

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-555

Microbiology Review(s)

NDA No.20-832
ChloraPrep One-step
Medi-Flex Hospital Products, Inc.

1 of 16

**Division of Anti-Infective Drug Products
Clinical Microbiological Review # 3.**

NDA # 21-555

Date Completed: September 20, 2002

Sponsor (IND)/Applicant (NDA):

Beckloff Associates, Inc (agent)
Medi-Flex Hospital Products, Inc.
Suite 750
8717 W. 110th St.
Overland Park, KS 66215

Chem/Ther. Type: Antimicrobial

Submission Reviewed: December 10, 2001

Providing for: Preoperative Skin Preparation and Patient preinjection skin preparation using a new product configuration called a Sepp®.

Product Name(s): ChloraPrep One-Step

Proprietary: chlorhexidine gluconate

Non-proprietary/USAN: chlorhexidine gluconate

Compendia: chlorhexidine gluconate

Code name/number: NA

Chemical name: 1,1'-Hexamethylenebis[5-(*p*-chlorophenyl) biguanide] di-D-gluconate

Structural formula: See USP Dictionary of USAN and International Drug Names, page 147

Molecular formula: C₂₂H₃₀C₁₂N₁₀·2C₆H₁₂O₇

Dosage form(s): 2% chlorhexidine gluconate in 70% isopropanol (IPA)

Route(s) of administration: Topical

Pharmacological Category: antiseptic

Dispensed: Rx X OTC

Review #1:

Initial Submission Dates

Received by CDER: January 15, 1997 (Volumes 1.1, 1.3, and 1.9)

Received by Reviewer: January 23, 1997

Review Completed: January 23, 1998

Supplements/Amendments:

Received by CDER: August 8, 1997 (Volumes 1.2 and 2.2)

Received by Reviewer: August 20, 1997

Review Completed: January 23, 1998

Review #2:

Initial Resubmission Dates

Received by CDER: January 13, 2000 (Volumes 1 through 11)

Received by Reviewer: January 13, 2000

Review Completed: July 11, 2000

Supplements/Amendments Resubmission dates:

Received by CDER: February 2, 2000

Received by Reviewer: February 2, 2000

Review Completed: July 11, 2000

Review #3:

Initial Resubmission Dates

Received by CDER: December 10, 2001 (Volumes 1 of 1)

Received by Reviewer: January 19, 2001

Review Completed: September 20, 2002

Supplements/Amendments Resubmission dates:

Received by CDER: September 12, 2002

Received by Reviewer: September 16, 2002

Review Completed: September 20, 2002

Related Documents: NA

Remarks:

On January 15, 1997 the applicant submitted a New Drug Application for ChloraPrep® One-Step (2% chlorhexidine gluconate) seeking approval for the indication ☐
1 Two product configurations were submitted, the first was a Sepp, which contained 0.67 mL of 2% chlorhexidine gluconate in 70% isopropanol (IPA), and the second was a Frepp, which contained — of 2% chlorhexidine gluconate in 70% isopropanol (IPA). Subsequently, on February 20, 1998 the Food and

ChloraPrep One-step

Medi-Flex Hospital Products, Inc.

Drug Administration, Division of Anti-infective Drug Products issued a not approvable letter under section 505(d) of the Act and 21CFR 314.125(b)(5) to Medi-Flex Hospital Products, Inc. The letter listed numerous deficiencies associated with the original submission of the ChloraPrep NDA when used as a

The deficiencies included non-compliance with the Federal Register Notice¹ requirements for the assessment of efficacy. In general, the deficiencies included inadequate *in vitro* spectrum of activity studies, clinical simulation trial design, validation of the neutralization system, and poor data presentation and analysis.

On January 13, 2000, the applicant, Medi-Flex Hospital Products, Inc resubmitted the NDA for the ChloraPrep product in the Frepp 3.0-mL applicator configuration but **not** for the original antiseptic indication

Instead, the applicant increased the volume of the Frepp product from 1.0 mL to 3.0 mL and now requested evaluation for preoperative skin prepping prior to invasive surgery. Thus, the responses by the applicant to the deficiencies identified in the original review for the 1.0 mL indication are in the context of the newly proposed indication and not of the previously submitted indication. Thus, some of the responses are applicable, in principle, to the indication of preoperative skin prepping and some are not. This reviewer will not address those that are not applicable to this indication.

The agency issued an approval letter to Beckloff Associates, agent for Medi-flex Hospital Products, on July 14, 2000 stating that ChloraPrep One-Step Frepp in the 3.0-mL applicator configuration was approved for the indication of preoperative skin preparation.

The most recent submission is dated December 10, 2001 for ChloraPrep One-Step when packaged as a Sepp (0.67mL/applicator) and is the subject of this review. The indication sought for this product configuration is for preoperative skin preparation prior to invasive surgery and for patient preinjection skin preparation.

Reviewers note: Although the agency has not established a minimal surface area for the preoperative skin preparation indication, there is concern that in this particular instance, there may be insufficient product volume for use as preoperative skin preparation. The proposed product is a Sepp and contains a total volume of 0.67 mL of 2% chlorhexidine gluconate in a 70% isopropanol vehicle. It is this reviewer's concern that the volume of product is so small as to limit the utility of this product as a preoperative skin prep prior to invasive surgery. If the agency agrees to approve this product configuration for such use, the maximal surface area to be prepared must be provided in the product label. In addition, the agency may wish to make recommendations that limit the product to specific types of surgery.

