for the individual products without specifying what differences in application might have occurred. 14 subjects were involved.

Results: Bacterial reductions were calculated at 30 seconds, 3 minutes and 10 minutes after prepping for the Swabstick and Maxi Swabsticks and at 10 minutes for ChloroPrep. The following table presents the results.

Table 16. Mean Log Reduction at the Groin Site

Sample	Maxi Swabstick	Swabstick	ChloraPrep
30 seconds	3.14	2.95	-
3 minutes	3.07	2.53	-
10 minutes	4.69	3.89	3.17

d. J  Comparison of Packaging Configurations

Study Title: R&D Evaluation and Comparison of the Antimicrobial Efficacy of a Preoperative Skin Preparation Applied in Three Different Configurations (Protocol No. 020208-103).

Investigator: 

Study Objectives: The following is taken directly from p. 119 of vol. 23 of the NDA:

The purpose of this study is to evaluate and compare the antimicrobial efficacy of a Preoperative Skin Preparation applied to the femoral vein site (inguinal) and abdominal site in three (3) different configurations.

Method: This was a pilot study to determine the proper application method for the Swabsticks and Maxi Swabsticks. The applicators were tested at both the abdomen and groin using 1, 2, and 4 minute prep times. In some cases, two applicators were used. Each configuration was tested on 4 subjects, using a 3 x 5 inch test area. 6 subjects were utilized. Bacterial reductions were measured only at 30 seconds after prepping.

Results: The results are expressed as mean log reduction from baseline.

Table 17. Mean Log Reductions at 30 seconds

Test Site	Prep Time (min)	Applicator	No. Applicators	Mean Log Reductions
Abdomen	1	Swabstick	1	2.10
Groin	2	Swabstick	2	3.11
Abdomen	2	Swabstick	1	2.67
Groin	4	Swabstick	2	2.41
Abdomen	1	Maxi Swabstick	1	2.20
Groin	2	Maxi Swabstick	1	2.85

**6.1.5. Clinical Microbiology**

This review is not yet available.

### 6.1.6. Efficacy Conclusions

Adequate evidence is available to establish the effectiveness of Chlorascrub as a patient preoperative skin preparation and as a patient preinjection skin preparation. As previously negotiated by the applicants and representatives of the Divisions of Anti-infective Drug Products and Over-the-Counter Drug Products, data from the pivotal studies at \_\_\_\_\_ support the indication of patient preinjection skin preparation and the effectiveness of the product as a patient preoperative skin preparation at the dry (abdominal) test site. The data from the pivotal studies at \_\_\_\_\_ support the effectiveness of the product as a patient preoperative skin preparation at the groin (wet) test site. Data from the \_\_\_\_\_ studies also support the contribution of both active ingredients to the total effect of the product. No additional information is needed to establish the effectiveness of the product. This product meets the requirements of the TFM for these indications. It performs as well as (or better than) Hibiclens, the positive control.

## 7. INTEGRATED REVIEW OF SAFETY

### 7.1. Methods and Findings

The applicant has demonstrated that Chlorascrub is safe for the proposed single use indications patient preoperative skin preparation and patient preinjection skin preparation.

There were two types of subject exposures, involving a total of 574 subjects in studies submitted to support the approval of Chlorascrub. A total of 333 subjects received a single topical application in the three pivotal efficacy studies and four pilot efficacy studies described above. The intended use of the product as a patient preoperative skin preparation and patient preinjection skin preparation is most similar to the use in these seven studies (i.e., single application without use of occlusive dressings).

The second type of exposure, involving a total of 241 subjects took place in the two safety studies which are typically required for topical drug products. These studies are designed to produce the maximal irritation and sensitization potential of the tested products. This is achieved by multiple consecutive applications of the products under occlusion. These studies were a 14-Day Cumulative Irritation Patch Test, protocol no. \_\_\_\_\_-01-108088-76, also identified SLM-SC-01, and a Repeat Insult Patch Test for the Evaluation of Sensitization, protocol no. \_\_\_\_\_-01-105168-76, also identified as SLM-SC-02.

Data from all nine studies were reviewed to assess the safety of Chlorascrub. Case reports and summaries were reviewed for reports of adverse events and for unexplained

subject withdrawal. The following table presents adverse events seen in subjects who received Chlorascrub during the clinical studies (please note that the test subjects typically received more than one test product).

Table 18. Summary Table of All Adverse Events in NDA 21-524  
N=574

Number of Subjects	N	%
With one or more AE	88	15.3
With no AE	486	84.7
With drug-related AE	0	0
With serious AE	1	0.02
With serious drug-related AE	0	0
Who died	0	0
Discontinued due to an AE	5	0.1
Discontinued due to a drug-related AE	0	0
Discontinued due to a serious AE	1	0.02
Discontinued due to a serious drug-related AE	0	0

As noted above, the investigator did not find that any adverse event was associated with drug use.

It should be noted that the majority of subjects with adverse events (57/88 or 65%) were in study SLM-SC-02, the \_\_\_\_\_ sensitization study. This study had the most test subjects in it and apparently had a more inclusive definition of an adverse event than the other studies (e.g., sore left knee, sore thumb, etc.). In any event, review of the adverse event listings reveals only two that may have been related to product use in the opinion of the reviewers. The first is described below under "Other Serious Adverse Events." The second occurred in study SLM-SC-01, the \_\_\_\_\_ irritation study. A subject in that study developed a "ringworm-like rash" on the torso, legs, and neck, but not on the drug test areas. The physician diagnosed this as an allergic response to an (unspecified) ingested substance.

#### 7.1.1. Deaths

No deaths occurred during the course of this development program.

#### 7.1.2. Other Serious Adverse Events

In study SLM-SC-02, the \_\_\_\_\_ sensitization study, subject no. 246 developed hives over the entire body and experienced difficulty in breathing. The subject was hospitalized for about 4 hours, and given adrenaline, an antihistamine injection, and hydrocortisone cream. The subject was discontinued from the study. Four days later, the patient still had hives, but the test sites were clear. One month later, the subject had

completely recovered. The physician did not do any followup testing to confirm the identity of the allergen, but “suspected” shellfish.

The sponsor was asked for all available additional information concerning this event, and submitted a reply on February 24, 2005. The reaction took place on May 27, 2001. Since May 27 was a Sunday, it is likely that the previous application of test materials was on the previous Friday (no applications were made on weekends). There is no additional information concerning the reasons for suspecting shellfish as the causative agent.

### 7.1.3. Dropouts and Other Significant Adverse Events

The following table presents the number of dropouts and the reasons for dropping out for the two safety studies performed by            (irritation and sensitization).

