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*APPLICATION NUMBER:*

**21-524**

**MICROBIOLOGY REVIEW**

NDA 21 524  
Chlorascrub  
Les Enterprises SoluMed Inc  
Clinical Microbiology Review

**DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)  
CLINICAL MICROBIOLOGY REVIEW**

NDA 21-524

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Reviewer: Connie R. Mahon, MS

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**DRUG PRODUCT NAMES:**

**Proprietary Name:** Chlorascrub™  
**Established Name:** Chlorhexidine Gluconate (CHG), Isopropyl Alcohol (IPA)  
**Structural Formula:** 1,1'-hexamethylenebis[5-(p-chlorophenyl)biguanide]digluconate, proan-2-ol

**PROPOSED DOSAGE FORM AND STRENGTH:** 3.15% w/v CHG with 70% IPA in the following packaging configurations: Swab, Swabstick, And Maxi Swabstick

**ROUTE OF ADMINISTRATION:** Topical

**PROPOSED INDICATION(s):** For skin antisepsis prior to surgery, injection —

**RELATED SUBMISSION REVIEWED:** IND 59 446, NDA 20 832, DMF Nos. —

**TYPE OF SUBMISSION:** New Drug Application under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, 21 CFR 314.54.

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**PURPOSE OF SUBMISSION:**

This New Drug application (NDA) is submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR 214.54. The Applicant, Les Entreprises SoluMed Inc submits the Application for Chlorasrub™ Swabstick, Maxi Swabstick and Swab.

Chlorasrub™ is a topical antiseptic that contains two active ingredients, 3.15% (w/v) chlorhexidine gluconate and 70% (v/v) isopropyl alcohol (IPA). The Applicant relies on the Agency's previous finding of safety of Chloraprep® (Medi-Flex, Inc, NDA 20-832), a topical antiseptic product with similar ingredients, 2% (w/v) chlorhexidine and 70% (v/v) isopropyl alcohol.

The Applicant submits data to support the registration of Chlorasrub for the following intended uses:

**Swabstick**

- Skin antiseptic
- Skin preparation prior to surgery
- Skin preparation prior to injection

**Maxi Swabstick**

- Skin antiseptic
- Skin preparation prior to surgery
- Skin preparation prior to injection

**Swab**

- Skin antiseptic
- Skin preparation prior to injection

### EXECUTIVE SUMMARY

The Applicant, Les Enterprises SoluMed, Inc, provides data on three pivotal trials conducted to demonstrate the antimicrobial efficacy of Chlorascrub™ when compared to the product vehicle and a reference product. Additional studies include two safety/dermal studies to evaluate the human skin irritation and sensitization potential of Chlorascrub™. The Applicant seeks approval for the following product packaging configurations and indications:

Swab:	Skin antiseptic	
	Skin preparation prior to injection	_____
Swabstick:	Skin antiseptic	
	Skin preparation prior to injection	_____
	Skin preparation prior to surgery	
Maxi Swabstick:	Skin antiseptic	
	Skin preparation prior to injection	_____
	Skin preparation prior to surgery	

In the efficacy studies, the following product packaging configurations were used to test the body sites for proposed indications:

**Swab:** Forearm

**Swabstick:** Groin, Abdomen

**Maxi Swabstick:** Abdomen, Groin

In vitro microbiological studies include antimicrobial susceptibility tests to determine spectrum of activity for the test product, its vehicle, and a reference control. Additional data provided by the Applicant are tests results from time-kill studies and validation of neutralization procedure.

Chlorhexidine gluconate (CHG) and isopropyl alcohol (IPA) have been widely used as antiseptic agents for many years. CHG has been incorporated in various hospitals and over-the-counter applications including surgical or pre-operative scrubs, health care personnel hand wash, and impregnation of medical devices.<sup>1,2</sup> Similarly, isopropyl alcohol is used as an antiseptic agent in a wide variety of products including hand lotions, liquid soaps, and numerous cosmetic products.<sup>3,4</sup>

CHG has antimicrobial activity against vegetative gram positive and gram negative bacteria but has no killing action against bacterial spores except at increased temperatures.<sup>5,6</sup> It also shows activity against certain viruses and fungal species, although the levels of activity against the latter vary from genera to genera and species to species.<sup>4</sup> Like other alcohols, isopropyl alcohol exerts its antimicrobial effect by denaturation of proteins and is shown to be active against most vegetative bacterial cells.<sup>7,8</sup>

During recent years, there are concerns regarding the emergence of resistance to chlorhexidine and cross-resistance to clinically significant antibiotics. Review of the literature provided by the Applicant suggests lack of definitive evidence to show that

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there is an increase in the rate or level of resistance to CHG in the clinical setting. Results of studies in an attempt to demonstrate development of resistance are contradictory because of varying methodologies employed and the amounts of CHG used in the studies. Although the development of reduced susceptibility to biocides caused by continuous exposure to CHG may occur, the level of resistance is reported to be low and the CHG concentration used in antiseptics is much higher than the level of resistance. Nevertheless, investigators suggest that reduced susceptibility of microorganisms to CHG must be constantly monitored.<sup>9</sup>

The spectrum of antimicrobial activity of Chlorascrub (SoluPrep), its vehicle IPA and the reference product Hibiclens, were evaluated. Of the 1104 isolates tested, 98.1% (1083) were inhibited by  $\leq 50 \mu\text{g/mL}$ . If the concentration of  $50 \mu\text{g/mL}$  represents a 1:630 dilution of the 3.15% CHG solution ( $3.15 \times 10^4 \mu\text{g/mL}$ ), it appears that the organisms tested were highly susceptible to this agent. The susceptibility results provided by the Applicant are comparable to those previously reported for this type of product.<sup>10</sup> The Applicant met the number of isolates for each species and ATCC strains to be tested specified in the Tentative Final Monograph (TFM) for Topical Antimicrobial Drug Products for Over-the-Counter Human Use (Federal Register 59[116]:31450-31451; 17 Jun 94)<sup>11</sup> except for *Klebsiella* species because of an oversight in the testing laboratory. The rationale for this deficiency is provided in the review. For counting purposes, the Applicant provided results for all coagulase-negative staphylococci as a combined group of organisms.

Results of the time-kill studies provided by the Applicant indicate that the test product at a final dilution of 1:10 achieved the >99.9% reduction in viable microbial cells in  $\leq$  three (3) minutes, for those species that produced growth. These results were comparable to those achieved by Hibiclens.

Results of the neutralization validation studies showed that the neutralization solution used in the testing was non-toxic and effectively neutralized the activity of Chlorascrub at a 1:10 dilution.

The Applicant described the procedures used in conducting these studies. The procedures were those recommended in the Proposed Amendment of ASTM Method E 1054-91, Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents, Standard Practice Guide for the Assessment of Antimicrobial Activity of Test Materials using a Time-kill Procedure, ASTM Standards, Volume 11.04<sup>12</sup>, and NCCLS M7 A5-2000, M11-A5-2001,<sup>13</sup> and M27-A2-2001.<sup>14</sup>

The results of the clinical studies performed for the indication as an antiseptic prior to skin \_\_\_\_\_ of injection indicates that the test products, Chlorascrub swab, Chlorascrub Swabstick, and Chlorascrub Maxi Swabstick, achieved the averaged microbial load reduction recommended by the TFM. For this indication, the proposed TFM recommends that microbial load reduction of  $\geq 1 \log_{10} \text{CFU/cm}^2$  is achieved within 30 seconds of application.

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For the indication as a skin preparation prior to surgery, the proposed TFM<sup>11</sup> recommends microbial load reduction of  $\geq 2 \log_{10}$  CFU/cm<sup>2</sup> of skin on the abdomen test sites and  $\geq 3 \log_{10}$  CFU/cm<sup>2</sup> of skin on the groin test sites within 10 minutes after application and must remain below the baseline count for 6 hours after application.

The results obtained from the clinical studies indicate that the test products MAXI Swabstick and Chlorascrub Swabstick and their respective vehicle controls, achieved the averaged microbial load reduction on the abdomen and groin as recommended by the TFM<sup>11</sup> for antiseptic pre-operative skin preparation. The 6-hour and 24-hour post-preparation microbial populations remained below baseline populations. There is a significant difference found in microbial load between the product vehicle and test products at 24 hour post-preparation in the inguinal and abdominal sites. The Test product maintained a lower level count than the active vehicle did. Based on the results of the within-treatment t-test, the decrease in microbial counts at 30 seconds, 10 minutes, 6 hours and 24 hours in all test articles is statistically significant.

The results from the neutralization validation study performed during the clinical simulation studies showed that the neutralizer was effective in neutralizing the test product and non-toxic to the test organism. These results indicate that effective neutralization of the antimicrobial agent should take place at sampling time points. Results of the toxicity test indicate that the neutralizer does not contribute to the killing effects of the antimicrobial.

#### **CONCLUSION AND RECOMMENDATION:**

The data provided by the Applicant indicate that Chlorascrub swab, Swabstick, and Maxi Swabstick products met the TFM requirements<sup>11</sup> for antiseptic and skin preparation prior to injection and therefore, are acceptable for approval. The pre-operative skin preparation Chlorascrub Swabstick, and Maxi Swabstick met the  $\geq 2 \log_{10}$  microbial reduction for the abdominal site and  $\geq 3 \log_{10}$  microbial reduction at the inguinal site and therefore are recommended for approval.

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## I. GENERAL INFORMATION

Chlorascrub™ is a topical antiseptic that contains two active ingredients, 3.15% (w/v) chlorhexidine gluconate and 70% (v/v) isopropyl alcohol. The Applicant relies on the Agency's previous finding of safety of ChlorPrep® (Medi-Flex, Inc, NDA 20-832), a topical antiseptic product with similar ingredients, 2% (w/v) chlorhexidine and 70% (v/v) isopropyl alcohol.