In addition, the product can be used as a surgical prep or in preparation of skin prior to injection. This Microbiology Reviewer has concern with the instructions because they state to prep an area no greater than 2.5 inches square for 2 minutes. Since the Sepp contains 0.67 mL of product, is there enough product volume to prep the 2.5 inches square site for 2 minutes?

The product under consideration contains 2% chlorhexidine gluconate (CHG) in a vehicle of 70% isopropanol (IPA). Both of these ingredients are active microbiologically and must be addressed under the combination drug policy. That is, the contribution of each active ingredient to the total efficacy of the product must be assessed. The Tentative Final Monograph for Health Care Antiseptic Drug Products¹ addresses the efficacy and classification of isopropanol at concentrations of 70 to 91.3 percent. It is stated in that reference that isopropanol is safe and effective as a patient preoperative skin prep when formulated to contain 70-90.3% IPA and assessed by the preoperative skin prepping method described in that document (Section 333.410). Chlorhexidine gluconate is determined by the agency to be a new drug and is not addressed in the TFM. Thus, the assessment of efficacy must be performed under the new drug process (Food, Drug, and Cosmetic Act, Section 505(b)).

In addition, since the agency issued an approval letter for the use of ChloraPrep One-Step for use as a preoperative skin preparation, we can conclude that the applicant already demonstrated the contribution of each of the active ingredients of the final formulation.

Conclusions/Recommendations:

The NDA ChloraPrep One-Step Seep was submitted for the indication of preoperative skin prepping prior to surgery or injection when used as directed.

The labeling directions should read as follows:

“On Dry Skin: Apply the antiseptic using repeated back and forth strokes of the sponge on the skin. Completely wet the treatment area with antiseptic. Use an application time of approximately thirty (30) seconds for dry skin areas of the body, such as the abdomen. Allow the area to air-dry for approximately thirty (30) seconds.

“On Dry Skin: Apply the antiseptic using repeated back and forth strokes of the sponge on the skin. Completely wet the treatment area with antiseptic. Use an application time of approximately thirty (30) seconds for dry skin areas of the body, such as the abdomen. Allow the area to air-dry for approximately thirty (30) seconds. Do not blot or wipe away.”

“On Moist Skin: Apply the antiseptic using repeated back and forth strokes of the sponge on the skin. Completely wet the treatment area with antiseptic. Use an application time of approximately two (2) minutes for moist skin areas of the body, such as the groin. Allow the area to air-dry for approximately one (1) minute. Do not blot or wipe away.”

“The maximum treatment area for one 0.67 mL Seep applicator is approximately forty-two (42) cm² or 6.5 inches square (2.55 ” x 2.55”). Do not blot or wipe away.”

In addition, the team members for this NDA need to discuss the proposal that we limit this product configuration for surgical sites associated with specific surgical procedures that require small volumes of product. That is, we should incorporate examples of surgical incisions that do not overly apply the product on large surface areas.

Microbiological Review

Introduction:

In the United States, approximately 23 million surgical procedures² are performed per year resulting in 0.95 million surgical site infections.³ Two years later that figure has risen to 27 million surgical procedures and it is estimated that 75% will occur in an outpatient, same-day operation by the turn of the century.⁴ In addition, surgical site infection rates vary with the surgical procedure performed and the level of bacterial contamination. A classification scheme has been developed to define the level of contamination as clean wound, clean-contaminated wound, and contaminated wound.⁵ Based on this scheme and the surgical procedure performed, infection rates have been found to be approximately 3-5% for clean wounds, 4-10% for clean-contaminated wounds, and 9-22% for contaminated wounds.^{3,5} The use of perioperative antibiotics reduces these rates to approximately 0.8%, 1.3% and 10.2% respectively for clean, clean-contaminated, and contaminated wounds.

Surgical site contamination can be attributed to several factors. These include the physiological state of the patient (general and local host immunocompetence, nutritional status, presence of diabetes, etc.), the surgical site and its location (tissue trauma and devitalization, presence of foreign material, etc.), the perioperative use of antibiotics as previously discussed, and the virulence and numbers of organisms present.⁶ The principle pathogens isolated from surgical site infections, as defined by the National Nosocomial Infections Surveillance (NNIS) system from 1986 to 1996, are presented in Table 1. The pathogens described in this table clearly may be found as normal inhabitants of the host and suggest that some surgical site infections may be of an endogenous origin. Thus, it is logical to assume that the use of topical antiseptics on the skin surface prior to invasive surgery may reduce the presence of the resident coagulase-negative staphylococci and Enterobacteriaceae in addition to the transient pathogens. The use of such products should result in the reduction of post surgical infections rates as previously observed by Lister.

Table 1. The incidence rate of pathogens from surgical site infections monitored over a ten-year period.^{7,8}

Pathogens	Percentage of Isolates*	
	1986-1989 (n=16,727) ⁷	1990-1996 (n=17,671) ⁸
<i>Staphylococcus aureus</i>	17	20
Coagulase-negative staphylococci	12	14
<i>Enterococcus</i> spp.	13	12
<i>Escherichia coli</i>	10	8
<i>Pseudomonas aeruginosa</i>	8	8
<i>Enterobacter</i> spp.	6	7
<i>Proteus mirabilis</i>	4	3
<i>Klebsiella pneumoniae</i>	3	3
Other <i>Streptococcus</i> spp.	3	3
<i>Candida albicans</i>	2	3
Group D streptococci (non-enterococci)	-	2
Other Gram-positive aerobes	-	2
<i>Bacteriodes fragilis</i>	-	2