Table 19. Reasons for Safety Study Dropouts

Protocol	No. Subjects Dropped of Total Recruited	Noncompliance	Schedule Conflict	Adverse Event	Other
14-Day Irritation (SLM-SC-01)	4 of 35	1	2	0	1
Sensitization (SLM-SC-02)	40 of 250	20	10	5	5

As noted above, the investigator did not evaluate any of the adverse events as being related to study drug. The “other” category includes those who left because they were “unwilling to continue” or chose not to participate for an unstated reason.

The following table presents the number of dropouts and the reasons for dropping out for the three pivotal efficacy studies.

Table 20. Reasons for Pivotal Study Dropouts

Protocol	No. subjects Dropped of Total Recruited	Baseline Bacteria too Few	Noncompliance	Schedule Conflict	Other
<u>          </u> (SLM-SC-03)	119 of 205	112	5	2	0
<u>          </u> (SLM-SC-04)	37 of 137	16	6	0	15
<u>          </u> (SLM-SC-08)	11 of 81	9	0	0	2

The “other” category includes those who voluntarily withdrew prior to the study date.

A separate table will not be presented for the supportive and pilot studies. No subjects were lost for reasons of adverse events.

**Reviewer’s Comment:** There are no drug-related adverse events reported. It should be noted that 15 subjects in the \_\_\_\_\_ pivotal study (SLM-SC-08) reported mild skin irritation during testing. This irritation was exhibited in eleven subjects at sites tested with 70% IPA, in ten subjects treated with Chlorascrub, and in one subject treated with Hibiclens. The sponsor theorizes that this may have been due to excessively vigorous application of Chlorascrub and vehicle, since this irritation was not seen in other clinical studies.

Overall, the events seen do not describe any other relationship to dose-response, time dependency of dropouts, drug-demographic, drug-disease or drug-drug interactions.

#### 7.1.4. Other Search Strategies

The case report forms were reviewed for additional safety information, but none was found. The literature has been reviewed by Dr. Peter Kim in his review of NDA 21-669. He found the following potential safety concerns with the use of products containing CHG. These toxicities have been recognized for some time and are dealt with in the labeling for presently approved CHG products:

- Deafness as a result of instillation into the middle ear
- Eye injury (corneal opacification) if permitted to enter and remain in the eye
- Excessive irritation when applied to genital areas (mucous membranes)
- Anaphylaxis
- Severe skin irritation/ulceration in infants weighing < 1000 grams and < 26 weeks gestation

#### 7.1.5. Common Adverse Events

There were no adverse events which were evaluated as being related to drug application. The most common unrelated events were: irritation of the skin at the study site in 29 patients (29/574 = 5%) and headache in 20 subjects (20/574 = 3.5%).

##### 7.1.5.1. Applicant’s Approach to Eliciting Adverse Events

The subjects were assessed for adverse events at each study visit. For the pivotal studies, this generally meant that assessments were made only on the study day. For the irritation and sensitization studies, assessments were made at each patch change.

#### 7.1.6. Less Common Adverse Events

Not applicable.

#### **7.1.7. Laboratory Findings**

No laboratory tests were performed during these studies.

#### **7.1.8. Vital Signs**

Vital sign readings were not taken on test subjects in these studies. See 7.1.9 below.

#### **7.1.9. Electrocardiograms (ECGs)**

No ECG's were performed during these studies. Because CHG is poorly absorbed, systemic effects have not been observed, except in cases of hypersensitivity.

#### **7.1.10. Immunogenicity**

The sensitization test described below was the only study of this type performed in support of the NDA.

#### **7.1.11. Human Carcinogenicity**

No studies of this type were performed.

#### **7.1.12. Special Safety Studies**

There were two special safety studies performed to assess the cumulative irritancy and contact sensitization potential of the product. Additionally, skin irritation was evaluated during the 3 pivotal efficacy studies. These studies are reviewed below. The adverse effects seen in the pivotal studies (if any) will also be listed.

##### **a. Cumulative irritation study**

Study title: Protocol for a 14-day Cumulative Irritation Patch Test (Protocol No. 01-108088-76, also referred to by sponsor as study SLM-SC-01).

Investigator: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Study Dates: May 15- 29, 2001

Study Objectives: The following is taken directly from the study protocol:

- 1) To evaluate the Sponsor's topical antibacterial product for induction of irritation.
- 2) To compare the irritation-inducing properties of the Sponsor's topical antibacterial product with that of a currently marketed topical antibacterial product

Method:

i. Study design: This was a paired-comparison study in which each subject served as his/her own control. Fourteen consecutive daily applications of 6 test substances were made to test sites on the paraspinal region of the back. The patches were removed after 24 hours and the test sites scored for irritation. The patches were then reapplied with fresh test articles and the procedure repeated. The products tested were:

- Chlorascrub
- Betadine (10%povidone-iodine)
- 70% IPA
- Hibiclens
- 0.1% sodium lauryl sulfate (positive control)
- 0.9% saline (negative control)

Chlorascrub was tested using a fully occlusive patch, a semi-occlusive patch, and with no occlusion. Betadine, 70% IPA and Hibiclens were tested using both fully occlusive and semi-occlusive patches. The positive and negative controls were tested with full occlusion only.

ii. Inclusion criteria: The following is taken directly from the protocol:

- a. Males and Females, age 18 years or older
- b. Signed informed consent
- c. Good general health, as determined by a medical history

iii. Exclusion criteria: The following is taken directly from the protocol:

- a. Insulin-dependent diabetes
- b. Pregnancy or nursing an infant
- c. Mastectomy for cancer involving removal of lymph nodes
- d. Treatment for any type of cancer within the last 6 months
- e. Clinically significant skin diseases which may contraindicate participation, including psoriasis, eczema, atopic dermatitis, leg ulcer, and active cancer
- f. Asthma requiring chronic or frequent medication
- g. Immunological disorders such as HIV positive, AIDS, rheumatoid arthritis and systemic lupus erythematosus
- h. Use of immunosuppressive drugs (steroid nose drops and/or eye drops are permitted)
- i. Chronic or frequent use of antihistamine medication or anti-inflammatory drugs, except as follows:

Acetaminophen	any dose
Regular strength aspirin	≤650 mg/day
Extra strength aspirin	≤500 mg/day
Ibuprofen	≤600 mg/day
Orudis KT	≤24 mg/day
- j. Topical drugs at patch site
- k. Medical conditions, which, in the Investigator's judgment, make the subject ineligible or places the subject at undue risk
- l. Participation in any patch test for irritation or sensitization within the last four weeks
- m. Damaged skin in or around test sites which include sunburn, extremely deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles or other disfiguration of the test site