### **Chlorhexidine gluconate**

First synthesized in the 1950's in laboratories in England where research for antimalarial agents was taking place, chlorhexidine was found to possess a high level of antibacterial activity, low toxicity in mammals, and high affinity for binding to skin and mucous membranes.<sup>7</sup> Because of these properties, chlorhexidine has been recognized as an effective antimicrobial agent for over 30 years. A wide range of antimicrobial products containing chlorhexidine have been developed and marketed worldwide, including the US. These products include surgical scrubs, health care personnel hand wash, pre-operative skin preparations, skin antiseptics, and many others.<sup>5,7</sup>

### Chemical Properties

Chlorhexidine gluconate solution is an aqueous solution of 1,1'-hexamethylenebis[5-(4-chlorophenyl)biguanide] di-D-gluconate. The drug substance contains not less than 19.0 percent and not more than 21.0 percent of (CHG)  $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$  (w/v). Chlorhexidine gluconate is manufactured as a 20% wt/vol aqueous solution. Because the antimicrobial activity of chlorhexidine is pH dependent, a pH range between          is ideal for stability. The optimum range of          corresponds to the pH of the body surfaces and tissues. At extreme acidic conditions, a gradual decrease in activity has been reported while at high alkaline pH, precipitation of the active component has occurred. Chlorhexidine is stable at room temperature but hydrolyzes at elevated temperatures (above 40°C).<sup>7</sup>

### Mechanism(s) of Action

Chlorhexidine shows both inhibitory and lethal actions against vegetative gram-positive and gram-negative bacteria; however, bacterial spores are resistant to its killing action even at high concentrations except at increased temperatures (98-100°C). It also shows activity against certain viruses and fungal species. The levels of activity differ from genera to genera and species to species. Acid-fast bacilli are inhibited but not killed by aqueous solution. Yeasts, including *Candida albicans*, are reported to be susceptible but fungicidal activity varies between species.<sup>6,7</sup>

The enhanced activity of chlorhexidine against GN species may be attributed to the mechanism of action of chlorhexidine. Because chlorhexidine is rapidly absorbed by

bacterial cells by virtue of the lipophilic groups of the drug molecules, cytological changes that induce permeability of the cells ensue. Electron microscopy and assays for characteristic outer membrane components demonstrated that sub lethal concentrations of chlorhexidine bring about changes in the outer membrane integrity of GN bacteria.<sup>2</sup> A series of associated cytologic and physiologic changes follow that lead to cell death. These series of events leading to cell death following the initial attraction toward the bacterial cell include strong and specific adsorption to certain phosphate-containing compounds on the bacterial surface; prevailing over the exclusion mechanism of the bacterial membrane.<sup>7</sup>

Chlorhexidine is a positively charged-molecule, therefore, it is strongly attracted to bacterial cells which are characteristically negatively charged. It has been reported that in an adequate amount of chlorhexidine, the surface charge of the bacterial cell is rapidly neutralized and become positively charged. The rapid changes in the charge of the bacterial cell membrane apparently cause damage to the permeability of the membrane and cause leakage of cytoplasm and nucleotides. The degree of charge reversal is proportional to the chlorhexidine concentration and becomes stabilized within 5 minutes. Although only secondary to the cause of death, the surface charge reversal is a major contributor to the rapid rate of killing associated with chlorhexidine. The rate of membrane disruption and cell leakage associated with exposure to chlorhexidine accelerates with increase in chlorhexidine concentration until it reaches a maximum. At bactericidal concentrations of 100 to 500 mg/L, leakage no longer occur, instead precipitation of cytoplasmic contents caused by interaction between chlorhexidine and phosphated elements in the cytoplasm takes place. As a result, the antimicrobial activity of chlorhexidine is immediate as well as persistent and cumulative.<sup>5</sup>

#### Mechanism(s) of Resistance

The means by which bacteria acquire resistance to antimicrobials remain inadequately defined, although repeated exposure to sub lethal concentrations of antibacterial agents contributes to their development. In general, there are four main sites in which antimicrobials exert their mechanisms of action in bacteria- cell wall synthesis, protein synthesis, nucleic acid synthesis, and cell membrane function. Unlike antibiotics which act selectively against specific cell targets, the overall mechanism of action of biocides appears to target one or several other sites within the cell; the overall damage to these sites results in the bactericidal effects of the biocide.<sup>10</sup> It has been reported, however, that many similarities exist between ways in which bacteria are able to resist the actions of antibiotics and biocides. Because of continuous and unrestrained usage of biocides and inclusion of materials such as benzalkonium chloride, chlorhexidine, and triclosan, in home cleaning and hygiene products, there are concerns that these mechanisms of resistance may confer cross- resistance to clinically important antibiotics. Although reports of cross-resistance between antibiotics used in humans and biocides are still comparatively few, microorganisms are exceedingly adaptable.<sup>16</sup>

The Applicant provided sufficient information regarding emerging resistance to chlorhexidine by means of published literature review. Review of the literature suggests

lack of evidence to show that there is an increase in the rate or level of resistance to chlorhexidine in clinical settings. Results of studies in an attempt to demonstrate development of resistance are contradictory because of varying methodologies employed and the amounts of CHG used in the studies. Although the development of reduced susceptibility to biocides in response of chlorhexidine exposure may be seen in vitro testing,<sup>12</sup> the level of resistance is low and that, the chlorhexidine concentration used in antiseptics is much higher than the level of resistance. Nevertheless, most investigators recommend that susceptibility and resistance of microorganisms to chlorhexidine should be monitored.

### **Isopropyl Alcohol**

The most widely used alcohol as an antiseptic agent is isopropyl alcohol (IPA). When used in concentrations of 60 % to 90%, it has a broad spectrum of activity, showing killing effects on bacteria, mycobacteria, fungi, and large, lipid-containing viruses but not against hydrophilic viruses. Alcohols in personnel hand wash, surgical scrub, and patient pre-operative skin preparations provide the most rapid and greatest reduction of microbial counts on skin. The antimicrobial activity of IPA is due to protein denaturation. Alcohol solutions containing 50% to 70% are found to be most effective.<sup>7</sup>

Because proteins are not readily denatured in the absence of water, higher concentrations above 95% are found to be less effective. A concern with alcohols is the flammability and potential for burn injury. The flash points of alcohols vary from 2°C to 24°C and depend on the type and concentration of alcohol present.<sup>7,8</sup>

## **II. IN VITRO INFORMATION**

To determine the appropriate *in vitro* testing to support the claim of a preoperative skin preparation, the Agency recommended that the Applicant refer to the Tentative Final Monograph (TFM) for Topical Antimicrobial Drug Products for Over-the-Counter Human Use (Federal Register 59[116]:31444-31445; 17 Jun 94). Effectiveness testing of patient preoperative skin preparation is described in the TFM for Topical Antimicrobial Drug Products for Over-the-Counter Human Use (Federal Register 59[116]:31450-31451; 17 Jun 94).<sup>11</sup>

### **Antimicrobial Susceptibility Studies**

The Applicant reports the results of the antimicrobial susceptibility tests performed on 1104 microbial isolates. Of these 660 (59.8%) were clinical isolates less than 2 years old and 906 (82.1%) were less than 3years old at the time when the study was performed. Microbial strains with known antimicrobial resistance were included as well as specific strains from the American type Culture Collection (ATCC) as indicated in the TFM.<sup>11</sup>

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The test product, SoluPrep® (Chlorascrub®) was provided by the Applicant to the testing laboratory as a 3.15% concentration dissolved in 70% isopropyl alcohol (IPA). Also provided were samples of commercially available 70% IPA, and Chlorhexidine gluconate as formulated in Hibiclens® (4% CHG) to be tested as comparison agents. (NDA 21-254, Vol 2.5 page 219).

The minimum inhibitory concentrations (MICs) were determined by broth microdilution method as described in the NCCLS (M7 A5-2000<sup>13</sup>, M11-A5-2001<sup>14</sup>, and M27-A2-2001<sup>15</sup>). The test media were varied accordingly with the species tested. SoluPrep and Hibiclens concentrations ranged from \_\_\_\_\_, based on the labeled content of 3.15% for SoluPrep and 4% for Hibiclens. The vehicle, IPA was tested over a range of 35% down to 4.4%.

Ten percent (10%) Polysorbate 80 and sodium thiosulfate, at 0.3% were also tested as reagents used in the neutralization procedure and were included in the MIC testing to determine if there was inhibitory activity on the panel of microorganisms being tested. The neutralizing solution, 3% lecithin and the neutralization suspension were also tested but because they produced opaque suspension, the Applicant reported that it was difficult to determine if growth had occurred. **Tables 1-4** show the in vitro antimicrobial susceptibility test results. For species with less than 10 strains tested, the MIC<sub>50</sub> and MIC<sub>90</sub> were not calculated. Actual MICs were rounded up to nearest log<sub>2</sub> dilution for calculating MIC<sub>50</sub> and MIC<sub>90</sub>.