* Pathogens representing <2% of isolates are not presented

Preclinical Studies

The preoperative skin prepping studies proposed in the FR Notice¹ have limitations in that they only allow assessment of product efficacy against the resident flora of healthy test panelists. In reality, these test panelists are surrogates for patients in various stages of illness and immunocompetence that are to undergo invasive surgery. As such, the test panelists may not carry, transiently, the kinds of pathogens that may be colonizing hospitalized patients. Since the clinical simulation tests have these inherent limitations, the agency must gather information on potential product efficacy from *in vitro* studies. Thus, the FR Notice¹ requires that the *in vitro* spectrum of activity and time-kill kinetic studies also be performed to gather additional information on product efficacy. The purpose of these preclinical studies is to demonstrate that products have a satisfactory spectrum of activity against pathogens that are likely to be encountered in these setting. The desired method for this assessment is the *in vitro* spectrum of activity established by minimum inhibitory concentration (MIC) and time-kill kinetic studies, which are performed with organisms that represent nosocomial pathogens¹.

The requirements for clinical simulation studies and the *in vitro* studies could be reduced, if not eliminated, provided the applicant performed clinical studies in settings, such as hospitals, where the intended use of the product is recognized.

***In vitro* Spectrum of Activity**

The FR Notice requires that the *in vitro* spectrum of activity be assessed using standardized minimal inhibitory concentration (MIC) methods⁹ against a selected panel of bacteria described within the notice. The requirement states that 50 strains of each species must be tested. Twenty-five of the strains must be fresh clinical isolates and the remaining 25 can be stocks strains obtained from the American Type Culture Collection (ATCC). The *in vitro* spectrum of each battery of 50 strains for each listed species must be evaluated against the product to be marketed, the product vehicle, and the active ingredient alone. For this product review, the active ingredient is chlorhexidine gluconate and 70% isopropanol. The vehicle and the active ingredient results are compared to the product formulation results to determine whether the vehicle has a positive or negative affect on the intrinsic activity of the active ingredient. The results are also used to evaluate the contribution of the vehicle to the antimicrobial activity of the product to be marketed.

Some applicants have stated that the *in vitro* spectrum of activity requirement is excessive. In order to address this issue and not compromise the scientific information gathered, the agency has agreed to let applicants test only 10 strains for the active ingredient (CHG) and the vehicle (70% IPA). The active ingredient (positive control) is represented by Hibiclens. Although we have agreed to these changes, the 10 strains tested must be selected from the original 50 strains that are used to test the product to be marketed. The evaluation of the product to be marketed with the 50 strains remains the standard requirement as described in the FR Notice. The ten strains must include 5 of the 25 ATCC strains tested versus the test product and 5 of the 25 fresh clinical isolates for a total number of 10 when possible.

The *in vitro* spectrums of activity studies were evaluated in Microbiology Review #2 completed July 11, 2000. The data presented in Table 2 of that review was evaluated to assess the spectrum of activity and potential utility of ChlorPrep One-Step as a topical antimicrobial versus the most probably post-surgical pathogens listed in Table 1. The reviewer concluded that this product is formulated with sufficient CHG to provide antiseptic activity against most pathogens listed in Table 1. The highest MIC observed in these studies was 200 µg/mL. Since the product is formulated to contain 20,000 µg/mL, it will provide about 100 fold more CHG than any MIC observed in the *in vitro* spectrum of activity studies.

In addition, this product contains 70% IPA and the Microbiology Reviewer concluded that the MIC studies could not assess the contribution of this active ingredient. Thus the overall performance of the combination product was assessed by the time-kill kinetic methods as described next.

Time-Kill Kinetic Studies

The FR Notice requires that the applicant perform time-kill kinetic studies with the ATCC strains described in that document. These ATCC strains were also used to conduct the *in vitro* spectrum of activity studies. It is realized that standardized methods

ChloraPrep One-step
Medi-Flex Hospital Products, Inc.

are not currently available but the methodological conditions that need to be controlled have been described by others.^{3,4} Generally, the end-point that is measured and considered significant is the time required to produce a 3 log₁₀ reduction (99.9%) from the initial baseline. Further, the FR Notice does state that a 1:10 dilution of the product should be evaluated especially if the product is used with water. This becomes problematic for products, such as ChloraPrep-One-Step, which are leave-on products and not intended to be used with water.

Generally, the time-kill kinetic study is performed to assess how quickly a 1:10 dilution of the test product and appropriate comparative controls kill bacteria. A 1:10 concentration is selected as an example of the concentration that is likely to reside on the hands for a product that are intended for use as a surgical hand scrub or healthcare personnel hand washes. Normally these products are used with water. It is assumed that the test product will be diluted to a concentration of 1:10 with water during product use.

If the product is used for the indication of preoperative skin prepping or skin preparation prior to venipuncture, or as a leave-on product, it is unlikely that the product will be diluted. However, the assessment of the product as a 1:10 dilution is also recommended because the efficacy (time-kill-kinetics) of the product can be assessed by this procedure. Especially since the leave on product is likely to be formulated with an alcoholic vehicle and another antimicrobial. ChloraPrep One Step is such an example. That other antimicrobial can be evaluated with the time-kill study and minimize the contribution of the alcoholic vehicle due to the 1:10 dilution. This approach helps provide information on the contribution of one of the antimicrobials. If the time-kill study is performed with the undiluted product, it may be possible to compare the results of diluted and undiluted product and possibly demonstrate the contribution of both active ingredients. The recommended time-kill time measurements described in the FR Notice are 0, 3, 6, 9, 12, 15, 20, and 30 minutes.