- n. Current participation in any clinical testing, including other studies being conducted at
- o. Known sensitization to medical adhesives, antibacterial agents, or the test article ingredients

iv. Dosage and duration of therapy: Thirty-one subjects completed the study. The test articles were applied to 2 x 2 cm<sup>2</sup> test sites on the right and left sides of the back in a blinded fashion and covered with occlusive or non-occlusive patches. As noted above, ChloroPrep was tested with full occlusion, semi-occlusion, and no occlusion. 0.2 mL of each test substance was used. The patches were left in place for 24 hours, removed and the test areas scored for irritation. Repeat applications were made to the same test sites for 14 days.

v. Evaluation parameters: The following scale was used to evaluate the test sites (taken from the protocol):

Applications will be terminated if strong reactions are observed. Residual reactions will be scored until the end of the study and if necessary until the site has cleared. A strong reaction is defined as:

- a) Any numerical score that has been appended with a letter grade of F, G, or H

OR

- b) Numerical score of 3, 4, 5, 6 or 7 regardless of the possible letter grade combination

All scores will be documented. The scoring scale will be as follows:

- 0 No evidence of irritation
- 1 Minimal erythema, barely perceptible
- 2 Moderate erythema, readily visible; or minimal edema; or minimal papular response
- 3 Strong erythema; or erythema and papules
- 4 Definite edema
- 5 Erythema; edema and papules
- 6 Vesicular eruption
- 7 Strong reaction spreading beyond test site

Effects on superficial layers of the skin should be recorded as follows

- A Slight glazed appearance
- B Marked glazing
- C Glazing with peeling and cracking
- F Glazing with fissures
- G Film of dried serous exudates covering all or a portion of the patch site
- H Small petechial erosions and/or scabs
- @ Additional comments as footnote

- v. Safety: Adverse events were monitored at each evaluation.

Results:

- i. Evaluability: Thirty-five subjects entered the study, and 4 failed to complete it. Two subjects withdrew due to schedule conflicts, one chose not to participate for undisclosed reasons, and one was withdrawn by the investigator because of noncompliance.
- ii. Demographics: Twenty-two females and 9 males completed the study. No further demographics are available. It should be noted that light-skinned individuals are used in these studies because it is easier to evaluate reactions in them.
- iii. Irritation scores: Results are presented as overall mean irritation scores. That is, the mean daily scores for each of the 14 evaluations have been totaled to provide a total mean score for each substance.

Table 21. Total Mean Irritation Scores (n=31)

Test substance and Mode	Mean Score
Chlorascrub fully occluded	35.5
Betadine fully occluded	32.5
70% IPA fully occluded	10.6
Hibiclens fully occluded	12.1
Chlorascrub semi-occluded	2.3
Betadine semi-occluded	9.0
70% IPA semi-occluded	1.6
Hibiclens semi-occluded	0.7
Chlorascrub open	0.0
0.1% SLS (positive control) fully occluded	32.7
Normal saline (negative control) fully occluded	0.9

- iv. Safety: There were 12 adverse events reported in 8 subjects. There were 6 reports of headaches, one of a ringworm-like rash discussed in section 7.1 above, and single reports of injured toe, eyelid swelling, sore back, diarrhea, and burned forearm (on oven).

**Reviewer's Comment: This study was performed according to a standard protocol. The results indicate that Chlorascrub, when tested by the standard fully occluded method, is roughly as irritating as are the positive control and Betadine. The labeling should reflect the high irritation potential of this product. It should not be acceptable to use Chlorascrub under occlusive conditions.**

b. Sensitization study

Study Title: A Repeated Insult Patch Test (Jordan-King Modification of the Draize Procedure) for the Evaluation of Sensitization (Protocol No. 01-105-168-76, also referred to by sponsor as study SLM-SC-02)

Investigator:

Study Dates: May 23- June 29, 2001

Study Objectives: The following is taken directly from the study protocol:

The purpose of this study is to evaluate the test article for the induction of contact sensitization by repetitive applications to the skin of human volunteers and to report any irritation observed with the test article.

Method:

i. Study design: This was a paired-comparison study in which each subject served as his/her own control. There was a 21-day induction period during which the test articles were applied to the deltoid region of one arm and covered with patches for 48 hours (72 hours on weekends). The protocol originally called for occlusive patches to be used, but the investigator found that irritation was unacceptably high at the Chlorascrub sites on the first day, so the patches were changed to a semi-occlusive type. Applications and patching were repeated for 9 cycles of 48 or 72 hours. The articles tested were Chlorascrub and 0.9% saline (negative control).

A 2 week rest period was observed (no applications). A 48 hour challenge patch was then applied to both arms, one to a naive site and one to the original site. Scoring was done at each patch change and at 48 and 96 hours after the challenge application.

ii. Inclusion criteria: These were the same as for the irritancy study above.

iii. Exclusion criteria: These were the same as for the irritancy study above.

iv. Dosage and duration of therapy: 210 subjects completed the study. The test articles were applied to the deltoid area of one arm in a blinded fashion and covered with semi-occlusive patches. 0.2 mL of each test substance was used. The patches were left in place for 48 or 72 hours on weekends, removed, and the test areas scored for irritation. 48 hour challenge patches were applied to both arms.

vi. Evaluation parameters: The following scale was used to evaluate the test sites (taken from the protocol):

Inflammatory Responses

0	=	No visible reaction
+	=	Slight, confluent or patchy erythema
1	=	Mild erythema (pink)
2	=	Moderate erythema (definite redness)
3	=	Strong erythema (very intense redness)

Definition of letter grades appended to a numerical grade:

E	=	Edema-swelling, spongy feeling when palpated
P	=	Papule-red, solid, pinpoint elevation
V	=	Vesicle- small elevation containing fluid
B	=	Bulla reaction- fluid-filled lesion (blister)
S	=	Spreading- evidence of the reaction beyond the Webril pad area
W	=	Weeping- result of a vesicular or bulla reaction- serous exudates
I	=	Induration- solid, elevated, hardened, thickened skin

#### Superficial Effects

g	=	Glazing
y	=	Peeling
c	=	Scab, dried film of serous exudates of vesicular or bulla reaction
d	=	Hyperpigmentation (reddish-brown discoloration of test site)
h	=	Hypopigmentation (loss of visible pigmentation at test site)
f	=	Fissuring- grooves in the superficial layers of the skin
@	=	Additional comments appear below or on the following page

vi. Safety: Adverse events were monitored at each visit.