**Table 1. In vitro antimicrobial susceptibility results of Chlorascrub, Hibiclens, and Isopropyl alcohol against gram negative bacterial isolates**

Organisms Tested	Number of isolates	SoluMed (Chlorascrub)			Hibiclens			IPA
		MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	Range (µg/mL)	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	Range (µg/mL)	%
<i>Acinetobacter anitratus</i>	17	16	32		16	32		>35
<i>Acinetobacter baumannii</i>	28	32	64		16	32		>35
<i>Acinetobacter lwoffii</i>	4	-	-		-	-		N/A
<i>Burkholderia cepacia</i>	21	64	128		32	128		>35
<i>Enterobacter aerogenes</i>	26	32	64		32	32		>35
<i>Enterobacter cloacae</i>	26	32	64		32	32		>35
<i>Escherichia coli</i>	51	4	4		2	4		>35
<i>Haemophilus influenzae</i>	28	16	32		16	32		>35
<i>Klebsiella pneumoniae</i>	16	32	64		16	32		>35

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<i>Klebsiella oxytoca</i>	11	32	64		32	32		>35
<i>Pseudomonas aeruginosa</i>	36	32	32		32	32		>35
<i>Proteus mirabilis</i>	36	32	64		32	64		>35
<i>Proteus vulgaris</i>	16	32	64		32	32		>35
<i>Serratia marscesens</i>	51	64	64		32	64		>35
<i>Stenotrophomonas maltophilia</i>	21	64	64		32	64		>35

CHG (3.5% w/v) = 3.15 gm/100mL = 3.15 x 10<sup>6</sup> µg/100mL  
 = 3.15 x 10<sup>4</sup> µg/mL

**Table 2. In vitro antimicrobial susceptibility results of Chlorascrub, Hibiclens, and Isopropyl alcohol against gram positive bacterial isolates**

Organisms Tested	Number of isolates	SoluMed (Chlorascrub)			Hibiclens			IPA
		MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	Range (µg/mL)	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	Range (µg/mL)	%
<i>Enterococcus faecalis</i>	31	16	16		8	16		>35
<i>Enterococcus faecium</i>	26	8	16		8	8		>35
<i>Enterococcus hirae</i>	1	-	-		-	-		>35
<i>Micrococcus luteus</i>	3	-	-		-	-		>35
<i>Streptococcus agalactiae</i>	53	8	8		8	8		>35
<i>Staphylococcus aureus (MS)</i>	53	4	4		2	2		>35
<i>Staphylococcus epidermidis (MS)</i>	16	4	4		2	4		>35
<i>Staphylococcus haemolyticus</i>	7	-	-		-	-		>35
<i>Staphylococcus hominis</i>	5	-	-		-	-		>35
<i>Streptococcus pneumoniae</i>	22	16	64		16	32		>35
<i>Streptococcus pyogenes</i>	51	4	8		8	8		>35
<i>Staphylococcus saprophyticus</i>	11	1	1		1	1		>35

**Table 3. In vitro antimicrobial susceptibility results of Chlorascrub, Hibiclens, and Isopropyl alcohol against resistant strains of bacterial isolates**

Organisms Tested	Number of isolates	SoluMed (Chlorascrub)			Hibiclens			IPA
		MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	Range (µg/mL)	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	Range (µg/mL)	%
<i>E. coli</i> ESBL+	6	-	-		-	-		>35
<i>H. influenzae</i> b-lac+	28	16	32		16	32		>35
<i>K. oxytoca</i> ESBL+	5	-	-		-	-		>35
<i>K. pneumoniae</i> ESBL+	5	-	-		-	-		>35
<i>P. aeruginosa</i> ciproR	15	32	64		32	32		>35
<i>E. faecalis</i> Van R	23	16	32		16	16		>35
<i>E. faecium</i> Van R	26	8	8		8	8		>35
<i>S. aureus</i> MR	53	4	8		2	4		>35
<i>S. epidermidis</i> MR	13	4	8		2	4		>35
<i>S. haemolyticus</i> MR	21	4	8		2	2		>35
<i>S. pneumoniae</i> Pen I	17	32	128		32	32		>35
<i>S. pneumoniae</i> PenR	17	64	64		32	32		>35

ESBL+ = extended spectrum β-lactamase producing strain  
 CiproR= Ciprofloxacin resistant  
 Van R= Vancomycin-resistant  
 MR= Methicilin-resistant  
 Pen I= Penicillin-intermediate  
 Pen R= Penicillin-resistant  
 β-lac+= β-lactamase-producing strain

**Table 4. In vitro antimicrobial susceptibility results of Chlorascrub, Hibiclens, and Isopropyl alcohol against yeasts and anaerobic bacterial isolates**

Organisms Tested	Number of isolates	SoluMed (Chlorascrub)			Hibiclens			IPA (%)
		MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	Range (µg/mL)	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)	Range (µg/mL)	%
<b>Yeasts</b>								
<i>Candida albicans</i>	57	32	32		32	32		>35
<i>Candida krusei</i>	17	16	32		16	64		>35
<i>Candida parasilopsis</i>	19	16	64		32	64		>35
<i>Candida tropicalis</i>	16	16	16		16	16		>35
<b>Anaerobic species</b>								
<i>Bacteroides fragilis</i>	55	16	16		16	32		>35
<i>Bacteroides thetaiotaomicron</i>	19	16	>35		16	32		>35
<i>Bacteroides species</i>	13	16	32		16	32		>35

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<i>P. brevia</i>	11	8	8	/	8	8	/	32
<i>E. lentum</i>	1	-	-		-	-		N/A

**COMMENTS:**

The spectrum of antimicrobial activity of SoluPrep, its vehicle IPA, and the reference product Hibiclens was evaluated. The minimum inhibitory concentrations (MICs) were determined by broth microdilution method as described in the NCCLS (M7 A5-2000<sup>13</sup>, M11-A5-2001<sup>14</sup>, and M27-A2-2001<sup>15</sup>). The test media were varied accordingly with the species tested. SoluPrep and Hibiclens concentrations ranged from \_\_\_\_\_ based on the labeled content of 3.15% for SoluPrep and 4% for Hibiclens. To convert SoluPrep (3.15% w/v) to µg/mL in the preparation for the MIC dilution testing, the following formula may be applied:

$$\text{CHG (3.5\% w/v)} = 3.15 \text{ gm/100mL} = 3.15 \times 10^6 \text{ µg/100mL}$$

$$= 3.15 \times 10^4 \text{ µg/mL as the starting concentration.}$$

The vehicle, IPA was tested over a range of 35% down to 4.4%. The vehicle 70% IPA (v/v) was diluted two-fold.

In accordance with the Tentative Final Monograph (TFM) FR 333.470 (1)(ii)<sup>11</sup> (Testing of health-care antiseptic drug products), 25 fresh clinical isolates and 25 laboratory strains of the organisms listed in the section are to be included in the *in vitro* testing to determine the *in vitro* antimicrobial spectrum of the antiseptic ingredient, vehicle, and the finished product. A total of 1104 isolates were tested; 896 aerobic strains, 99 anaerobic isolates, and 109 yeast isolates, combined. Of these 660 (59.8%) were clinical isolates less than 2 years old and 906 (82.1%) were less than 3years old at the time when the study was performed. Microbial strains with known antimicrobial resistance were included as well as specific strains from the American type Culture Collection (ATCC) as indicated in the TFM<sup>11</sup>. For each species listed in the TFM, a minimum of 50 clinical isolates and laboratory strains were tested, except for the following species:

- Staphylococcus epidermidis* (29)
- Staphylococcus haemolyticus* (28)
- Staphylococcus hominis* (5)
- Micrococcus luteus*(3)
- Staphylococcus saprophyticus* (11)
- Klebsiella species* (37)

When asked regarding the number of isolates tested, the Applicant's interpretation of the TFM requirements was to test the CNS as a group and not as individual species. For counting purposes, the Applicant consolidated all of the coagulase-negative staphylococcal species as a group, thereby meeting the number of isolates to be tested. The Applicant also asserted that those species, frequently encountered as contaminants, are of questionable clinical significance except in certain situations. The MIC range of the CNS species was \_\_\_\_\_. Because *M. luteus* is a colonizing skin flora, it is seldom recovered or identified from clinical specimen. Although *Micrococcus* rarely causes infections or problems in the body, those with compromised immune systems,

such as occurs with HIV+ patients, have been known to get skin infections caused by *Micrococcus luteus*. The skin infections, or chronic cutaneous infections, result in pruritic eruptions of the skin in some areas as well as scattered papule lesions with or without central ulcerations. *Micrococcus* as the cause of infections is easy to overlook because infections caused by this bacterium are rare as well as the bacterium is a natural part of the skin's bacterial flora.<sup>18</sup> The Applicant claimed that it would be extremely difficult to obtain the required number of clinical isolates of *M. luteus*.

Several years ago, isolation of coagulase-negative staphylococci from clinical sample, i.e. blood cultures, would be interpreted as most likely a contaminant because these organisms are members of the skin flora and rarely cause disease. With the advent of advances in medicine, such as the use of prosthetic devices, instrumentation, and organ transplantation, however, the make up of the patient population has greatly changed. Iatrogenic infections in this patient population caused by these organisms may occur following or as a result of medical treatment or procedures. Of the CNS species, *S. epidermidis* and *S. haemolyticus* are the most clinically significant. Nevertheless, coagulase-negative staphylococcal species including *S. hominis*, an occasional isolate from wound and blood cultures, and *S. saprophyticus*, a frequent cause of urinary tract infections in young women, are becoming more significant.<sup>20</sup>

The Applicant provided the MIC results of 37 of the 50 strains of *Klebsiella* species required in the TFM. When asked to explain, the Applicant responded that it was due to an oversight at the laboratory that conducted the study (written response from Applicant dated 30 March 2005). The MICs of the 37 *Klebsiella* isolates ranged from \_\_\_\_\_  $\mu\text{g/mL}$ ; the MICs of extended-spectrum  $\beta$ -lactamase (ESBL) producing strains and the MICs of the non-ESBL producing strains did not differ. *Klebsiella* species are usually found in the gastrointestinal tracts of humans and animals. *K. pneumoniae*, the most commonly isolated species, is a frequent cause of lower respiratory tract infections among hospitalized patients. *K. pneumoniae* and other *Klebsiella* species have also been recovered from wound infections, urinary tract infections, and bacteremia.<sup>15</sup> However, clinical study of post surgical wound infections found that gram positive bacteria account for 42% of the isolates while among the gram negative organisms, *E. coli* 10%, and *P. aeruginosa* 8%, account for 18% of the isolates.<sup>21</sup>

The results of the in vitro susceptibility tests show that SoluPrep was slightly more active against aerobic gram positive bacteria when its activity is compared to aerobic gram negative strains, with MIC<sub>90</sub> of 16  $\mu\text{g/mL}$  and 64  $\mu\text{g/mL}$ , respectively. The highest MIC<sub>90</sub>s obtained were that of *Burkholderia cepacia* and penicillin-intermediate *S. pneumoniae* with MIC<sub>90</sub> of 128  $\mu\text{g/mL}$ . Among the anaerobic species tested, most bacterial species produced MICs of 16  $\mu\text{g/mL}$ . The activity of SoluPrep was comparable to those obtained with Hibiclens. With regards to the activity of SoluPrep against yeasts, the susceptibility varied among the different species, with MIC ranges from \_\_\_\_\_  $\mu\text{g/mL}$ . *C. albicans* showed a slightly higher MIC<sub>50</sub> than other *Candida* species (MIC<sub>50</sub> of 32  $\mu\text{g/mL}$  vs. 16  $\mu\text{g/mL}$  for other species), except for *C. parasilopsis*, showing the MIC<sub>90</sub>

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of 64 µg/mL .