The time-kill-kinetic study is an attempt to establish a relationship between the rates of kill in vivo versus the rate of kill during the clinical simulation studies where bacterial reductions at reference time points are also assessed. There is no standardized protocol for the time-kill kinetic study but the protocol submitted is evaluated to assure that it follows accepted scientific principles.

The time-kill kinetic studies were conducted by [redacted] (protocol 960615) and submitted as study PKA01007. The studies were conducted with the undiluted product since the product is applied to the site undiluted and is not removed by rinsing. Nineteen species of bacteria were tested with ChloraPrep (2% CHG in 70% isopropanol), isopropanol alone, CHG alone, and Betadine (1% free iodine). Sampling for enumeration was performed at 15 and 30 seconds, the sample neutralized and enumerated. In essence, the product was tested in a manner consistent with its potential use and the results were not surprising. The results, presented in Tables VIII through XI (Microbiology Summary, Volume 1.1, pages 96-103, January 15, 1997), clearly demonstrate that the ChloraPrep product produced >5 log₁₀ reduction at 15 and 30 seconds as expected for all

species except *Micrococcus lutea* (3.60 log₁₀ reduction). Isopropanol produced almost identical results to the combination product

The results of the time-kill kinetic study performed with an aqueous 2% CHG were interesting. A 5.0-log₁₀ reduction was produced at 30 seconds with most species evaluated. The exceptions were no effect (kill) for *Enterococcus faecium* (0.11 log₁₀ reduction) and some effect for *Streptococcus pyogenes* (1.96 log₁₀ reduction) at 30 seconds. Slightly better results were obtained with *Staphylococcus aureus* (1.92 log₁₀ reduction) and *Staphylococcus saprophyticus* (3.81-log₁₀ reduction). If we compared the MIC results with the time-kill kinetic results, we would expect the more sensitive an organism to CHG (lower MIC) to be killed more rapidly by the 2% CHG concentration. Comparison of the MIC results of the organisms studied in the time-kill kinetics experiment does not support this hypothesis entirely. For example, *Enterococcus faecium* and *Streptococcus pyogenes* have the lowest CHG MICs (≤ 0.61 $\mu\text{g/mL}$) of the strains tested but also had the lowest time-kill kinetic reductions of 0.11 log₁₀ and 1.96 log₁₀ at 30 seconds, respectively. This is an interesting observation given that the CHG concentration used in the time-kill kinetic study is may fold the MIC of the organism. These results clearly show the effect of time on microbial efficacy; the MIC studies are 18 hours exposures and the time-kill studies are less than one-hour exposures.

These observations clearly suggest that the MIC information must be used in conjunction with time-kill kinetics results in assessment of efficacy of active ingredients and product performance. Low MIC values and high time-kill kinetic rates were expected for the combination product and that is what was achieved. We conclude that the isopropanol contributes the immediate antimicrobial activity of the product against most pathogens tested. However, it is not known how long the isopropanol remains on the skin during actual use. The data would suggest that the longer the exposure to isopropanol (skin prep time) the better the probable outcome.

Global summary of the preclinical studies: The applicant provided the requisite preclinical studies for ChloraPrep One-Step. The data indicates that the product has an expected spectrum of activity attributable to the CHG and that the IPA vehicle contributes the rapid antimicrobial activity as measured by time-kill kinetic studies.

Product Label Evaluation:

Review of the of the label (Volume 1 of 1, Item 2, December 10, 2001 submission) proposed for the Sepp product configuration provides insight into the type(s) of clinical simulation studies and directions for use that will be required to demonstrate product efficacy. The label directs the user to use the appropriate set of instructions depending on

the type of site(s) being prepped. The Sepp labels provided in Item 2 of the NDA submission states:

Use: For the preparation of the patient's skin prior to surgery or injection.

The directions state:

“dry surgical site (such as **abdomen or arm**): Use repeated back-and-forth strokes of the applicator for approximately **30 seconds**. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately thirty (30) seconds. Do not blot or wipe away.”

“moist surgical sites (such as the **inguinal fold**): Use repeated back-and-forth strokes of the of the applicator for approximately **2 minutes**. Completely wet the treatment area with antiseptic. Allow the area to air-dry for approximately **one (1) minute**. Do not blot or wipe away.”

“The maximum treatment area for one applicator is approximately 42 cm² (approx. 2.5 x 2.5 in.) Discard the applicator after a single use.

Note: This reviewer bolded sections of the text in order to emphasize the information that needs to be derived from the clinical studies. These sections will not be bolded in the product label. The bolded and underlined text is the information bolded by the applicant.

Summary: Based on these instructions, the applicant is required to perform the preoperative skin prepping clinical simulation study and the skin prepping prior to injection studies with the Sepp product using the directions and maximum surface area previously described.

Clinical Simulation Studies

Preoperative skin prepping clinical simulation study: The assessment of a product as an effective preoperative skin prep is described in the Tentative Final Monograph¹ and states that a preoperative skin prep study must be performed and meet the efficacy requirements as described therein. Subjects admitted to the study are to be identified as meeting the groin portion, the abdomen portion, or both of these body sites. Once a subject, having the required baseline bacterial populations at these sites, is admitted into the study, the test product treatment is randomly assigned to one contralateral site and the control product to the other. Efficacy is demonstrated by reduction of the microbial flora at each site from a predetermined baseline at specified time intervals. For the abdomen, the requirement is a $\geq 2.0 \log_{10}$ cfu/cm² reduction and for the groin a $\geq 3.0 \log_{10}$ cfu/cm² reduction at the 10-minute time interval. In addition, the microbial flora can not supercede the statistical mean baseline by the end of the 6th hour post product use. This assessment is required because it has been suggested that antiseptic product use causes bacterial population shifts and enhanced bacterial populations that may result in post surgical infections.