#### Results:

i. Evaluability: 250 subjects entered the study, and 40 failed to complete it. 20 subjects were noncompliant with the protocol. 10 dropped themselves because of a schedule conflict. One had a sunburn and was dropped, and four “disliked study procedures” and were unwilling to continue. Five were discontinued due to adverse events (see below).

ii. Demographics: 129 females and 81 males completed this study. Again, it should be noted that light-skinned individuals are most often used in these studies because it is easier to observe reactions in them.

iii. Sensitization reactions: As noted earlier, there were frequent inflammatory reactions of 1-3 in the Chlorascrub group at the first patch removal. As an example, 59 of the test subjects had irritation scores of 0 for Chlorascrub after the first cycle, while 205 subjects had 0 scores for saline at the same time. After the patches were changed to a semi-occlusive type, these reactions were fewer.

However, in terms of reactions after the challenge application, the subjects reacted similarly to both test materials. At the original challenge site (that is, the test site which was used to apply the test products during induction was patched at challenge), there were only four subjects for Chlorascrub and five for saline with scores of 1. The only sites which displayed a score of 2 at challenge were to saline (four at 48 hours and 3 at 96 hours).

iv. Safety: There were 57 subjects with adverse events in this study. Five dropped out because of adverse events. These were: the hypersensitivity reaction (presumably to shellfish) described above; pneumonia; bursitis; head pain as a result of a car accident; and continuing back/neck pain from a previous car accident.

There were 69 adverse events in the 57 subjects. The following table lists them (none were evaluated as related to drug use).

Table 22. Adverse Events (n=69)

Event	Number
Headache	27
Flu/Cold Symptoms	11
Back Pain	5
Stiff/sore arm/leg/thumb	5
Vomiting/nausea	4
Toothache	2
Injured wrist/thumb	2

There were also single reports of allergic reaction, arm swelling (in cast), food poisoning, pneumonia, accident, kidney pain, bursitis, anxiety, sore neck, elective surgery, menstrual cramps, and tendonitis.

**Reviewer's Comment:** This study was also performed according to a standard protocol. The results indicate that Chlorascrub had a low potential to cause contact sensitization.

c. Irritation studies performed during pivotal studies and adverse event listings.

i. [redacted] pivotal study (SLM-SC-03)

The skin at each test site was evaluated for irritation at baseline and when samples were taken post-prepping, at 10 minutes and 6 and 24 hours. The forearm site was evaluated at 24 hours only. Erythema, edema, rash and dryness were evaluated on a scale from 0= none to 3= severe.

Results: No irritation was seen for vehicle or Hibiclens at any time. One subject had a reading of 2 for rash at the groin site treated with Chlorascrub at 6 hours. Edema, erythema and dryness scores of 1 for one patient at 6 hours were also seen at the groin site for Chlorascrub. No irritation was seen at any forearm site.

At the abdomen site, for Chlorascrub, there was one reading of 2 for rash at 6 hours, and one reading of 1 for both erythema and rash at 24 hours. No adverse events were reported for this study.

ii. [redacted] pivotal study (SLM-SC-04)

Skin irritation was read using the same system as was described for the [redacted] study above. No irritation of any sort was observed at any time.

There were nine reports of adverse events in 8 subjects. These were seven reports of erythema under the dressing edge, which the evaluator assessed as being due to the

tape or dressing itself, and reports of fever and vomiting and congestion and cough in one patient.

iii. [redacted] pivotal study (SLM-SC-08)

[redacted] Skin irritation was read using the same system as was described for the [redacted] study above. Fifteen subjects had erythema readings of 1 (or mild) at the 10 minute sampling period. Ten of these were at Chlorascrub sites, eleven at IPA sites, and one at a Hibiclens site. These are included in the adverse event listings above.

**Reviewer's Comment: The sponsor ascribes the mild irritation seen in the [redacted] study to the vigorous application method used for Chlorascrub and IPA. It is noted that the only other reports of rash, erythema, etc. occurred in the [redacted] study at Chlorascrub sites. The laboratory did not report these occurrences as adverse events.**

#### **7.1.13. Withdrawal Phenomena and/or Abuse Potential**

These phenomena are not applicable to this drug product.

#### **7.1.14. Human Reproduction and Pregnancy Data**

The applicant did not submit data on the reproductive toxicity potential of this product. However, there have been no concerns with reproductive toxicity in the Agency's prior reviews of safety for products containing CHG and IPA.

#### **7.1.15. Assessment of Effect on Growth**

This product will not have any effect on the growth of pediatric subjects.

#### **7.1.16. Overdose Experience**

CHG is poorly absorbed through the skin, making overdosage unlikely.

#### **7.1.17. Postmarketing Experience**

There is no post-marketing experience with this product.

## **7.2. Adequacy of Patient Exposure and Safety Assessments**

### **7.2.1. Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety**

A total of 574 subjects were exposed to the proposed drug product. All of the subjects were from the U.S.

Two hundred fifty six of the subjects participated in the three pivotal efficacy studies. In these studies, exposure to the abdomen consisted of a one-time application to a 7 x 7 inch area. Exposure on the inguinal region consisted of a one time application to areas of 7 x 7 inches or 3 x 7.5 inches.

Seventy-seven subjects participated in pilot studies at \_\_\_\_\_  
\_\_\_\_\_ These were also single-time applications to areas ranging from 3 x 5 inches to 7 x 7 inches.

The irritation testing consisted of 14 consecutive applications of 0.2 mL of the test products to sites which were then occluded or semi-occluded. In the sensitization study, 0.2 mL of the test substance were applied 9 times over a period of 3 weeks and covered with semi-occlusive patches. Another 0.2 mL application was made at challenge.

The safety testing was adequate for single use of Chlorascrub for the desired indication. Given the lack of systemic absorption, no additional safety evaluation is needed for the single-use indications. However, should the sponsor choose to pursue an indication that allows for multiple uses, additional studies will be needed to support such use.

The subject data base was adult and primarily Caucasian. There is no data or literature to suggest that race, sex, age, etc. is significant in the safe use of topical antiseptics with the exception of use in young children (under 2 months of age), and especially premature children. These infants may have skin which is less competent than older individuals, and therefore caution must be exercised in applying irritating products. There is also the likelihood of increased absorption of chemicals through immature skin.

### **7.2.2. Description of Secondary Clinical Data Sources Used to Evaluate Safety**

None.

### **7.2.3. Adequacy of Overall Clinical Experience**

The experience in testing of Chlorascrub is adequate given its intended (one-time) use in individuals being prepared for medical procedures. The adverse event profile is adequately addressed in the irritation and sensitization studies, and in the simulated clinical studies. This product displays the same types of potential toxicities as were seen in other products of this type (e.g. ChloroPrep).

**7.2.4. Adequacy of Special Animal and/or In Vitro Testing**

No special testing of the types described above was performed, nor was any necessary.

**7.2.5. Adequacy of Routine Clinical Testing**

Not applicable. No routine clinical testing was performed, nor was any necessary for this product.

