CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-832

MICROBIOLOGY REVIEW

TIMPER

REVIEW TO HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW #3 OF NDA

JUN - 6 2000

June 6, 2000

A. 1. NDA: 20-832 BC

2. TYPE OF SUPPLEMENT: NA

3. SUPPLEMENT PROVIDES FOR: NA

4. APPLICANT/SPONSOR: Medi-Flex Hospital Products Inc
8717 W 110th, Suite 750
Overland Park, KS 66210

5. MANUFACTURING SITE: [redacted]

6. DRUG PRODUCT NAME: Chlorhexidine Gluconate 2%
Proprietary: Chloraprep
Nonproprietary:
Drug Priority Classification: 2S

7. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Topical solution of 2% Chlorhexidine Gluconate in 70% isopropyl alcohol packaged in a plastic applicator.

8. METHOD(S) OF STERILIZATION: [redacted]

9. PHARMACOLOGICAL CATEGORY: Surgical Scrub Sponge

B. 1. DOCUMENT/LETTER DATE: March 16, 2000
2. RECEIPT DATE: March 17, 2000
3. CONSULT DATE: March 23, 2000
4. DATE OF AMENDMENT: March 16, 2000
5. ASSIGNED FOR REVIEW: April 12, 2000
6. SUPPORTING/RELATED DOCUMENTS: Microbiology Reviews of NDA 20-832 dated 9/4/97 and 12/23/97.

C. REMARKS: This amendment addresses microbiology deficiencies regarding residual ethylene oxide levels after sterilization of the applicator.

D. CONCLUSIONS: This submission is recommended for approval on the basis of product quality microbiology.

/S/ 6/6/00

Bryan S. Riley, Ph.D.
Microbiology Reviewer

/S/ 6/12/00

cc.: Original NDA 20-832
HFD 520/Division File
HFD 520/Project Manager
HFD 520/J. Timper
HFD 805/Consult File
HFD 805/ B. Riley

Drafted by: Bryan Riley, Ph.D. 6/6/00
R/D initialed by: Peter Cooney, Ph.D.

JUL 13 2000

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 2

NDA # 20-832 **Date Completed:July 11, 2000**

Sponsor (IND)/Applicant (NDA):
Medi-Flex Hospital Products, Inc.
Suite 750
8717 W. 110th St.
Overland Park, KS 66215

Chem/Ther. Type: Antimicrobial

Submission Reviewed: January 14, 2000
Providing for: Preoperative Skin Prepping

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: $C_{22}H_{30}C_{12}N_{10}\cdot 2C_6H_{12}O_7$

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

Route(s) of administration: Topical

Pharmacological Category: antiseptic

Dispensed: Rx___X___ OTC_____

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 30, 1998

Supplements/Amendments:

Received by CDER: August 8, 197 (Volumes 1.2 and 2.2)
Received by Reviewer: August 20, 1997
Review Completed: January 30, 1998

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

Related Documents: NA

Remarks:

On February 20, 1998 the Food and 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 [redacted]. The deficiencies included non-compliance with the Federal Register Notice' requirements. In general, the deficiencies included inadequate *in vitro* spectrum of activity studies, clinical simulation trial design, validation of the neutralization system [redacted]

On January 13, 2000, the applicant, Medi-Flex Hospital Products, Inc resubmitted the ChloraPrep product NDA [redacted]
Instead, the applicant is now requesting that the product be evaluated for preoperative skin prepping prior to invasive surgery. Thus, the responses by the applicant to the deficiencies identified in the original review [redacted] indication are in the context of the new indication and not that previously submitted. Therefore, some of the responses are applicable, in principle, to the indication of preoperative skin prepping.

The product under consideration contains 2% chlorhexidine gluconate (CHG) in a vehicle of 70% isopropanol (IPA). Both of theses 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 Products[1] 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 3.410). 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)).

The configuration of the drug delivery device also has changed. The device now contains 3.0 milliliters (mL) of product in an ampoule that is contained within the body of the applicator (a plastic tube). The tube has two plastic "wings" which extend about 45 degrees from the body of the tube and when pinched toward the central axis of the tube, they serve to crush the ampoule, which releases the product. When inverted right side up, the product is pulled to the sponge head by gravity and by compression of the sponge, which wets the sponge and then can be used to prep the site. The prep site will be limited to that described in the clinical simulation studies (130 mm^2 or 20 in^2).