The antimicrobial activity of SoluPrep against resistant strains showed varied results. When compared with susceptible strains, ciprofloxacin- resistant *P aeruginosa*, methicillin-resistant *S. aureus* and *S. epidermidis*, and vancomycin -resistant enterococci, showed no significant differences in SoluPrep MICs. However, the MICs for ESBL-producing *E. coli* were higher than those that did not produce ESBL. A similar observation can be made with regards to penicillin resistant- or intermediate *S. pneumoniae* when compared with penicillin-susceptible strains. The MIC<sub>50s</sub> of the resistant strains were 2- to 4- fold higher than the susceptible ones, although the MIC<sub>90</sub> for the three groups were more similar.

### CONCLUSION:

The Applicant provides in vitro susceptibility tests results on the bacterial and yeast species listed in the TFM. Although the number of isolates for each species and ATCC strains required to be tested to demonstrate in vitro effectiveness was met for most species. For counting purposes, the Applicant combined the coagulase-negative staphylococci as a group (total 73), therefore, meeting the recommended number of isolates to be tested. Because *M luteus* is a common skin colonizer and although has been recovered from clinical samples, infections with this organism is rare. Therefore, the number of isolates tested may be considered acceptable. The number of isolates of *Klebsiella species* (37) recommended for testing was not met because of an oversight at the testing laboratory that conducted the study. The Reviewer finds the number of isolates tested acceptable for this study. The MIC results provided by the Applicant are comparable to those previously reported for this type of product.<sup>5, 22</sup>

### Time Kill Studies

Time-kill studies were done to demonstrate the *in vitro* bactericidal and fungicidal activity of the test product. The time-kill studies were conducted according to the draft "Standard Practice Guide for the Assessment of Antimicrobial Activity of Test materials using a Time-Kill Procedure, ASTM Standards, Vol 11.04<sup>12</sup>. The following panel of microorganisms was tested.

- *S. aureus* ATCC 6538
- *S. aureus* ATCC 29213
- *S. epidermidis* ATCC 12228
- *M. luteus* ATCC 7468
- *E. faecalis* ATCC 29212
- *E. coli* ATCC 11229
- *E. coli* ATCC 25922
- *P. aeruginosa* ATCC 15442
- *P. aeruginosa* ATCC 27853
- *S. marcescens* ATCC 14756

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Neutralizer reagents include 3% lecithin, 10% polysorbate 80, and 0.3% sodium thiosulfate. Blood agar plates without neutralizer were used for subcultures and recovery counting method. The Test Product, SoluPrep was tested at final dilutions of 1:10 and 1:100; Hibiclens at a single dilution of 1:100. The inoculum was prepared to the concentration of McFarland 0.5 standard turbidity as determined with a densitometer. The resulting initial microbial population was approximately  $2-6 \times 10^6$  CFU/mL. Following the TFM, microbial  $\log_{10}$  reduction for each challenge microorganism was determined, following exposures to the product, samplings at zero, 3 min., 6 min., 9 min., 12 min., 15 min., 20 min., and 30 min. were taken. All plates were incubated at 37°C for 24 hours and then the number of viable cells was determined. Calculations were based on the method described in the ASTM procedure<sup>12</sup>. Table 5 shows the baseline microbial population (CFU/mL) for each species tested. Tables 6-8 show the microbial  $\log_{10}$  reductions for each challenge organism following exposures to the product at each sampling time.

**Table 5. Original Microbial Population Raw Count (CFU/mL)**

Bacterial Species	Raw Count (CFU/mL)							
	Sample Time (min)							
	0	3	6	9	12	15	20	30
<i>S. aureus</i> 6538								
<i>S aureus</i> 29213								
<i>E faecalis</i> 29212								
<i>S epidermidis</i> 12228								
<i>M luteus</i> 7468								
<i>E coli</i> 11229								
<i>E coli</i> 25922								
<i>P aeruginosa</i> 15422								
<i>P aeruginosa</i> 27853								
<i>S marcescens</i> 14756								

0 time= immediate (<3 minutes)

**Table 6 Time Kill Studies  $\log_{10}$  Reduction from Original Microbial Population Chlorasrub 1:10 Final Concentration**

Bacterial Species	Sample Time (min)							
	0	3	6	9	12	15	20	30
<i>S. aureus</i> 6538	2.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
<i>S aureus</i> 29213	2.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
<i>E faecalis</i> 29212	0.4	3.2	4.4	3.7	3.0	4.0	4.0	4.0
<i>S epidermidis</i> 12228	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
<i>M luteus</i> 7468	No growth	No growth	No growth	No growth	No growth	No growth	No growth	No growth
<i>E coli</i> 11229	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1
<i>E coli</i> 25922	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2

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<i>P aeruginosa</i> 15422	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
<i>P aeruginosa</i> 27853	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1
<i>S marcescens</i> 14756	4.6	4.3	4.3	4.3	4.3	4.3	4.3	4.3

0 time= immediate (<3 minutes)

**Table 7 Time Kill Studies Log<sub>10</sub> Reduction from Original Microbial Population  
 Chlorascrub 1:100 Final Concentration**

Bacterial Species	Sample Time (min)							
	0	3	6	9	12	15	20	30
<i>S. aureus</i> 6538	0.5	4.2	4.2	4.2	4.2	4.2	4.2	4.2
<i>S aureus</i> 29213	0.1	4.0	4.0	4.0	4.0	4.0	4.0	4.0
<i>E faecalis</i> 29212	0.1	0.7	1.2	1.8	2.3	2.5	3.7	3.7
<i>S epidermidis</i> 12228	2.5	3.6	3.6	3.6	3.6	3.6	3.6	3.6
<i>M luteus</i> 7468	No growth	No growth	No growth	No growth	No growth	No growth	No growth	No growth
<i>E coli</i> 11229	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1
<i>E coli</i> 25922	2.6	4.2	4.2	4.2	4.2	4.2	4.2	4.2
<i>P aeruginosa</i> 15422	3.4	4.2	4.2	4.2	4.2	4.2	4.2	4.2
<i>P aeruginosa</i> 27853	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1
<i>S marcescens</i> 14756	0.4	3.6	4.0	4.3	2.9	2.9	4.3	4.3

0 time= immediate (<3 minutes)

**Table 8 Time Kill Studies Log<sub>10</sub> Reduction from Original Microbial Population  
 Hibiclens 1:100 Final Concentration**

Bacterial Species	Sample Time (min)							
	0	3	6	9	12	15	20	30
<i>S. aureus</i> 6538	3.8	4.2	4.2	4.2	4.2	4.2	4.2	4.2
<i>S aureus</i> 29213	2.4	3.8	4.0	4.0	4.0	4.0	4.0	4.0
<i>E faecalis</i> 29212	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
<i>S epidermidis</i> 12228	2.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
<i>M luteus</i> 7468	No growth	No growth	No growth	No growth	No growth	No growth	No growth	No growth
<i>E coli</i> 11229	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1
<i>E coli</i> 25922	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
<i>P aeruginosa</i> 15422	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
<i>P aeruginosa</i> 27853	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1
<i>S marcescens</i> 14756	3.8	4.3	4.3	4.3	4.3	4.3	4.3	4.3

0 time= immediate (<3 minutes)

**COMMENTS:**

Time-kill studies show that at 1:10 and 1:100 dilutions, SoluPrep produced  $\geq 3$  log (>99.9%) killing effect in  $\leq 3$  minutes on organisms that produced growth, except for *Enterococcus faecalis* ATCC 29212 where at 1:100 dilution of SoluPrep,  $\geq 3$  log reduction was not achieved until after 20 minutes of exposure. Whereas, at the same dilution, Hibiclens achieved a 99.9% reduction in viable organisms in  $\leq 3$  minutes for all organisms tested. During the initial review, it was noted by the Reviewer that *Micrococcus luteus* ATCC 7468 failed to grow in these studies. When asked to explain, the Applicant responded that *M luteus* grows very poorly in the broth media used to prepare in the starting inoculum and has always been a problem in conducting these experiments. During the review of the time-kill studies, the Reviewer noted that the viability controls showed inconsistent microbial counts and microbial reductions over the course of test time. The Applicant explained that the reduction in viable cells in the viability control tubes was within the acceptable limits of error for this procedure, and that the minor reduction may probably be due to clumping of the organisms. It was also noted that in testing *E. coli* ATCC 11229, the viability control plates were reportedly dropped, but the test procedure was not repeated. The Applicant explained that the plates that were dropped were only for the 6 minutes time interval and that excluding this time interval from the analysis had no effect on the trend noted for all other time intervals.

**CONCLUSION:**

The results of the studies provided by the Applicant indicate that the test product SoluPrep (Chlorascrub) at a final dilution of 1:10 achieved a  $\geq 99.9\%$  reduction in viable microbial cells in  $\leq 3$  minutes for those that produced growth. These results are comparable to those achieved with Hibiclens (4% CHG).