The assessment of a **product intended for use prior to injection** uses the same protocol as for a preoperative skin prepping product. The only difference is that the sampling time point (30 seconds after product use) is performed only for a dry skin site and the efficacy requirement is $\geq 1.0 \log_{10} \text{ cfu/cm}^2$ immediately (~30 seconds) after product use.

A pivotal study was provided in compliance with New Drug Application and TFM efficacy requirements for topical antiseptic drug products. []
[] performed the study according to protocol # 990622.. using a 0.67-mL Sepp. The title of the study is "Evaluating the Safety and Efficacy of SEPP® Applicators Containing ChloraPrep™ for use as a Patient Preoperative Skin Preparation and SEPP® Applicators Containing ChloraPrep™ for the Preparation of the Skin Prior to Injection." The objective of the study is to evaluate the safety and immediate and persistent antimicrobial properties of a preoperative skin preparation test product and evaluate the effectiveness of the same test product for skin preparation prior to injection.

The study design is a randomized, uncontrolled, open label evaluation of ChloraPrep One Step (lot #905083). Determination of the difference from baseline (CFU/cm² of skin) were performed at 30 seconds, 10 minutes, and 6 hours for the abdomen and at 10 minute and 6 hour sampling times for the groin. The 30-second time frame on the abdomen is used to assess the efficacy of the product for use prior to injection. The remaining time frames are used to assess the efficacy of the test product for the preoperative skin prepping indication.

The protocol was evaluated for compliance with the TFM **study design** recommendation since modifications to the study can unduly influence outcome. It is clear, after reviewing the protocol that the study design is not the study design recommended in the tentative final monograph. The applicant states that the open label study design was chosen because the sampling time, site, and location will be blinded to the technologist handling the plates, counting the results, and recording the data.

Reviewer's comments: The problematic issue is the design of the pivotal clinical simulation study. It does not include a positive control. A pivotal clinical simulation study must be performed with a marketed positive control, a product that is approved and marketed for the indication under evaluation. The positive control is used to validate the investigator(s) ability to accurately and reproducibly performing the study. Since the indication is preoperative skin prepping, the recommended positive control is Hibiclens (4% chlorhexidine gluconate), a finished product the agency has used in numerous experiments. In the instance presented in this NDA, the applicant designed a 1-arm study that evaluates only the test product. Since the study is not adequately controlled, it can not be accepted as a pivotal trial.

Deficiency: The pivotal clinical simulation protocol (protocol # 990622. was designed such that it excluded an appropriate approved product control arm. The approved product control arm is used to validate the conduct of

the study in the hands of the investigators thus allowing us to have confidence in the data obtained for the product under investigation. In this reviewer's opinion, these studies can not be viewed as pivotal studies. They will be viewed as supportive studies. In the mind of this reviewer, this is not a scientific issue because as we will see, a 2% chlorhexidine gluconate in a 70% isopropanol vehicle has already been approved as a Frepp. Further, evidence presented later in this review will demonstrate that this product is an effective preoperative skin prepping product. The issue that we face as a regulatory agency is a regulatory issue, not a scientific issue. Are we willing to accept an uncontrolled pivotal study in the approval of a product? We did approve the Frepp product using clinical simulation studies and study design that did not include an approved and marketed product arm. These studies (See Review #2) did provide a vehicle control arm (70% IPA) and a 2% CHG control arm. It is logical to accept those studies because 70% IPA is considered an effective preoperative skin prep as described in the TFM. If we accept the uncontrolled clinical simulation studies submitted in this NDA, we establish a regulatory precedence that we may later regret.

7 preoperative skin prepping clinical simulations study:
In addition to the requirement previously discussed, the protocol was evaluated to assess compliance with required baselines, appropriate test site selection, method, and material recommendations. Evaluation of the protocol indicates that the appropriate test sites were used, and methods and materials were followed with minor modifications and should not have a bearing on results. A change was made to the minimum baseline entry criteria for the abdomen.

Reviewer's comments: A modification was made to the protocol that may be problematic. The issue is the modification of the minimum number of bacteria required per centimeter squared for entry of panelists into the study for the dry (abdomen) skin site. In past reviews and in the Tentative Final Monograph, the agency required $\geq 3\text{-log}_{10}$ cfu/cm² on the abdomen and $\geq 5\text{-log}_{10}$ cfu/cm² on the inguinal area. However, companies stating that they had to screen large panels to find panelists with these numbers and they filed numerous complaints to this effect. Since the efficacy requirements are a $\geq 2\text{-log}_{10}$ reduction/cm² and a $\geq 3\text{-log}_{10}$ reduction/cm² at the 10-minute time interval for the abdomen and inguinal areas, the agency agreed to let companies use $\geq 2.5\text{-log}_{10}$ cfu/cm² and $\geq 4\text{-log}_{10}$ cfu/cm² as the minimum bacterial count requirements for the abdomen and inguinal test sites, respectively. This change will still allow us to measure the reduction required to demonstrate efficacy and allow for variability of the assay method.