Conclusions/Recommendations:

The NDA ChloraPrep One-Step was submitted for the indication of preoperative skin prepping when used as directed. The applicant provided the requisite studies, which included the *in vitro* spectrum of activity, the time-kill kinetic, and two adequate and reasonable controlled preoperative skin prepping studies. Based on the outcome of these studies, it is the opinion of the Microbiology Review Officer that the NDA be approved for the indication of preoperative skin prepping prior to invasive surgery. The labeling directions should read as follows:

"Dry repeated back and forth strokes of the sponge
Completely wet the treatment area with antiseptic
Allow the area to air-dry for approximately (30) seconds. Do not blot or wipe away."

"Moist repeated back and forth strokes of the sponge
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 130 cm^2

In addition, the team members for this NDA need to discuss the fact that for all practical purposes, these studies did not include an approved drug product as a control. If this study is accepted, we may set a regulatory precedence that may be difficult to overcome in the future.

Finally, even though the applicant performed clinical simulation studies that provided evidence that at the end of 24 hours the ChloraPrep continued to produce a suppressive effect of the resident microbial flora, any labeling or advertising associated with this observation should not be allowed. The reason is simple, we do not know what these observations mean and would have to extrapolate their significance.

APPEARS THIS WAY
ON ORIGINAL

Microbiological Review

Introduction:

In the United States, approximately 23 million surgical procedures[2] 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. They 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]
Staphylococcus aureus	17	20
Coagulase-negative staphylococci	12	14
Enterococcus spp.	13	12
Escherichia coli	10	8
Pseudomonas aeruginosa	8	8
Enterobacter spp.	6	7
Proteus mirabilis	4	3
Klebsiella pneumoniae	3	3
Other *Streptococcus* spp.	3	3
Candida albicans	2	3
Group D streptococci (non-enterococci)	-	2
Other Gram-positive aerobes	-	2
Bacteriodes fragilis	-	2

* Pathogens representing <2% of isolates are not presented

Preclinical Studies

The preoperative skin prepping studies proposed in the FR Notice[1] 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 Notice[1] 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 are 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 pathogens[1].

The requirements for clinical simulation studies but not the *in vitro* studies could be reduced, if not eliminated, if the applicant was to perform clinical studies in settings, such as hospitals, where the intended use of the product is germane.

In vitro Spectrum of Activity

The FR Notice requires that the *in vitro* spectrum of activity be assessed using standardized minimal inhibitory concentration (MIC) methods[9] against a selected panel of bacteria that are described within that 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, the product vehicle to assess the contribution of the vehicle to the spectrum of activity, and to the active ingredient alone. For this review, the active ingredient is chlorhexidine gluconate. The vehicle and the active ingredient results are also compared to the product formulation results to determine whether the vehicle has an effect on the intrinsic activity of the active ingredient or whether it augments it.

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 required, I have agreed to let applicants test only 10 strains for the active ingredient (CHG) and the vehicle. The active ingredient is represented by Hibiclens. However, the 10 strains tested must be selected from the original 50 strains tested with the finished product. This still 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* spectrum of activity studies are provided in the submission dated April 1, 1999 and were performed by [redacted]
Approximately 1,175 strains (40% fresh clinical isolates) representing all of the genera and species listed in the FR Notice were evaluated by the reference[redacted] Susceptibility testing was performed for the test product (2% CHG in 70% IPA), aqueous chlorhexidine gluconate (2% CHG), Hibiclens (4% CHG), IPA, and povidone iodine. The 2% CHG control was included in the study to show that the IPA is not contributing or measurable affecting the intrinsic antimicrobial activity of the CHG. We expect the test product and control to produce similar results. In addition, a [redacted] of 70% IPA was also evaluated to demonstrate that at lower concentration of the test product, the activity is due solely to the CHG component.

The media was also evaluated to ascertain the effect of the supplements on MIC results. The data presented suggest that [redacted] result in an increase of MIC's by 2 to 4 fold. The reproducibility of the susceptibility studies were evaluated by the inclusion of three quality control strains

and the assumption was made that if >95% of the results were within a 3 dilution range (mode± 1 tube dilution), the results for each agent were acceptable. The *in vitro* MIC results are presented in Table 2.