**Neutralization Validation Studies**

Chemical agents commonly known as neutralizers or inactivators are often used in the evaluation of the bactericidal effects of antimicrobial agents, antiseptics, and disinfectants. The neutralizers selected for performing these evaluations should not only be able to completely inactivate all bactericidal activity of the residual antimicrobial agent but must also be inherently non-toxic to the test organisms.<sup>23</sup> The neutralizer system must be validated to make certain that the neutralizing solutions function accordingly.

Neutralization validation studies were performed to ensure that the neutralizing agent used in all post-exposure testing was non-toxic to the microorganisms and was effective in neutralizing the inhibitory effects of the antimicrobial agent. The Applicant described the methods in the Proposed Amendment of ASTM Method E 1054-91, *Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents, August, 2001*,<sup>12</sup> as the methods used to validate the neutralizing agents and the process of neutralization used in these studies. Trypticase soy broth (TSB) with neutralizing agents 10% polysorbate 80, 3% lecithin, and 0.3% sodium thiosulfate, was evaluated to determine its ability to neutralize chlorhexidine gluconate in the SoluPrep formulation. Tests to determine if the

neutralizing agents have toxic effects on the microorganisms were also performed. The two strains used in the validation studies were *Escherichia coli* ATCC 11229 and *Staphylococcus aureus* ATCC 6538. In these validation studies, as specified by the ASTM method,<sup>12</sup> the product and neutralizers were mixed prior to the addition of the microorganism. Viability of test strains and product effectiveness to inhibit microorganisms were set up as growth control and effectiveness control, respectively. Tables 9-10 show the results and interpretations of the neutralization validation studies.

**Table 9. Neutralization evaluation In vitro Studies  
*Escherichia coli* ATCC 11229**

Test	Sample Time	Agar Medium	Mean CFU/mL	Mean CFU/mL of All plates (14) counted	Log <sub>10</sub> reduction from original microbial count	Comments
Efficacy	0 min	BAP	95.125	95.5	1.9800034	Effective
		TSA+N	95.875			
	30 min	BAP	97.75	96.625	1.9850895	
		TSA+N	95.5			
Toxicity	0 min	BAP	95.625	95.875	1.9817054	Non-toxic
		TSA+N	96.125			
	30 min	BAP	97.5	98.1875	1.9920562	
		TSA+N	98.875			
Viability	0 min	BAP	97.625	96.0625	1.9825539	Positive growth control
		TSA+N	94.5			
	30 min	BAP	98.75	97.1875	1.9876104	
		TSA+N	95.625			
Activity	0 min	BAP	0	0	0	Test product active
		TSA+N	0			
	30 min	BAP	0	0	0	
		TSA+N	0			

**Table 10 Neutralization evaluation In vitro Studies  
*Staphylococcus aureus* ATCC 6538**

Test	Sample Time	Agar Medium	Mean CFU/mL	Mean CFU/mL of All plates (14) counted	Log <sub>10</sub> reduction from original microbial count	Comments
Efficacy	0 min	BAP	112.0	113.75	2.0555951	Effective
		TSA+N	115.0			
	30 min	BAP	117.125	115.43	2.062319	
		TSA+N	113.75			
Toxicity	0 min	BAP	118.25	116.625	2.066792	Non-toxic
		TSA+N	115.0			
	30 min	BAP	118.625	117.063	2.06842	
		TSA+N	115.5			

Viability	0 min	BAP	116.125	116.188	2.065161	Positive growth control
		TSA+N	116.25			
	30 min	BAP	120.5	120.625	2.081437	
		TSA+N	120.75			
Activity	0 min	BAP	0	0	0	Test product active
		TSA+N	0			
	30 min	BAP	0	0	0	
		TSA+N	0			

#### COMMENTS:

The results of the neutralization studies show that the neutralizer used in the study was not toxic to either organism tested. The neutralizing solution was effective in completely neutralizing the effects of the test solution at 1:10 dilution. However, the Applicant reported that in an undiluted concentration of the test solution, preliminary experiments indicated that the neutralizer was not able to completely neutralize the test solution. Results of the preliminary experiments were not provided. The implications of these findings were not provided. The test solution without neutralizer showed 100% effectiveness at killing both test organisms at a 1:10 dilution.

#### CONCLUSION:

The results of the neutralization studies show that the neutralizing agent was non-toxic and was effective at a 1:10 dilution of the test product.

#### OVER ALL SUMMARY AND CONCLUSION: IN VITRO STUDIES

The in vitro studies of the antimicrobial spectrum of activity of Chlorascrub (3.15% in 70% isopropyl alcohol) showed that, of the 1104 organisms tested, 1083 (98.1%) were inhibited by <50 µg/mL of Chlorascrub. Hibiclens, the reference product used in the studies inhibited a total of 1097(99.4%) at the same concentration. Twenty one strains of bacteria showed a Chlorascrub MIC of >50 µg/mL. The MIC results obtained by the Applicant and presented for review were comparable to those previously reported for this type of product.

The results of the time-kill studies indicate that the test product Chlorascrub at a final dilution of 1:10 achieved a > 99.9% reduction in viable microbial cells in <3 minutes of exposure, with the exception of *Micrococcus luteus*, where the organisms failed to grow in the study. These results were comparable to those achieved with Hibiclens.

In the neutralization validation studies, the Applicant reported that the methods used to validate are those recommended in the Proposed Amendment of ASTM Method E 1054-91, *Standard Test Methods for Evaluation of Inactivators of Antimicrobial Agents*, August, 2001.<sup>12</sup> The neutralization solution consists of 10% polysorbate 80, 3% lecithin, and 0.3% sodium thiosulfate. The results show that the solution effectively neutralized the activity of Chlorascrub at a 1:10 dilution and no toxicity was detected.

### III. ANTIMICROBIAL CLINICAL EFFICACY STUDIES

#### A. Background and Introduction

The Applicant submits the results of three efficacy and safety clinical trials to support the approval of three product configurations of Chlorascrub (3.15% chlorhexidine in 70% isopropyl alcohol), namely, swab, Swabstick, and Maxi Swabstick, as a topical antiseptic for the following indications:

- Skin preparation prior to injection
- Skin preparation prior to surgery (pre-operative)
- Help reduce bacteria that potentially can cause skin infection

The products are for hospital and professional use only. The three drug products have been classified under dosage form swab. The table below summarizes the proposed uses for each packaging configurations (test products).

**Table 11 Proposed Uses for each Test Product Packaging Configuration**

Proposed Uses (Indications)	Packaging Configuration (Test Products)		
	Swab	Swabstick	Maxi Swabstick
Pre-operative skin prep	NA	X	X
Pre-injection	X	X	X
Antiseptic	X	X	X

NA= Not applicable

X= Indicated

Preliminary clinical studies were performed to determine the optimum concentration of Chlorascrub test product, the optimum treatment time, area, and application technique. Based on these studies, the optimum concentration of 3.15% of chlorhexidine in 70% IPA was chosen. The optimum treatment times for each anatomical sites were the following: 30 seconds (plus 30 seconds drying time) on the forearm; 1.5 minutes (plus 1.5 minutes drying time) on the abdomen, and 2 minutes (plus 1.5 minutes drying time) on the groin. The optimum treatment area and doses chosen for each applicator appropriate for the following anatomical sites were as follows:

**Table 12 Summary of Treatment area and doses for each anatomical site**

Applicator	Doses	Size of treatment Area	Anatomical Site
Swab	1 mL	2.5 x 2.5 inches	Forearm
Swabstick	1 mL	4 x 4 inches	Abdomen and Groin
Maxi Swabstick	1 mL	7 x 7 inches	Abdomen and Groin

### **Test Materials**

Swab contains 3% (w/v) CHG with 70% IPA. The applicant provided the testing facility with documentation for the Product Code 101.5- Chlorascrub Swab – containing 3.15% CHG with 70% IPA. Active Vehicle- Chlorascrub Swab Vehicle contained 70% IPA. Test articles were to be applied over a 2.5 x 2.5 inches area of the forearm and allowed to air dry for 30 seconds.

Swabstick, contains 3% (w/v) CHG with 70% IPA. The applicant provided the testing facility with documentation for the Product Code 102.02- Chlorascrub Swabstick – containing 3.15% CHG with 70% IPA. Active Vehicle- Chlorascrub Swabstick Vehicle (labeled 102.05) contained 70% IPA. These applicators are to be applied for 2 minutes over a 4 x 4 inches area of skin and allowed to air dry for 1.5 minutes

Maxi Swabstick, contains 3% (w/v) CHG with 70% IPA. The applicant provided the testing facility with documentation for the Product Code 102.06- Chlorascrub Maxi Swabstick – containing 3.15% CHG with 70% IPA ; Active Vehicle- Chlorascrub Maxi Swabstick Vehicle. The Applicant provided documentation that the Product Code 102-06- was saturated with 5.0 mL of 70% IPA only. These applicators were to be applied topically for two minutes over a 7 x 7 inch area of skin and allowed to air dry for 1.5 minutes.

Reference Product- Hibiclens contains 4% CHG to be applied topically for 2 minutes and dried with a sterile towel and applied for another 2 minutes and dried with another sterile towel. Hibiclens was applied over a 2.5 x 2.5 inches area on the forearm, 7 x 7 inches area of skin (when used to compare with Maxi Swabstick) and 4 x 4 inches area of skin (when used to compare with Swabstick).

### **Criteria for Evaluation**

Per TFM<sup>11</sup>, for efficacy, the product is considered effective as an antiseptic prior to skin — or injection if it shows microbial load reduction of  $\geq 1 \log_{10}$  CFU/per sq cm of skin on the forearm or abdomen (dry site); as a skin preparation prior to surgery,  $\geq 2 \log_{10}$  CFU/per sq cm of skin on the abdomen and  $\geq 3 \log_{10}$  CFU/per sq cm of skin on the groin test sites within 10 minutes after product application, and the CFU for each test site does not exceed baseline counts 6 hours after product application.