The change made by the applicant is a further reduction of the abdomen entry criteria from $\geq 2.5\text{-log}_{10}$ cfu/cm² (≥ 300 cfu/cm²) to $\geq 2.2\text{-log}_{10}$ cfu/cm² (≥ 158 cfu/cm²) for the abdomen. The significance of this change is not clear but it can be concluded that a bacterial population sufficient to show a 2-log_{10} cfu/cm² is not present. However, it may

be moot if the bacterial populations actually studied supercede the acceptable baseline of $\geq 2.5\text{-log}_{10}\text{ cfu/cm}^2$ ($\geq 300\text{ cfu/cm}^2$). Review of the data was performed with this thought in mind (see Tables 1 and 2 below). Sixty-three (63) panelist were screened for inclusion in the study with the goal of obtaining 40 abdomen and 40 groin sites for evaluation. Approximately 27 panelists provided abdomen and groin results and these are presented in Table 2 (Appendix IX) of the submission. Panelists were evaluated for abdomen and groin baseline counts and based on this evaluation, 19 panelist met the baseline abdomen and groin counts as described by the applicant. In addition, 6 additional panelist were found to have acceptable abdomen counts and 1 panelist to have acceptable groin counts. Thus, 25 panelist having bilateral baseline counts (right and left abdomen) were considered acceptable and provided 49 independent observations. It appears to this reviewer that one abdomen test site was excluded from the analysis due to low baseline counts (panelist 56, left abdomen). It was noted that panelist 33, although qualified for analysis, was excluded from the analysis. This individual will be included in the FDA analysis.

The results presented in Table 1 below show that of the 54 evaluable abdomen sites (27 panelist), 50 abdomen sites (25 panelist) were considered evaluated, and only one (1/50, 2.2%) had microbial counts less than the minimum approved for evaluation in the clinical simulation study. About 60% (29/50) of the panelist evaluated had baseline counts suggested in the TFM FR Notice.

Table 1. Proportion as a percent (%) of evaluable abdomen subjects used in the statistical analysis that had baseline values below the required $\geq 2.5\text{-log}_{10}\text{ cfu/cm}^2$.

Test Facility	Product tested	Abdomen Proportion	Percent (%)
—	ChloraPrep One Step	1/50* 29/50**	2.2 59.8

*Number of panelist with values $< 2.5\text{-log}_{10}\text{ cfu/cm}^2$ /total number of panelist in the study. Data derived from Table 2 "Results Tables" presented by applicant in Appendix IX of December 10, 2001 submission.

** Number of panelist with $\geq 3\text{-log}_{10}\text{ cfu/cm}^2$ as described in the TFM.

The results presented in Table 2 below show that of the 54 evaluable groin sites (27 panelist), 40 groin sites (20 panelist) were considered evaluated in that they all had bacterial populations $\geq 4.0\text{-log}_{10}\text{ cfu/cm}^2$, the minimum approved for evaluation in the clinical simulation study.

Table 2. Proportion as a percent (%) of evaluable groin subjects used in the statistical analysis that had baseline values below the required $\geq 4.0\text{-log}_{10}$ cfu/cm².

Test Facility	Product tested	Groin Proportion	Percent (%)
—	ChloraPrep One Step	14/54* 40/40**	26.0 100.0

*Number of panelist with values $< 4.0\text{-log}_{10}$ cfu/cm²/total number of panelist evaluated in the study. Data derived from Table 2 "Results Tables" presented by applicant in Appendix IX of December 10, 2001 submission.

** Number of panelist with $\geq 4\text{-log}_{10}$ cfu/cm² as described in the TFM.

Reviewers comment: We can conclude that sufficient numbers of panelist are available to provide the 40 evaluable abdomen and groin tests sites with the required minimal baseline values.

Of additional interest will be whether neutralizers were used during enumeration at time frames other than where indicated by the TFM protocol. Evaluation of the protocol reveals that neutralizers were used as directed in the TFM and this issue is no longer of concern. Evaluation of the effectiveness of the neutralizer will be performed later in this review.

The results of the preoperative skin prepping study performed by [] are presented in Table 3. The data presented in Table 3 is a duplication of the tables provided by the applicant and represents the extent of the statistical evaluation of the abdomen and groin data by the applicant. It would appear that the only statistical analysis performed by the applicant was calculation of the mean (\bar{x}) and provides no analysis of the deviation from the mean (\pm SD) to help assess the reproducibility of the data.

These data show that ChloraPrep (lot # 910019) produced the required preoperative skin prepping reduction of $\geq 2\text{-log}_{10}$ reduction/cm² and a $\geq 3\text{-log}_{10}$ reduction/cm² at the 10-minute time interval for the abdomen and inguinal areas for, respectively. The next required measurement is at 6 hours post product use. Evaluation of this data suggests that suppression of the microbial flora occurred and was maintained below the established baseline for the required duration of 6 hours.

The applicant also performed enumeration at approximately 30 seconds to demonstrate the immediate affect of ChloraPrep when used as a preinjection skin preparation product. This assessment was performed only for the abdomen as suggested in the TFM and clearly meets the $\geq 1\text{-log}_{10}$ reduction/cm². This single test site is not a reasonable representation of the test sites likely to be used in the preparation of skin prior to injection and additional test sites are desired as tested by other applicants. For example, areas that

should be tested due to the uniqueness of the microbial flora include the areas around the chest (subclavian vein), neck (jugular vein), and the leg (femoral vein).

Table 3. [redacted] preoperative skin prepping bacterial reductions (\log_{10}) achieved with the ChloraPrep One-Step, at the designated enumeration time frames and body sites.