Table 2. The *in vitro* Minimum Inhibitory Concentration (MIC) range of select antiseptic drug products and their controls versus the pathogens listed in the Tentative Final Monograph.[1]

Microorganism (n)	Test Product		Control Used		Geometric mean ratio*
	CHG-IPA	CHG-H_20	Hibiclens	PVP-I	
Acinetobacter baumanii (24)				>3125	1.03
A. calcoaceticus (5)				6250	1.15
A. lwoffi (21)				>1562	1.39
Bacteriodes caccae (1)				>12500	NA
B. distasonis (9)				>1562	1.17
B. fragilis (50)				>3158	1.60
B. ovatus (11)				>6250	1.88
B. thetaiotaomicron (21)				>3125	1.69
B. vulgatus (3)				>6250	1.00
Burkholderia cepacia (18)				>3125	0.96
Candida albicans (51)				>3125	1.21
C. glabrata (1)				>6250	NA
C. krusei (14)				>3125	1.28
C. lusitaniae (1)				>3125	NA
C. parapsilosis (11)				>6250	1.24
C. tropicalis (17)				>3125	1.31
Clostridium difficile (10)				>782	1.00
Enterobacter aerogenes (25)				>6250	0.78
E. cloacae (25)				>6250	0.62
Enterococcus faecalis van^s (34)				>6250	1.08
E. faecalis van^r (20)				>3125	1.00
E. faecium van^s (32)				>3125	1.09
E. faecium van^r (20)				>3125	1.03
E. hirae (1)				>6250	NA
Escherichia coli (50)				>6250	1.37
Haemophilus influenzae BLNAS (27)				>782	1.0
H. influenzae BLNAR (6)				>3125	1.00
H. influenzae βlac+ (20)				>1562	0.90
Klebsiella oxytoca(4)				>12500	1.00
K. pneumoniae (36)				>6250	1.00
K. pneumoniae ESBL (10)				>6250	1.07
Micrococcus luteus (2)				>3125	NA
Prevotella bivia (9)				>195	1.17
Propionibacterium acnes (5)				>195	1.15
Proteus mirabilis (36)				>3125	1.04
P. vulgaris (20)				>6250	1.46
Pseudomonas aeruginosa (51)				>6250	1.07
P. fluorescens/putida (10)				>6250	1.00
Serratia marcescens (53)				>6250	1.08
Staphylococcus aureus meth^s (30)				>1562	1.52
Staphylococcus aureus meth^r (20)				>1562	1.35
S. epidermidis meth^s (23)				>1562	1.34

S. epidermidis meth^r (52)		>782	1.17
S. haemolyticus (50)		>1562	1.31
S. hominis (18)		>390	1.25
S. saprophyticus (50)		>782	1.62
S. simulans (15)		>1562	1.05
Stenotrophomonas maltophilia (20)		>3125	1.11
Streptococcus agalactiae (25)		>6250	0.97
S. pneumoniae pen^s (22)		>3125	1.13
S. pneumoniae pen^r (13)		>3125	1.00
S. pneumoniae pen^R (18)		>3125	1.00
S. pyogenes (55)		>1562	1.00

* Geometric mean ratio = CHG-IPA geometric mean/Hibiclens Geometric mean. The geometric mean = the n^{th} root of the product of n numbers.

There are several evaluations that need to be performed with the data presented in Table 2. The first is a description of the susceptibility of the pathogens most likely involved in post surgical infections (Table 1).

The ten-year NNIS study suggests that *Staphylococcus aureus* in the predominant post surgical pathogen and evaluation of Table 2 demonstrates that the methicillin sensitive and resistant *Staphylococcus aureus* strains are susceptible to concentration ≤6.25 μg/mL of ChloraPrep One-Step (CHG-IPA) or CHG-H_20 and ≤3.12 μg/mL of Hibiclens. Since the ChloraPrep One-Step contains 2% CHG (20,000 μg/mL) and the product is a leave-on product, we expect the CHG concentration to be sufficient to kill any *Staphylococcus aureus* strains encountered as transients. The time-kill study will verify this potential.