### **Methods**

Inclusion Criteria for Subjects

The subjects were healthy individuals between 18-70 years old with no evidence of dermatoses, dermatitis, inflammation or injuries to groin treatment areas. Main criteria for inclusion were  $\geq 2 \log_{10}$  CFU/per sq cm of skin of the forearm test sites,  $\geq 2.5 \log_{10}$  CFU/per sq cm on the skin of the abdominal test sites and ,  $\geq 4.5 \log_{10}$  CFU/per sq cm on the skin of the groin test sites when sampled at baseline test day.

The pre-test phase of the study was a 14-day period prior to the screening week during which the subjects are to avoid use of hygiene products with antibacterial activity.

Treatment area and application sites

The test products, active vehicle controls, and reference product were applied to the designated treatment area and anatomical application sites configuration as shown on Table 13.

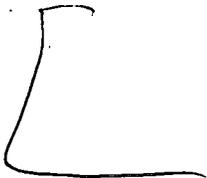
**Table 13. Test Article Configuration at Each Clinical Test Site**

Clinical Test Site	Test article configuration Treatment area and application sites				
	Swab	Swabstick		Maxi Swabstick	
	Forearm	Abdomen	Groin	Abdomen	Groin
	2.5 x 2.5 in	X	4 x 4 in	7 x 7 in	X
	2.5 x 2.5 in	4 x 4 in	X	X	7 x 7 in
	X	X	X	X	3 x 7.5 in

X= Not done

Treatment Site Collection and Sampling Procedures

Sampling procedures from treatment baseline site for each of the body were performed as follows:

1. 
2. 
3. 

The scrub method was repeated with an additional 3 mL of sampling fluid and both samples were pooled into a sterile tube.

Pivotal Studies at Clinical Tests Sites

Pivotal efficacy and safety studies were conducted by the Applicant to obtain approval for Chlorascrub as a topical antiseptic for pre-injection and pre-operative skin preparation. Two pivotal safety studies were conducted at \_\_\_\_\_ Two additional pivotal efficacy and safety studies were conducted at \_\_\_\_\_ and \_\_\_\_\_ clinical study SLM-SC-03 and clinical study SLM-SC-04, respectively. A third pivotal safety and efficacy study was conducted at \_\_\_\_\_

During the clinical development, it was established that in \_\_\_\_\_, Maxi Swabstick applicator would be tested on the abdomen, and Swabstick applicator on the groin; while at \_\_\_\_\_, Swabstick applicator would be tested on the abdomen and Maxi Swabstick on the groin, in a cross-over study design, as summarized below. Both clinical test sites performed tests on forearms using the Chlorascrub Swab, Swabstick, and Maxi Swabstick test products, vehicle and reference control articles. The table below summarizes the test article configurations.

**Table 14 Summary of Test article configuration at each Clinical test site for each anatomical site**

Clinical Test Site	Test article configuration				
	Swab	Swabstick		Maxi Swabstick	
	Forearm	Abdomen	Groin	Abdomen	Groin
_____	X	0	X	X	0
	X	X	0	0	X

X= done  
 0=not done

A third pivotal safety study was conducted at \_\_\_\_\_ – SLM-SC-08- because the study conducted at \_\_\_\_\_ did not meet the TFM test requirements at the groin site at ten (10) minute sample time for all three treatment test articles, (test article, vehicle and reference product) Results of the studies at \_\_\_\_\_ are shown below on Tables 22 and 23 of this review. When asked to conduct another study, the Applicant was informed by \_\_\_\_\_ that the evaluability rate at \_\_\_\_\_ was only 20%. In a teleconference (11/19/2003, Vol 2.1 page 129), according to the Applicant, the Division agreed that the third pivotal study may be conducted at \_\_\_\_\_ to evaluate the efficacy and safety of the test product, its vehicle, and the reference product as a pre-operative skin preparation on just the groin site for ten (10)minutes, six hours, and 24 hours after application.

Neutralization Studies

Each clinical site where pivotal studies were conducted performed neutralization validation tests to assure the validity of the neutralizer used in the recovery medium. All sites followed similar procedures.

A neutralization validation study was performed to verify the validity of the neutralizer(s) used in the sampling solution. The neutralizer was tested to 1) determine the effectiveness of the neutralizer for inactivating the microbiocidal properties of the antimicrobial agent. 2) Make certain that no components of the neutralizing process and agents cause an inhibitory or toxic effect on target microorganisms for recovery. The in vitro neutralization assay performed was based on the ASTM Standard E 1054-02 Standard Methods for Evaluation of Inactivators of Antimicrobial Agents.<sup>12</sup> The test organism used for the neutralization study was *Staphylococcus epidermidis* ATCC 12228.

### Neutralization Procedure



The numbers control, toxicity, and test article evaluations were performed in a similar manner as described before, with the exception of the numbers control, where the scrub solution contained sterile water without neutralizer instead of the test article. The toxicity control was performed with sterile water in place of a test article and plated on TSA with and TSA without neutralizer. The test article was performed with scrub solution without neutralizer.

### **B. Evaluation of the Antimicrobial Efficacy of the Chlorascrub™ Swab, Swabstick and Maxi Swabstick as an antiseptic for SKIN PREPARATION PRIOR TO INJECTION**

To be approved for the pre-injection skin preparation indication, Swab, Swabstick, and MAXI Swabstick must reduce the mean numbers of bacteria by 1 log<sub>10</sub>/cm<sup>2</sup> on the dry skin site within 30 seconds after application.

The immediate and persistent antimicrobial effects of the pre-injection skin preparation were evaluated on the forearm (median cubital area) and abdominal site. The test products were Chlorascrub (SoluPrep) Swab (3.15% CHG in 70% IPA), Swabstick, and Maxi Swabstick, active vehicle controls Swab, Swabstick, and Maxi Swabstick in 70% IPA, and reference product, Hibiclens. The test products, corresponding vehicle controls, and reference product, were applied topically over 2.5 x 2.5 inches (with the Swab) on the forearm, 4 x 4 inches (with Swabstick), and 7 x 7

inches (with the MAXI Swabstick) on the abdomen, respectively.

Performed at \_\_\_\_\_, (Clinical Evaluation (SLM-SC-03)(Vol 2.26 Section 10.4.3 pages 43-69), a minimum of 60 human subjects for the forearm and abdominal portions were enrolled, utilizing bilateral products applications. Each of the 3 products configurations was evaluated on forty (40) anatomical sites for each exposure periods. The immediate and persistent effects of the test articles were evaluated at 30 seconds and 24 hrs after skin prepping the forearm; 30 seconds, 10 minutes, 6 hours and 24 hours post-skin prepping the abdominal and groin sites.

**Summary of Results of the Clinical Efficacy Studies for the Indication Pre-Injection Skin Preparation (Vol 2.1 Sec 3.8.2.4 pages 157-160)**

The following tables (Tables 15 and 16) below show the mean log<sub>10</sub> reduction of bacterial count from the averaged baseline and test-day baseline colony counts. The averaged baseline count is given.

**Study Site:** \_\_\_\_\_

**Test Article: Swab**

**Anatomical Site: Forearm**

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**Table 15. Clinical Study SLM-SC-03 (Study # 020509-103)**

Test articles	Averaged log <sub>10</sub> Baseline count	Mean log <sub>10</sub> reductions (from averaged baseline)		Mean log <sub>10</sub> reductions (from test-day baseline)	
		30 secs	24 hrs	30 secs	24 hrs
Chlorascrub Swab	3.28	2.70	2.55	2.64	2.49
IPA	3.17	2.69	2.37	2.65	2.32
Hibiclens	3.27	2.75	2.41	2.69	2.35

**Test Article: MAXI Swabstick**

**Anatomical Site: Abdomen**

Treatment Area: 7 x 7 inches

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**Table 16. Clinical Study SLM-SC-03 (Study # 020509-103)**

Test articles	Averaged log <sub>10</sub> Baseline Count	Mean log <sub>10</sub> reductions (from averaged baseline)				Mean log <sub>10</sub> reductions (from test-day baseline)			
		30 secs	10 min	6 hrs	24 hrs	30 secs	10 min	6 hrs	24 hrs
Chlorascrub	3.37	2.79	2.86	2.83	3.09	2.65	2.72	2.70	2.96
IPA	3.27	2.72	2.57	2.51	2.49	2.59	2.44	2.38	2.36
Hibiclens	3.36	2.33	2.11	2.58	2.50	2.30	2.08	2.55	2.47

**Comments:**

In this study, the Applicant reported that the log<sub>10</sub> bacterial counts (at test day baseline and averaged baseline) of subjects assigned to the different test articles were not

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statistically significant (p value=0.93). For the indication as an antiseptic for skin preparation prior to injection \_\_\_\_\_ the TFM requires a  $\geq 1 \log_{10}$  reduction in CFU/cm<sup>2</sup> of skin on the dry skin site (forearm or abdomen) within 30 seconds and should remain below the baseline count for 24 hours after application.

The results of these studies show the  $\log_{10}$  CFU/ cm<sup>2</sup> reduction of bacterial load from baseline count was achieved at 30 seconds sampling time by each test articles, Swab Swabstick and Maxi Swabstick and remained below the baseline count for 24 hrs after the application.

The results from the neutralization validation study performed during the clinical simulation studies showed that the neutralizer was effective in neutralizing the test product and non-toxic to the test organism.

\_\_\_\_\_ conducted clinical studies (Clinical Evaluation (SLM-SC-04)(Vol 2.26 Section 10.4.4 pages 70-107) to evaluate and compare the antimicrobial effectiveness of the test articles as an antiseptic for pre-injection preparation. In these studies, data from 33 forearm and 42 abdominal sites treated with the test products were obtained; 32 forearm and 40 abdominal sites with IPA, and 32 forearm and 35 abdominal sites treated with Hibiclens were evaluated. The test products were Chlorascrub (SoluPrep) Swab (3.15% CHG in 70% IPA), Swabstick, and Maxi Swabstick, active vehicle controls Swab , Swabstick, and Maxi Swabstick in 70% IPA, and reference product, Hibiclens.