Enumeration	Abdomen (N=49)	Groin (N=40)
Baseline	Not provided	Not provided
30 seconds	2.63	Not provided
10 minutes	2.77	3.87
6 hours	2.11	3.10

Reviewer's comments:

- From the Microbiological perspective, the results of the [redacted] clinical simulation preoperative skin prepping study and the skin prepping prior to injection study are within the efficacy parameters described in the TFM. They did employ acceptable techniques as described in the TFM.
- The test laboratory did not use an appropriate trial design in the conduct of this study.
- The FDA statistician should provide a more rigorous analysis of the data provided and confirm the conclusions presented by the applicant.
- The review team needs to assess whether they will accept an uncontrolled clinical simulation study as a pivotal study in the assessment of ChloraPrep efficacy. It is this reviewer's opinion that we should not.

Validation of the Neutralization system: (See APPENDIX VIII of the 12/2001 submission) The neutralizer effectiveness protocol followed the standard operating procedure described as 1009.10(1) Option III and the recommendations set forth by ASTM standard E1054-91, "Standard Practices for Evaluating Inactivation of the Antimicrobial Agents Used in Disinfectant, Sanitizer, Antiseptics or reserved Products." The protocol (Volume 5 of 11, Protocol #990326.. Appendix VIII) was not described in sufficient detail to allow evaluation. Basically, an ampoule of ChloraPrep was crushed, 1.0 mL of the expressed fluid taken from the device and added to a test tube containing 9.0 mL of neutralizer, and mixed. Then approximately 300 cfu of an overnight culture of unspecified organism were added to the neutralizer to produce a 30 cfu/mL concentration, mixed and at 30 seconds and 30 minutes, a 1.0 mL aliquot taken and plated on to Tryptic Soy Agar. The CFU concentration of the starting inoculum was determined by plating. The results provided suggest that neutralization occurred at 30 seconds and thus at 30 minutes as demonstrated by the recovery of the indicator in the neutralized solution versus the initial inocula.

Deficiency: The neutralizer validation information provided by [redacted] is not adequate to validate the system. In fact, the applicant has not demonstrated

that the neutralizers used are not toxic to the indicator organism used in the study as required in the ASTM reference they provide. In addition, they have not provided the proper controls required in the ASTM reference. Further, the evaluation of a sample obtained after a single preparation of skin is not sufficiently representative of the possible variation likely to be encountered during the clinical simulation trial. At least 10 samples must be obtained from as many panelists, the samples pooled, and the neutralization validation performed with the pooled sample. Finally, the FDA requires that the marker organism is to be added into the neutralizer prior to the addition of the sample to be neutralized. This request for information was sent to the Project manager so that it could be requested of the applicant. When the information is supplied, it will be reviewed as a separate review.

Response to neutralizer deficiency:

In response to the Information Request Letter dated June 26, 2002 sent from the agency requesting additional neutralizer validation information, the applicant sent, on September 16, 2002, a facsimile with the appropriate responses. The document was submitted by Beckloff Associates, Inc and discusses the prior use of the neutralizer protocols submitted for this NDA as protocols that were previously used and accepted in prior submission. Although it is true that these protocols were submitted in past submissions, they were also found deficient because of the abbreviated information that was submitted in the NDA. We required clarification of the information before the NDA for the Frepp was approved. Apparently neither the test facility nor the applicant learned from past experiences and they submitted the same type of abbreviated report for this NDA 21-555.

As before, the applicant used the same protocol to perform an *in vitro* assessment of the neutralizer. The following questions were asked to understand the reason for conducting the test *in vitro* as opposed to obtaining clinical simulation samples of antiseptic for the assessment.

1. *Provide an assessment of the maximum tolerated concentration of neutralizer for the targeted pathogens, as specified in the ASTM method.*

The applicant responds that the study was provided in Appendix VIII of the Sepp Applicator Clinical Statistical Report submitted September 10, 2001 application. The microorganisms tested for the maximal tolerated concentration included *Staphylococcal aureus* and *Escherichia coli*. The data provided is for a single concentration of neutralizer.

Reviewer comment: The ASTM method states that the proposed neutralizer should be added in varying concentrations to peptone water and the effect of each on survival of a targeted pathogen assessed. In this instances, only on concentrations was either assessed or provided so that an independent assessment of the appropriate neutralizer concentration can not be made by the agency. However, the data provided does allow us to assess the concentration provided and the data suggests that it is not toxic. The response will be accepted.

2. *Justify the volume of antiseptic used in the validation of the neutralizer and address the following comments:*

a. *Why was one milliliter of ChloraPrep OneStep used to validate the neutralizer?*
Since validation was performed with one milliliter of ChloraPrep in 9.0 milliliters of neutralizer (1:9 ratio), the applicant tried to keep the same ratio during the conduct of the clinical simulation studies. Thus, since the Sepp only contains 0.67 mL of product and that is what was applied to the skin, the neutralizer used should have a volume of approximately 6.0 ml to assure the same ratio used to validate the neutralizer.

Reviewer comment: This response does not answer the question but does provide details as to the volume of neutralizer used in the study.

b. *Justify the relationship of this volume () and that found in the clinical simulation samples.*

The applicant references the fact that in prior studies performed by [redacted] and submitted to the agency were performed with antimicrobial actually obtained after use in a clinical simulation study. The validation of neutralizer using this system confirmed the results obtained with the *in vitro* method used by [redacted].

Reviewer comment: The response is satisfactory.

3. *Provide precision and interpretation of the data by transforming to square root values and t-test analysis, as required by ASTM.*

The applicant provided the transformation information and statistical analysis requested. The data suggests that the neutralizer did not cause a decrease in the survival of the marker pathogens.