**7.2.6. Adequacy of Metabolic, Clearance, and Interaction Workup**

Not applicable. CHG is poorly absorbed except through immature skin.

**7.2.7. Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study**

None. The applicant has made adequate efforts to identify potential adverse events.

**7.2.8. Assessment of Quality and Completeness of Data**

Overall, the quality and completeness of the safety data were adequate to determine the safety of Chlorascrub.

**7.2.9. Additional Submissions, Including Safety Update**

None.

**7.3. Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

No adverse events were designated as treatment related by the investigators. However, predictive studies indicate that skin irritation is possible with use of Chlorascrub, especially when applied vigorously. The product must be labeled for vigorous application at the ~~site~~ site as a result of the clinical studies. Therefore, some skin irritation is likely.

**7.4. General Methodology**

**7.4.1. Pooling Data Across Studies to Estimate and Compare Incidence**

There were no adverse events which were linked to drug application, so pooling data is not applicable.

#### **7.4.2. Explorations for Predictive Factors**

All patients in the Chlorascrub clinical studies were adult (to age 70). Since no adverse events were designated as drug related, it is only possible to make general statements concerning products of this type. It is expected that infants less than 2 months of age and especially premature infants, will be more likely to suffer skin irritation as a result of use of this product. Therefore, the label should recommend against such use. It is also possible that aged patients, who often have fragile skin, would be more vulnerable to skin irritation from using this product.

#### **7.4.3. Causality Determination**

It is likely that this product will cause skin irritation in normal use. There were two adverse events which were not felt to be related to drug use by the sponsor which have may been associated with hypersensitivity: one severe allergic reaction and one "ringworm-like rash." In both cases, the investigator felt that the effects were due to food allergies, though no challenge tests were performed to fix causality.

### **8. ADDITIONAL CLINICAL ISSUES**

#### **8.1. Dosing Regimen and Administration**

As is true for other products that have been granted these indications in the past, the sponsor has provided data that establishes that it can achieve the log reductions required by the TFM.

#### **8.2. Drug-Drug Interactions**

Not applicable.

#### **8.3. Special Populations**

None, with the exception of contraindication in infants less than 2 months of age (see below).

#### **8.4. Pediatrics**

The labeling states that Chlorascrub may be used on patients  $\geq 2$  months of age. The sponsor requests a partial waiver for infants younger than 2 months of age, based on the precedent set for ChlorPrep (2% CHG/70% IPA). In the ChlorPrep application, studies in the younger infants were waived because of safety concerns (irritancy, possibility of enhanced absorption) that made such studies questionable in terms of the risk to the test subjects who would be involved. The same situation applies here, and the waiver should

be granted. Efficacy for children 2 months of age and older may be extrapolated from the studies in adults, as there is no reason to expect that efficacy will be different in children than in adults.

### **8.5. Advisory Committee Meeting**

Not applicable.

### **8.6. Literature Review**

Reference is made to the excellent literature review by Dr. Peter Kim in his review of NDA 21-669, CHG Antiseptic Cloths. This review is applicable to the Chlorascrub application.

### **8.7. Postmarketing Risk Management Plan**

Not applicable.

### **8.8. Other Relevant Materials**

None.

## **9. OVERALL ASSESSMENT**

### **9.1. Conclusions**

The medical reviewer concludes that Chlorascrub has been established as effective for the indications patient preoperative skin preparation and patient preinjection skin preparation as outlined in the TFM. The pivotal efficacy studies at \_\_\_\_\_ sufficiently support the patient preinjection indication, as well as the patient preoperative abdominal (dry) site as required by the TFM. The studies at \_\_\_\_\_ support the patient preoperative inguinal (wet) site required by the TFM. Chlorascrub is at least as effective as the positive control, Hibiclens, as a patient preoperative skin preparation. The \_\_\_\_\_ studies provide adequate evidence of the contribution of both active ingredients to the efficacy of the product.

Chlorascrub meets the TFM requirements for a patient preinjection skin preparation. It is not expected that CHG would make a contribution to the effect of the product for injection, since this indication is evaluated 30 seconds after prepping, and CHG is a slower acting antimicrobial than 70% IPA.

Based on the available safety information Chlorascrub is safe for the single use indications described above. Given the lack of systemic absorption, no additional safety evaluation is needed. The irritancy study establishes that Chlorascrub is an experimental cumulative irritant when repeatedly applied under occlusive dressings. Therefore, should

the sponsor choose to pursue an indication which would require repeated applications of the product, appropriate safety studies that simulate the proposed clinical use would be necessary.

The sensitization test did not demonstrate that Chlorascrub has a measurable potential for sensitization. However, previous reports indicate that certain individuals may be hypersensitive to applications of CHG to the mucous membranes. There is no clinical data or literature to suggest that the product would act differently in patients of varying sex, age  $\geq 2$  months, race, etc.

## 9.2. Recommendation on Regulatory Action

From the clinical perspective, Chlorascrub is safe and effective for the proposed uses and may be approved after labeling has been revised (see below).

## 9.3. Recommendation on Postmarketing Actions

### 9.3.1. Risk Management Activity

Not necessary or recommended.

### 9.3.2. Required Phase 4 Commitments

Not necessary or recommended.

### 9.3.3. Other Phase 4 Requests

None.

## 9.4. Labeling Review

The draft labeling submitted by the sponsor has been reviewed, along with the labeling for other recently approved CHG-containing products. The following comments are applicable:

A. In the "Drug Facts" section of the labeling:

1. In the "Uses" section, the second bullet should read:

• ~~\_\_\_\_\_~~

2. In the "Uses" section, the bullet '~~\_\_\_\_\_~~' should be deleted. This statement is acceptable elsewhere in the labeling, but is not a recognized indication.

3. In the "Do not use" section, the statement concerning use in infants should be rephrased as follows:
    - In premature or low birth weight infants, or ~~children~~ children less than 2 months of age because the potential for excessive skin irritation and increased drug absorption
  4. In the "Do not use" section, the bullet concerning ~~\_\_\_\_\_~~ deleted and incorporated in a new section (see below).
  5. A new section titled "When using this product" should be added, to read as follows:

**When using this product**, keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with cold water right away and contact a physician.
  6. A new section titled "Stop use and ask a doctor" should be added, to read as follows:

**Stop use and ask a doctor** if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition.
- B. On the carton labels (e.g., 50 Individual Swabsticks):
1. The comments above concerning "Drug Facts" should be applied to this label also.
  2. There are bullets on the front panel. The following revisions should be made:
    - i. ~~\_\_\_\_\_~~
    - ii. The words ~~\_\_\_\_\_~~ should be deleted from the second bullet.
- C. On the individual containers (e.g., One Swabstick, 1.6 mL each):
- i. The phrase, ~~\_\_\_\_\_~~ should be deleted from the front panel.
  - ii. On both the front and back panels, the following statement should appear in the largest possible type:

IMPORTANT: See carton for complete safety information.
- D. On the shipping label (e.g., 10 Boxes of 50 Individual Swabsticks): The comments above concerning "Drug Facts" should be applied.