#### Neutralization Studies

A neutralization study was performed to assure the validity of the neutralizer used in the recovery medium.

#### **Indication: Pre-Injection Skin Preparation**

**Study Site:** \_\_\_\_\_

**Test Product: Swab**

**Anatomical Site: Forearm**

Treatment size: 2.5 x 2.5 inches

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**Table 17 Clinical Study SLM-SC-04 / \_\_\_\_\_ (01-108607-11)**

Test articles	Averaged baseline count	Mean $\log_{10}$ reductions (from averaged baseline)		Mean $\log_{10}$ reductions (from test-day baseline)	
		30 secs	24 hrs	30 secs	24 hrs
Chlorascrub Swab	3.20	2.01	2.22	2.02	2.23
IPA	3.33	1.98	1.81	1.92	1.76
Hibiclens	3.16	1.99	2.28	2.04	2.33

**Test Product: Swabstick**

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**Anatomical Site: Abdomen**

Treatment size: 4 x 4 inches

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**Table 18 Clinical Study SLM-SC-04 (01-108607-11)**

Product	Averaged baseline count	Mean log <sub>10</sub> reductions (from averaged baseline)				Mean log <sub>10</sub> reductions (from test-day baseline)			
		30 secs	10 min	6 hrs	24 hrs	30 secs	10 min	6 hrs	24 hrs
Chlorascrub	3.27	2.38	2.23	2.38	2.54	2.37	2.22	2.37	2.53
IPA	3.33	2.04	2.24	2.49	2.13	2.08	2.29	2.53	2.17
Hibiclens	3.28	2.03	2.04	2.49	2.17	1.98	1.99	2.44	2.13

**Comments:**

The Applicant reports that the log<sub>10</sub> bacterial counts of the subjects assigned to the different test articles were not significantly different from the averaged baseline (p value= 0.2781). The results from these studies show that the test products met the proposed reduction of  $\geq 1 \log_{10} \text{CFU/cm}^2$  required for an antiseptic for skin preparation prior to injection \_\_\_\_\_ and the log<sub>10</sub> CFU/cm<sup>2</sup> remained below the baseline count for 24 hours after application.

The results from the neutralization validation study performed during the clinical simulation studies showed that the neutralizer was effective in neutralizing the test product and non-toxic to the test organism.

**OVER ALL CONCLUSION FOR THE INDICATION AS AN ANTISEPTIC PRIOR TO \_\_\_\_\_ INJECTION**

For the indication as an antiseptic prior to \_\_\_\_\_ injection, the proposed TFM recommends microbial load reduction of  $\geq 1 \log_{10} \text{CFU/cm}^2$  of skin microbial load within 30 seconds after application on a dry skin site and must remain below the baseline count for 24 hours after application.

The results obtained from the clinical studies performed at \_\_\_\_\_ indicate that the test products Chlorascrub Swab, MAXI Swabstick and Chlorascrub Swabstick, their respective vehicle controls and reference product Hibiclens, achieved the averaged microbial load reduction recommended by the TFM for antiseptic pre-injection skin preparation.

The results from the neutralization validation study performed during the clinical simulation studies showed that the neutralizer was effective in neutralizing the test product and non-toxic to the test organism. These results indicate that effective neutralization of the antimicrobial agent should take place at sampling time points. The results of the toxicity tests indicate that the neutralizer does not contribute to the killing

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 effects of the antimicrobial.

**Evaluation of the Antimicrobial Efficacy of the Chlorascrub™ Swab, Swabstick and Maxi Swabstick as PRE-OPERATIVE SKIN PREPARATION**

Per TFM <sup>11</sup>, to be approved for the pre-operative skin preparation indication, Swabstick, and MAXI Swabstick must reduce the mean numbers of bacteria by  $\geq 2 \log_{10}$ CFU/cm<sup>2</sup> on the dry skin site (abdomen) and  $\geq 3 \log_{10}$ CFU/cm<sup>2</sup> in moist area (groin) within 10 minutes after application and must not exceed the baseline counts six (6) hours after product application.

Clinical Evaluation (SLM-SC-03)(Vol 2.26 Section 10.4.3 pages 43-69)

The clinical studies to demonstrate efficacy of Chlorascrub Swabstick and Maxi Swabstick, as pre-operative skin preparations, were conducted at \_\_\_\_\_ Corresponding vehicle controls and Hibiclens as the reference product control were also tested. At \_\_\_\_\_, the immediate and persistent antimicrobial effects of the test products for pre-operative skin preparations were evaluated. At \_\_\_\_\_, Maxi Swabstick, its vehicle and Hibiclens, were tested on the abdomen; Swabstick, its vehicle, and Hibiclens as reference control, were tested on the groin site. The results from these clinical studies are shown below.

**Test Article: MAXI Swabstick**

Anatomical Site: Abdomen

Treatment size: 7 x 7 inches

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**Table 19 Clinical Study SLM-SC-03 ( Study # 020509-103)**

Test articles	Mean log <sub>10</sub> reductions (from averaged baseline)				Mean log <sub>10</sub> reductions (from test-day baseline)			
	30 secs	10 min	6 hrs	24 hrs	30 secs	10 min	6 hrs	24 hrs
Chlorascrub	2.79	2.86	2.83	3.09	2.65	2.72	2.70	2.96
IPA	2.72	2.57	2.51	2.49	2.59	2.44	2.38	2.36
Hibiclens	2.33	2.11	2.58	2.50	2.30	2.08	2.55	2.47

**Test Article: Swabstick**

Anatomical Site: Groin

Treatment size: 4x4 inches

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**Table 20 Clinical Study SLM-SC-03 ( Study # 020509-103)**

Test Article	Mean log <sub>10</sub> reductions (from averaged baseline)				Mean log <sub>10</sub> reductions (from test-day baseline)			
	30 secs	10 min	6 hrs	24 hrs	30 secs	10 min	6 hrs	24 hrs
Chlorascrub	2.92	3.36	3.05	3.5	2.89	3.32	3.01	3.50
IPA	2.72	3.04	2.67	1.75	2.71	2.97	2.66	1.78
Hibiclens	2.37	2.48	2.71	2.81	2.33	2.46	2.70	2.78

At \_\_\_\_\_ Maxi Swabstick, its vehicle and Hibiclens as reference control, were tested on the groin site; Swabstick, its vehicle and Hibiclens as reference control, were tested on the abdomen. The results from these studies are shown below.

**Test Article: MAXI Swabstick**

**Anatomical Site: Groin**

Treatment size: 7x7 inches

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**Table 21 Clinical Study SLM-SC-04 (01-108607-11)**

Product	Mean log <sub>10</sub> reductions (from averaged baseline)				Mean log <sub>10</sub> reductions (from test-day baseline)			
	30 secs	10 min	6 hrs	24 hrs	30 secs	10 min	6 hrs	24 hrs
Chlorascrub (MaxiSwab)	2.20	2.38	2.68	3.22	2.06	2.28	2.68	3.09
IPA	2.44	2.23	2.66	1.90	2.35	2.18	2.61	1.75
Hibiclens	1.51	1.26	2.05	2.53	1.38	1.22	1.97	2.40

**Test Product: Swabstick**

**Anatomical Site: Abdomen**

Treatment size: 4x4 inches

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**Table 22 Clinical Study SLM-SC-04 (01-108607-11)**

Product	Mean log <sub>10</sub> reductions (from averaged baseline)				Mean log <sub>10</sub> reductions (from test-day baseline)			
	30 secs	10 min	6 hrs	24 hrs	30 secs	10 min	6 hrs	24 hrs
Chlorascrub (Swabstick)	2.38	2.23	2.38	2.54	2.37	2.22	2.37	2.53
IPA	2.04	2.24	2.49	2.13	2.08	2.29	2.53	2.17
Hibiclens	2.03	2.04	2.49	2.17	1.98	1.99	2.44	2.13

Clinical studies to demonstrate efficacy were conducted at \_\_\_\_\_ to evaluate and compare the immediate and persistent antimicrobial activity of Maxi Swab, Maxi Swab Vehicle and Hibiclens for pre-operative skin preparations, and 2) evaluate and compare the safety of all three test articles. The study tested 41 groin sites with Maxi Swab; 41 groin sites with Maxi Swab Vehicle and 41 groin sites with Hibiclens.

**Test Product: MAXI Swabstick**

**Anatomical Site: Groin**

Treatment size: 3.5 X 7 inches

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**Table 23 Clinical Study SLM-SC-08 (521-1021)**

Product	Mean log <sub>10</sub> reductions (average of screening and treatment day baseline)		
	10 min	6 hrs	24 hrs
Chlorascrub (Maxi Swabstick) (41)	3.9	4.1	4.3
Vehicle(41)	3.6	2.9	2.7

Hibiclens(41)	3.0	3.4	3.7
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**Comments:**

The results from the studies conducted at \_\_\_\_\_ (SLM-SC-03) show that the test product Chlorascrub Maxi Swabstick, its vehicle control, and reference product, Hibiclens, achieved the microbial reduction of  $\geq 2\log_{10}$  CFU/cm<sup>2</sup> of skin on the abdomen test site within 10 minutes after application and did not exceed the baseline counts at 6 and 24 hours after application. The test product Swabstick and its vehicle control when tested on the groin site, achieved the microbial load reduction of  $\geq 3 \log_{10}$  CFU/cm<sup>2</sup> of skin on the groin within 10 minutes after application; however, the reference product Hibiclens failed to meet the microbial load reduction of  $\geq 3 \log_{10}$  CFU/cm<sup>2</sup> within 10 minutes after application per TFM <sup>11</sup>proposed recommendations.