Reviewer comment: The response is satisfactory

In conclusion, it is this reviewers recommendation that the agency not accept this study as a pivotal study due to the numerous protocol design violations and lack of appropriate validation of the neutralization system. However, it should be noted that the agency has already approved the product in a separate product configuration known as a Frepp using adequate and well-controlled studies.

151

Albert T. Sheldon, Jr. Ph.D.
Team Leader, Microbiology Reviewer

Cc: Original NDA No. 21-555
Microbiologist, HFD-520
File name: N22-555_fin.doc

SMicro/ATSheldon

DepDir/LGavrilovich

Cc: Original NDA #
HFD-473

ChloraPrep One-step

Medi-Flex Hospital Products, Inc.

HFD-520/DepDir/LGavrilovich

HFD-520/Smicro/ATSheldon

¹ Tentative Final Monograph for Health Care Antiseptic Drug Products; Proposed Rule. Federal Register Notice, Vol. 59., No. 116, Friday, June 16, 1994

² Centers for Disease Control and Prevention, National Center for Health Statistics. Vital and Health Statistics, Detailed Diagnoses and Procedures, National Hospital Discharge Survey 1994. Vol 127. DHHS Publication, 1997.

³ Wenzle, RP 1992. Preoperative Antibiotic Prophylaxis. New Eng. J. Med. 326:337-339.

⁴ Hecht, AD. 1995. Creating Greater Efficiency in Ambulatory Surgeries. J. Clin. Anesth. 7:581-584

⁵ Altemeire WA, Burke JF, Pluitt BA, et.al., 1976. Manual of Control Infection in Surgical Patients. Philadelphia: JB Lippincott; pages 29-30.

⁶ Kernodle DS, and Kaiser AB. 1995. Surgical and Trama Related Infections. In Principles and Practices of Infectious Diseases, Churchill Livingston; Pages 2742-2756.

⁷ Mayhall CG. 1993. Surgical Site Infections Including Burns. Prevention and Control of Nosocomial Infections. Williams & Wilkins; pages 614-664.

⁸ Centers for Disease Control and Prevention. National Nosocomial Infectious Surveillance (NNIS) reprot, data summary form October 1986-April 1996, 1996. Am J Infect Control 24:380-388.

⁹ Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fourth Edition, Approved Standard. NCCLS Document M7-A4. NCCLS, 940 West Valley Road, Suite 1400 Wayne, Pennsylvania.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Albert Sheldon
9/20/02 02:00:43 PM
MICROBIOLOGIST

Lillian Gavrilovich
9/25/02 05:57:48 PM
MEDICAL OFFICER

Note: NDA 20-832 Supplement-003 provided for a new indication and a new delivery system/dosage form. This application became a new NDA in August, 2002, and was assigned NDA number 21-555.

APPEARS THIS WAY
ON ORIGINAL

Product Quality Microbiology Review

Review for HFD-550

2 OCTOBER 2002

NDA: 21-555

Drug Product Name

Proprietary: Chloraprep

Non-proprietary: chlorhexidine gluconate 2%

Drug Product Classification: S

Review Number: 1

Subject of this Review

Submission Date: 10 December 2001

Receipt Date: 12 December 2001

Consult Date: 21 August 2002

Date Assigned for Review: 6 September 2002

Submission History (for amendments only)

Date(s) of Previous Submission(s): N/A

Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor

Name: Medi-Flex Hospital Products

Address: 8717 West 110th ST Suite 750; Overland Park, KS 66210

Representative: Michael C. Beckloff

Telephone: 913-451-3955

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Approvable Pending Resolution of Microbiology Deficiencies

Product Quality Microbiology Data Sheet

- A. 1. TYPE OF SUPPLEMENT: N/A
2. SUPPLEMENT PROVIDES FOR: N/A
3. MANUFACTURING SITE: [] J
4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Topical Applicator, 2% solution in 70% isopropyl alcohol
5. METHOD(S) OF STERILIZATION: [] J
6. PHARMACOLOGICAL CATEGORY: Pre-operative skin preparation, pre-injection skin preparation
- B. SUPPORTING/RELATED DOCUMENTS: N/A
- C. REMARKS: The drug product (chlorhexidine gluconate) was previously reviewed in a "Frepp" applicator as part of NDA 20-832 for the indication of pre-operative skin preparation. This application provides for a "Sepp" applicator for the drug product for the indications of pre-operative, and pre-injection, skin preparation. The drug product is contained in a sealed ampule inside the applicator. The drug product applicator, but not the drug product itself, is sterilized. [] J

filename: 21555.doc

APPEARS THIS WAY
ON ORIGINAL

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – This submission is approvable pending resolution of product quality microbiology deficiencies (see section H. “List of Microbiology Deficiencies and Comments” on the last page of this review).
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is
- B. **Brief Description of Microbiology Deficiencies** – The applicant did not provide the results of the studies performed to validate the process.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – The agency is unable to assess the efficacy of the sterilization process without the results of the validation experiments. An insufficient sterilization process would present at least a moderate risk to patients due to the potential introduction of resistant microorganisms onto the surgical site.

III. Administrative

- A. **Reviewer's Signature** _____ **/s/**
- B. **Endorsement Block**
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
Peter H. Cooney, Ph.D. (Microbiology Supervisor)
- C. **CC Block**
N/A

Redacted _____

1

page(s) of trade secret

and/or confidential

commercial information

(b4)

G. LABELING – N/A

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

1. The applicant did not include the results of the sterilization process validation studies for the Sepp applicators.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bryan Riley
10/2/02 01:02:49 PM
MICROBIOLOGIST

Peter Cooney
10/2/02 01:10:41 PM
MICROBIOLOGIST