## **9.5. Comments to Applicant**

The labeling comments listed above should be conveyed to the sponsor.

**Appears This Way  
On Original**

**Appears This Way  
On Original**

Appendices

I. Log Reductions at Groin Site by Subject (Study)

II. Log Reductions at Forearm Site by Subject (Study)

III. Log Reductions at Abdominal Site by Subject (Study)

IV. Log Reductions at Groin Site by Subject (Study)

Appendix I. Log Reductions at Groin Site by Subject (Study)

Patient No.	10 Minute			6 Hours			24 Hours		
	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens
1	2.41	-	3.22	5.45	-	2.93	-	-	-
2	4.06	-	1.99	1.74	-	1.27	2.16	-	2.13
4	2.05	2.30	-	3.41	0.82	-	1.70	0.17	-
7	5.19	-	0.91	2.99	-	1.90	1.39	-	1.77
9	-	-	-	4.14	-	3.17	3.05	-	1.58
13	-	2.24	1.92	-	-	-	-	1.43	3.64
14	-	-	-	1.91	2.24	-	2.30	1.63	-
19	2.58	4.53	-	-	-	-	2.24	4.45	-
23	2.31	-	1.77	-	-	-	5.43	-	2.51
24	-	2.78	-	-	1.56	-	-	0.99	-
25	1.51	1.95	-	2.27	1.75	-	-	-	-
26	-	5.56	1.17	-	-	-	-	1.37	2.79
29	-	-	-	3.06	2.14	-	3.13	6.54	-
32	1.92	-	4.22	2.25	-	2.37	3.74	-	0.93
36	-	-	-	5.43	4.52	-	5.56	2.06	-
41	-	3.30	3.29	-	1.51	2.19	-	1.14	2.49
42	3.30	2.94	-	5.18	3.75	-	-	-	-
43	3.20	5.87	-	1.92	2.17	-	3.23	1.40	-
44	-	1.96	1.76	-	-	-	-	2.12	2.34
59	-	2.53	1.21	-	2.95	2.23	-	0.69	1.37
62	-	2.33	1.18	-	1.98	1.72	-	0.01	-
63	4.63	-	2.88	-	-	-	2.40	-	2.00
67	3.38	3.62	-	-	-	-	1.34	0.83	-
76	3.07	-	1.46	3.23	-	2.49	-	-	-
77	4.33	2.76	-	3.11	2.81	-	-	-	-
78	3.55	-	1.61	1.14	-	1.24	2.29	-	2.06
80	-	3.16	1.27	-	1.33	2.33	-	-	-
84	-	4.09	3.09	-	1.33	2.18	-	-	-
85	3.16	-	2.02	2.54	-	1.94	-	-	-
86	2.70	4.06	-	5.46	2.40	-	-	-	-

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90	3.90	-	2.66	4.03	-	2.87	-	-	-
91	-	4.60	2.90	-	2.79	2.58	-	-	-
92	4.02	4.34	-	-	-	-	3.01	2.25	-
93	3.48	3.12	-	2.38	3.66	-	3.63	2.89	-
94	-	-	-	1.82	-	1.57	4.18	-	1.76
95	-	1.72	1.78	-	2.09	2.43	-	-	-
100	-	-	-	2.99	-	1.62	3.12	-	4.13
102	5.86	-	3.41	-	-	-	2.51	-	1.69
107	-	3.65	0.98	-	-	-	-	1.22	1.37
109	4.10	-	1.92	2.09	-	1.92	2.32	-	5.37
111	-	-	-	2.76	2.69	-	5.94	4.02	-
113	5.08	2.38	-	-	-	-	1.85	1.26	-
115	-	1.75	1.57	-	4.14	3.54	-	1.86	3.42
117	3.38	3.29	-	1.59	2.32	-	-	-	-
118	3.53	-	2.53	4.09	-	3.54	-	-	-
119	2.58	-	1.71	-	-	-	6.27	-	2.11
120	-	-	-	1.65	3.00	-	2.09	1.27	-
121	-	-	-	3.46	-	4.74	2.22	-	3.76
124	2.91	2.09	-	2.04	2.02	-	3.77	0.87	-
126	5.09	-	3.08	-	-	-	5.09	-	5.36
128	-	-	-	-	4.81	3.27	-	0.98	1.93
130	5.37	2.00	-	2.32	2.91	-	-	-	-
137	-	-	-	-	2.56	3.16	-	0.72	2.59
138	2.17	2.69	-	3.64	6.00	-	4.52	1.88	-
141	1.33	-	1.10	-	-	-	3.87	-	1.99
142	-	3.40	5.14	-	3.72	2.26	-	-	-
147	-	-	-	2.28	-	2.60	2.48	-	2.84
151	4.35	-	4.91	3.78	-	2.79	3.80	-	6.13
152	-	-	-	2.11	-	2.84	2.94	-	2.52
154	-	-	-	-	3.00	2.48	-	1.31	1.83
155	2.27	-	1.61	2.65	-	2.07	4.41	-	2.62
161	-	3.19	2.61	-	3.13	3.25	-	2.80	3.79
162	-	3.41	4.98	-	-	-	-	1.17	1.55
165	-	-	-	4.11	2.05	-	4.91	4.56	-
168	-	2.71	5.75	-	2.17	3.76	-	-	-
172	-	-	-	3.01	-	3.09	4.66	-	1.63
173	4.86	-	-	5.08	-	-	5.74	-	-
174	-	-	-	-	4.26	3.74	-	1.72	3.28
177	-	2.60	2.08	-	-	-	-	1.73	2.47
186	1.91	-	1.56	2.24	-	2.19	-	-	-
188	2.92	-	-	2.87	-	-	-	-	-
189	2.79	2.08	-	2.57	1.73	3.20	-	-	5.55
191	-	1.59	1.90	-	1.09	2.18	-	-	-

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193	-	-	-	-	2.80	3.50	-	1.20	3.82
195	2.32	-	1.81	2.89	-	4.98	3.41	-	4.11
197	2.51	1.69	-	-	-	-	5.06	1.38	-
204	2.31	2.55	-	2.64	2.61	-	3.19	0.79	-
205	3.66	2.48	-	-	-	-	5.10	1.10	-
209	-	2.19	-	-	2.22	-	-	1.70	-
210	-	-	4.84	-	2.74	3.69	-	2.23	2.43