The results of the tests performed at \_\_\_\_\_ (SLM-SC-04) show that the test articles Chlorascrub Swabstick and its vehicle control, met the recommended microbial reduction of  $\geq 2\log_{10}$  CFU/cm<sup>2</sup> of skin on the abdomen test site within 10 minutes after application and did not exceed the baseline counts at 6 and 24 hours after application. The reference product Hibiclens achieved the microbial reduction of  $\geq 2\log_{10}$  CFU/cm<sup>2</sup> of skin on the abdomen test site within 10 minutes using the averaged baseline count but not the test-day baseline count.

When tested on the groin site, all test articles (Chlorascrub Maxi Swabstick, its vehicle and reference product controls) failed to meet the proposed microbial load reduction of  $\geq 3\log_{10}$  CFU/cm<sup>2</sup> of skin on the groin test site within 10 minutes after application. To examine the reasons why all the test articles did not achieve the  $\geq 3\log_{10}$  CFU/cm<sup>2</sup> reduction on the groin site within 10 minutes after application, \_\_\_\_\_ conducted another study and determined that in the clinical study (SLM-SC-03), a treatment size of 3 x 5 inches was used with the Swabstick applicator on the groin but in the clinical study, ( SLM-SC-04), a treatment area of 7x7 inches was used with the Maxi Swabstick applicator on the groin ( SLM-SC-04) ( Vol 2.1 Sec 3 page 168) according to the Applicant. \_\_\_\_\_ then conducted the study using a treatment area of 5x6 inches with Maxi Swabstick, an area that is closer to the treatment area used in the clinical study SLM-SC-03, according to the Applicant's report. In this study, where the size of the treatment area was reduced and the treatment area was changed from below the tendon to above the tendon on the groin resulted in Chlorascrub achieving the evaluation criteria of  $\geq 3\log_{10}$  CFU/cm<sup>2</sup> reduction; however, the study was discontinued because of low numbers of subjects meeting the screen and baseline inclusion criteria.

In a teleconference with the Agency on 19 November 2003, the Applicant received permission from the Division to conduct a new pivotal clinical study at \_\_\_\_\_ (SLM-SC-08) to test the efficacy of Chlorascrub Maxi Swabstick only on the groin for 10 minutes, 6 hours and 25 hrs after application. The results are shown on Table 23. Using the average of screening and treatment day baseline log-transformed bacterial counts, as

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shown, the Chlorascrub test product Maxi Swabstick reduced the averaged number of bacterial by  $3.9 \log_{10} \text{CFU/cm}^2$  on the groin, the vehicle by 3.6, and the reference product, Hibiclens, achieved a  $3.0 \log_{10}$  reduction. At  a treatment area of 3 x 7.5 inches was used.

Table 24 below shows a summary of the mean  $\text{Log}_{10}$  reductions achieved (average of screening and treatment day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts) within 10 minutes, six (6) hours, and 24 hours post-preparation using the Swabstick and MAXI Swabstick Pre-operative Skin Preparation Test Articles and controls. In this table, it shows that the  $\log_{10}$  reductions of  $\geq 2 \log_{10} \text{CFU/cm}^2$  of skin on the abdomen were achieved using the Chlorascrub Swabstick, Maxi Swabstick, respective vehicle controls, and reference product Hibiclens. When tested on the groin site, Chlorascrub Swabstick and Maxi Swabstick, respective vehicle controls, and reference product Hibiclens achieved the microbial load reduction of  $\geq 3 \log_{10} \text{CFU/cm}^2$  of skin after 10 minutes of application. The 6-hour and 24-hour post-preparation microbial populations remained below baseline populations. There is a significant difference found in microbial load between the product vehicle and test products at 24 hour post-preparation in the inguinal and abdominal sites. The test product maintained a lower level count than the active vehicle did.

**Table 24. Summary of Mean Log<sub>10</sub> Reductions Achieved after Using the Swabstick and MAXI Swabstick Pre-operative Skin Preparation Test Articles and Controls by Sampling Site, Sampling Time and Study – Forearm for support of Preinjection Site Preparation and Abdomen and Groin for support of Preoperative Skin Preparation.**

Sampling Site Sampling Time Study	Chlorascrub (Test Product)		Isopropyl Alcohol (Active Vehicle Product)		Hibiclens (Comparator Product)	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
<b>Forearm Site</b>						
Log Reduction <sup>1</sup> at:						
30 Seconds						
SLM-SC-03	41	2.7 (2.3,3.1)	41	2.7 (2.4,3.0)	38	2.8 (2.4,3.1)
SLM-SC-04	41	2.0 (1.6,2.3)	38	1.9 (1.6,2.3)	41	1.9 (1.5,2.2)
24 Hours						
SLM-SC-03	41	2.5 (2.2,2.9)	41	2.4 (2.0,2.7)	38	2.4 (2.0,2.8)
SLM-SC-04	41	2.0 (1.7,2.4)	37	1.8 (1.4,2.2)	37	2.1 (1.8,2.4)
<b>Abdomen Site</b>						
Log Reduction <sup>1</sup> at:						
10 Minutes						
SLM-SC-03	40	2.9 (2.5,3.2)	42	2.6 (2.2,2.9)	40	2.1 (1.7,2.5)
SLM-SC-04	46	2.2 (1.9,2.5)	45	2.2 (1.9,2.5)	41	2.1 (1.8,2.3)
6 Hours						
SLM-SC-03	40	2.8 (2.5,3.1)	42	2.5 (2.2,2.9)	40	2.6 (2.2,2.9)
SLM-SC-04	46	2.4 (2.1,2.7)	45	2.4 (2.2,2.7)	41	2.4 (2.1,2.6)
24 Hours						
SLM-SC-03	40	3.1 (2.9,3.3)	42	2.5 (2.2,2.8)	40	2.5 (2.1,2.9)
SLM-SC-04	46	2.5 (2.3,2.7)	44	2.1 (1.8,2.5)	40	2.1 (1.8,2.5)
<b>Groin Site</b>						
Log Reduction <sup>1</sup> at:						
10 Minutes						
SLM-SC-03	41	3.4 (3.0,3.7)	39	3.0 (2.7,3.4)	39	2.5 (2.1,2.9)
SLM-SC-04 <sup>2</sup>	48	2.2 (1.9,2.5)	49	2.2 (1.9,2.5)	49	1.3 (1.0,1.7)
SLM-SC-08	41	3.9 (3.6,4.2)	41	3.6 (3.3,3.9)	41	3.0 (2.6,3.3)
6 Hours						
SLM-SC-03	42	3.0 (2.7,3.4)	39	2.7 (2.3,3.0)	40	2.7 (2.4,3.0)
SLM-SC-04 <sup>2</sup>	49	2.7 (2.3,3.1)	46	2.4 (2.0, 2.8)	50	1.9 (1.6,2.2)
SLM-SC-08	41	4.1 (3.8,4.4)	41	2.9 (2.6,3.1)	41	3.4 (3.1,3.7)
24 Hours						
SLM-SC-03	40	3.5 (3.1,3.9)	37	1.7 (1.3,2.2)	38	2.8 (2.4,3.2)
SLM-SC-04 <sup>2</sup>	45	3.2 (2.9,3.5)	43	1.9 (1.5,2.2)	40	2.4 (2.0,2.7)
SLM-SC-08	41	4.3 (4.0,4.7)	41	2.7 (2.4,2.9)	41	3.7 (3.4,4.1)

CI = confidence interval.

<sup>1</sup> Log Reduction = average of Screening and Treatment Day baseline log-transformed bacterial counts minus post-treatment log-transformed bacterial counts.

<sup>2</sup> Data included for completeness. Study SLM-SC-08 was conducted on the groin site after problems identified with application used in Study SLM-SC-04 (volume 1, section 3 page 169).

Note: Only subjects with data available from a treatment pair for a given sampling time point are included in this summary table. This table was prepared by the Agency Statistics Reviewer.

**OVER ALL CONCLUSION FOR THE INDICATION AS PRE-OPERATIVE SKIN PREPARATION**

For the indication as a skin preparation prior to surgery, the proposed TFM recommends microbial load reduction of  $\geq 2 \log_{10}$  CFU/cm<sup>2</sup> of skin on the abdomen test sites and  $\geq 3 \log_{10}$  CFU/cm<sup>2</sup> of skin on the groin test sites within 10 minutes after application and must remain below the baseline count for 6 hours after application.

The results obtained from the clinical studies performed at \_\_\_\_\_ indicate that the test products MAXI Swabstick and Chlorascrub Swabstick, their respective vehicle controls, achieved the averaged microbial load reduction on the abdomen as recommended by the TFM<sup>11</sup> for antiseptic pre-operative skin preparation. However, the reference product Hibiclens failed to achieve the averaged microbial load reduction at the groin site in all clinical simulation studies performed at 3 locations. The 6-hour and 24-hour post-preparation microbial populations remained below baseline populations. There is a significant difference found in microbial load between the product vehicle and test products at 24 hour post-preparation in the inguinal and abdominal sites. The Test product maintained a lower level count than the active vehicle and reference product. Based on the results of the within-treatment t-test, the decrease in microbial counts at 30 seconds, 10 minutes, 6 hours and 24 hours in all test articles is statistically significant.

The results from the neutralization validation study performed during the clinical simulation studies showed that the neutralizer was effective in neutralizing the test product and non-toxic to the test organism. These results indicate that effective neutralization of the antimicrobial agent should take place at sampling time points. The results of the toxicity test indicate that the neutralizer does not contribute to the killing effects of the antimicrobial.

**CONCLUSION AND RECOMMENDATION:**

The data provided by the Applicant indicate that Chlorascrub swab, Swabstick, and Maxi Swabstick products met the TFM<sup>11</sup> requirements for antiseptic and skin preparation prior to injection \_\_\_\_\_, and therefore, are acceptable for approval. The pre-operative skin preparation Chlorascrub Swabstick, and Maxi Swabstick met the  $\geq 2 \log_{10}$  microbial reduction for the abdominal site and  $\geq 3 \log_{10}$  microbial reduction at the inguinal site and therefore recommended for approval.

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