Appendix II. Log Reductions at Forearm Site by Subject- 30 second time point

Patient No.	Chlorascrub	IPA	Hibiclens
2	2.37	-	3.45
4	-	4.19	3.15
7	1.88	-	2.69
9	-	-	2.76
13	3.32	-	1.71
19	2.55	-	1.33
25	1.17	3.87	-
26	1.82	-	3.47
29	1.51	1.09	-
32	1.73	0.98	-
43	2.12	-	1.59
76	2.65	-	-0.01
77	3.49	1.19	-
80	-	2.00	-
84	2.16	2.11	-
85	-	5.08	5.16
90	4.53	-	3.62
91	2.09	3.29	-
92	4.03	-	3.78
93	-	2.28	2.77
95	4.32	-	3.68
100	1.67	-	2.95
102	1.67	-	4.01
107	-	2.98	2.00
109	1.91	-	2.31
111	0.74	-	2.21
115	3.27	3.43	-
117	3.61	-	-
118	1.19	1.55	-
119	-	1.38	2.11
120	-	1.12	1.83
121	-	2.07	2.49
124	2.98	0.80	-
128	3.76	3.54	-
130	3.06	2.12	-
137	-	2.47	2.84
138	-	2.07	2.17
141	3.14	-	2.68
142	2.05	2.22	-
147	2.62	2.24	-
151	4.15	-	1.73

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152	-	3.15	2.56
154	-	2.20	2.38
155	2.37	2.90	-
160	2.85	2.92	-
161	3.54	-	3.30
162	-	2.08	1.19
165	-0.02	2.46	-
168	1.31	-	2.06
172	3.15	3.13	-
173	-	3.28	3.53
174	-	2.91	2.33
175	0.90	2.89	-
177	-	3.74	2.89
180	4.33	3.74	-
186	-	3.10	-
189	-	2.32	5.25
191	2.68	-	2.39
193	4.62	-	3.87
195	4.89	4.53	-
205	-	2.19	2.00
209	-	3.25	-
210	-	3.30	-

Appendix III. Log Reductions at Abdominal Site by Subject

Patient No.	10 Minute			6 Hours			24 Hours		
	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens
1	2.23	0.84	-	2.41	1.89	-	2.71	-0.16	-
2	2.07	2.87	-	1.94	-0.24	-	3.30	2.87	-
3	2.23	-	2.27	2.19	-	2.80	3.26	-	3.50
4	1.37	2.41	-	2.02	2.81	-	1.18	-1.02	-
5	-	1.37	1.98	-	2.32	2.46	-	1.42	-1.74
6	-	1.88	2.14	-	2.46	2.14	-	-	-
8	2.40	-	0.67	2.40	-	2.78	2.40	-	2.78
9	2.50	-	-	2.50	-	-	2.50	-	-
12	1.72	-	-	1.99	-	-	2.89	-	-
13	2.34	-	2.56	2.04	-	2.86	2.04	-	2.86
14	-0.41	-0.09	-	1.15	1.97	-	2.67	1.92	-
15	1.86	-	2.32	2.34	-	2.02	0.35	-	1.84
16	-	3.74	2.78	-	3.44	2.08	-	3.74	2.60
17	1.89	-	2.26	2.67	-	2.74	2.97	-	3.04
18	1.34	0.51	-	1.28	2.17	-	1.40	2.96	-
20	2.88	2.46	-	0.22	-0.51	-	1.87	2.44	-
21	2.45	-	2.58	2.45	-	2.58	1.68	-	0.93
22	4.75	-	2.91	4.75	-	3.32	3.97	-	3.48
23	3.55	3.14	-	3.55	3.14	-	1.77	3.14	-
24	-	1.92	2.89	-	2.87	2.89	-	2.17	2.89
25	-	2.02	-	-	0.43	-	-	2.02	-
26	-	-0.68	0.41	-	2.44	3.91	-	-1.08	0.16
29	-	-	-	4.41	-	2.88	5.54	-	2.89
36	1.39	-	2.55	1.64	-	1.01	1.64	-	0.19
37	-	4.16	2.69	-	4.03	3.53	-	4.50	4.23
39	1.97	-	3.17	2.30	-	3.17	3.08	-	3.17
40	2.51	-	1.67	3.91	-	3.13	3.91	-	2.78
41	-	2.41	2.08	-	2.41	1.38	-	2.21	2.08
42	-	1.80	2.60	-	2.70	3.20	-	2.70	1.63
45	3.47	-	0.52	2.03	-	3.74	0.95	-	1.38
46	-	3.36	-0.17	-	3.36	-0.15	-	1.22	2.43
49	-	3.02	1.51	-	1.15	2.39	-	3.02	3.23
51	-	2.56	1.65	-	3.40	2.13	-	3.40	2.43
52	2.64	-	2.27	-1.40	-	2.45	2.64	-	2.75
54	1.71	-	2.75	0.91	-	2.15	2.36	-	2.15
55	2.76	-	-	2.37	-	-	3.12	-	-
56	-	-	1.38	-	-	2.08	-	-	2.38
57	-	2.24	2.16	-	2.54	2.10	-	3.14	2.10
58	3.42	-	2.16	3.20	-	3.32	3.90	-	3.62
60	2.93	-	1.88	3.23	-	3.20	3.23	-	1.03

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61	-	0.36	2.82	-	1.56	3.30	-	1.79	1.22
63	2.25	-	2.11	-0.11	-	1.28	1.32	-	-0.63
64	2.06	2.70	-	2.25	2.70	-	2.76	2.70	-
67	3.80	3.74	-	3.80	3.44	-	1.57	3.74	-
68	3.28	3.62	-	3.28	3.62	-	3.28	3.62	-
69	-	2.05	-	-	1.91	-	-	0.63	-
70	1.88	-	1.81	2.48	-	2.23	2.78	-	2.41
71	-	1.82	-	-	2.60	-	-	2.60	-
72	-	2.92	2.36	-	2.92	2.66	-	1.56	1.09
73	1.85	2.21	-	1.97	2.04	-	1.75	2.23	-
77	2.44	1.97	-	1.79	1.55	-	2.44	2.45	-
78	2.60	2.48	-	2.90	2.78	-	2.20	2.30	-
84	3.04	2.67	-	3.04	2.67	-	3.04	2.67	-
85	3.14	3.20	-	3.14	2.90	-	2.54	1.92	-
88	-0.02	2.52	-	2.43	3.00	-	2.43	2.22	-
89	1.25	3.20	-	3.87	2.90	-	3.57	3.20	-
90	-	2.10	2.36	-	2.58	2.06	-	2.28	2.96
91	-	2.62	1.35	-	2.62	2.13	-	2.62	2.43
92	2.48	2.45	-	2.48	2.45	-	-	2.48	-
93	1.14	0.69	-	3.04	3.73	-	3.04	0.69	-
96	4.60	3.68	-	4.60	5.04	-	3.82	2.96	-
97	0.89	2.14	-	1.96	3.27	-	3.00	1.02	-
99	-1.58	-	-	2.50	-	-	2.50	-	-

Appendix IV. Log Reductions at Groin Site by Subject

Patient No.	10 Minute			6 Hours			24 Hours		
	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens	Chlorascrub	IPA	Hibiclens
1	-	-	-	2.29	-	2.39	1.97	-	2.74
2	1.95	2.89	-	3.10	2.86	-	2.03	1.40	-
3	0.98	-	-0.68	-	-	-	2.85	-	-
4	-	3.00	1.30	-	-	-	-	-	-
5	-	1.45	0.59	-	-	-	-	0.25	1.44
6	3.12	-	-	2.78	-	-	-	-	-
8	-	1.92	-	-	-	-	-	0.08	-
9	-	1.11	-	-	1.30	-	-	-	-
10	-	-	-	-	3.76	-	-	1.73	-
11	-	1.99	1.15	-	1.18	1.10	-	2.92	1.38
12	-	4.27	2.29	-	2.84	2.43	-	-	-
13	-	-	-	-	1.18	1.40	-	1.45	0.72
14	-	-	-	-	-	0.23	-	-	-
16	-	-	0.67	-	-	-	-	-	2.60
17	-	1.99	0.87	-	1.91	2.57	-	-	-
18	3.72	3.25	-	-	-	-	3.41	1.14	-
19	-	1.81	-	-	1.49	-	-	-	-
20	2.06	1.73	-	-	-	-	2.84	4.06	-
21	1.39	1.47	-	-	-	-	5.04	0.44	-
22	1.79	2.66	-	2.32	2.13	-	2.74	1.61	-
23	-	3.98	1.59	-	-	-	-	1.44	3.01
24	2.11	-	1.93	-	-	-	2.17	-	-
25	-	-	-	3.89	2.31	-	-	1.63	-
26	1.15	0.72	-	2.18	2.40	-	-	1.85	-
27	2.62	-	-	-	-	-	4.74	-	-
28	-	-	4.38	-	-	4.38	-	-	-
29	1.95	1.56	-	-	-	-	3.05	-0.12	-
30	-	0.31	-	-	-	-	-	-0.07	-
31	-	5.69	2.44	-	3.09	2.06	-	-	-
33	-	-	-	1.68	-	0.54	3.59	-	-
34	-	-	-	-	4.36	-	-	4.66	-
35	-	2.27	-	-	4.42	-	-	-	-
36	-	1.72	0.66	-	-	-	-	0.27	2.67
37	-	-	-	2.37	1.14	-	1.90	1.48	-
38	-	-	-	-	1.22	-	-	-	-
39	-	1.74	0.66	-	1.69	2.33	-	-	-
40	1.30	-	0.50	-	-	-	3.59	-	2.41
41	2.49	2.85	-	4.53	2.95	-	1.65	2.15	-
42	2.74	4.48	-	1.13	3.42	-	-	-	-
43	2.13	1.82	-	1.17	1.88	-	-	-	-

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45	3.37	1.91	-	1.94	4.01	-	1.72	-	-
46	2.71	-	0.71	2.30	-	-	-	-	-
47	2.86	-	3.73	0.83	-	1.21	2.54	-	0.79
48	2.02	-	2.07	2.68	-	2.88	-	-	-
49	-	-	-	-	2.09	2.00	-	1.89	2.09
51	-	2.56	0.39	-	1.97	1.29	-	1.81	3.35
52	-	-	-	1.45	4.52	-	2.53	1.14	-
53	-	-	-	2.42	1.90	-	3.23	1.82	-
54	-	1.12	1.12	-	4.03	2.06	-	1.70	2.41
55	2.73	2.26	-	2.94	2.37	-	3.22	1.84	-
56	1.66	1.39	-	1.71	0.07	-	-	-	-
57	1.26	0.62	-	1.82	0.78	-	-	-	-
58	2.90	-	-0.17	1.40	-	1.68	-	-	-
61	-	-	-	2.18	-	1.87	2.64	-	1.85
62	-	-	0.24	-	-	1.42	-	-	-
63 <sup>r</sup>	-	1.26	-	-	2.64	-	-	-	-
64	2.92	-	1.67	1.49	-	3.55	1.77	-	1.48
65	0.34	-	0.82	0.74	-	0.89	-	-	-
67	1.91	3.03	-	-	-	-	3.09	6.16	-
68	-	-	-	1.07	-	-	2.83	-	-
70	2.89	-	1.28	-	-	-	2.76	-	0.39
71	-	-	-	4.80	-	1.45	4.80	-	3.75
72	3.32	4.68	-	-	-	-	3.32	2.24	-
73	1.70	-	3.31	-	-	-	2.93	-	-
74	1.47	1.22	-	4.58	1.95	-	-	-	-
75	-	-	-	3.82	-	2.72	5.25	-	4.39
76	3.75	-	0.59	5.38	-	3.89	3.18	-	2.33
77	2.11	-	1.14	4.17	-	1.80	3.50	-	2.80
78	2.18	-	1.20	2.71	-	2.06	2.98	-	4.05
79	-	1.50	0.94	-	5.22	2.12	-	2.48	-
80	-	3.15	2.86	-	5.90	3.14	-	2.76	4.47
81	1.88	-	1.02	5.62	-	1.37	5.02	-	2.04
82	-	-	-	-	5.08	3.28	-	2.04	1.71
84	-	-0.05	0.64	-	-	-	-	2.04	-
86	4.13	3.03	-	3.35	2.05	-	2.03	2.74	-
87	-	-	-	1.52	-	2.63	4.38	-	5.46
88	-	1.44	1.70	-	-	-	-	-	-
89	4.54	-	-0.13	3.97	-	1.89	4.65	-	1.60
90	-	1.80	0.90	-	-	-	-	2.06	2.19
91	-	2.00	-	-	1.40	-	-	-	-
92	-	-	-	-	3.18	-	-	2.29	-
93	-	1.38	1.01	-	1.35	1.48	-	0.31	-
94	-	2.51	0.36	-	1.65	1.79	-	-	-

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95	-	-	-	-	3.79	1.34	-	0.51	2.79
96	1.16	-	0.65	3.40	-	1.29	-	-	-
97	1.47	-	1.18	-	-	-	2.77	-	-
98	-	-	-	1.55	-	0.34	1.02	-	0.37
99	-	-	-	5.65	-	2.29	5.17	-	-
101	-	-	-	1.62	-	1.68	1.54	-	2.47

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/s/

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