The next most frequent pathogen is represented by the coagulase-negative *Staphylococcus* spp. The type strain is represented by *Staphylococcus epidermidis* and includes methicillin$^{s\&r}$ strains, and the species *S. haemolyticus, S. hominis, S. saprophyticus*, and *S. simulans*. The coagulase-negative staphylococci are all susceptible to CHG-IPA and a concentration of ≤6.25 μg/mL. Thus the ChloraPrep One-Step should be equally effective against the coagulase-negative staphylococci but he time-kill study needs to verify this extrapolation.

Enterococci spp have also becoming prevalent in post-surgical infections. The MIC data presented in Table 1 suggests that vancomycin sensitive and resistant strains of *Enterococcus faecalis* and *Enterococcus faecium* are susceptible to ChloraPrep One-Step at concentrations of ≤12.5 μg/mL. These Enterococci should be susceptible to the action of CHG and the IPA since it is present 1000-fold greater than the MIC of the pathogens. Again, this potential should be augmented with the time kill-kinetic studies.

The Enterobacteriaceae represented by *Enterobacter aerogenes, A. cloacae, Escherichia coli, Klebsiella pneumoniae, K. pneumoniae* (ESBL), Proteus *vulgaris*, and *Pseudomonas aeruginosa* are the next most prevalent post-surgical wound pathogens. The MIC of these genera/species is ≤50.0 μg/mL which is some 400 fold less than the concentration of CHG found in ChloraPrep One-Step.

The other pathogens listed in Table 1 were evaluated as a group. The data presented in Table 2 contains strains that represent the Table I pathogens and they all have MIC's that are ≤200.0 μg/mL which is the highest MIC encountered for all strains tested. This MIC value is some 100 fold less then the concentration of CHG found in ChloraPrep One-Step and should be sufficient to function as an effective antimicrobial as measured by this method. The time kill study is needed to support this s assumption.

Reviewers comments: The data presented in Table 2 was evaluated to assess the spectrum of activity and potential utility of ChloraPrep One-Step as a topical antimicrobial versus the most probably post-surgical pathogens listed in Table 1. The data suggests 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 MIC studies do not assess the contribution of this active ingredient. The overall performance of the product must be assessed by the time-kill kinetic studies.

The second evaluation that needs to be performed is the possible effect of the formulation on the intrinsic antimicrobial activity of CHG. Thus, comparisons of the ChloraPrep One-Step (CHG-IPA) and CHG-H_20 data are required (See Table 2). The data show that the MIC range for all pathogens evaluated between the two formulation are nearly identical with some minor variation possible due to the error of the method. In no case is the difference greater than ± 1 tube dilution. In addition, a comparison of the geometric mean ratio of the CHG-IPA/CHG-H_20 (data not presented) suggests that the ratios range from 0.88 to 1.15 but a majority are within the expected ratio of approximately 1 which demonstrates parity between ChloraPrep One-Step and the 2% aqueous CHG formulation. Thus, we can conclude that the formulation has no effect on the intrinsic activity of the chlorhexidine gluconate when measured by this method. A more definitive study that will provide additional evidence of no effect is the time-kill kinetic study because it measures effect over much shorter time frames.

A comparison of the ChloraPrep One-Step MIC results with the Hibiclens MIC test results are warranted since the Hibiclens is the reference product used to validate all in vitro and in vivo clinical simulation studies. An informative method of comparison is the geometric mean ratio of the two products. The geometric mean is the n^{th} root of the product of n numbers and is a value that describes the population MIC. Since the applicant provided geometric mean MIC values for the ChloraPrep One-Step results and Hibiclens products, the relationship of the two values can be made by a simple ratio calculation. This information in presented in Table 2. The Hibiclens geometric mean was used as the denominator and that of the ChloraPrep One-Step as the numerator. If the two products have equivalent antimicrobial activity, the ratio is 1.0, if Hibiclens has more activity (lower MIC) than ChloraPrep One-Step the value is >1.0, and vise versa. It is clear from inspection of Table 2 that a majority of the values are >1.0 suggesting that Hibiclens has better antimicrobial activity than does ChloraPrep One-Step.

Of special interest are the strains that cause post-surgical infections (Table 1). *Staphylococcus aureus* and the coagulase-negative staphylococci are the most prevalent post-surgical site pathogens. The Staphylococcal geometric mean MIC ratios ranged from 1.05 to 1.62, thus suggesting that Hibiclens would be a better antimicrobial against these pathogens. The Group D enterococci have geometric mean MIC ratios of 1.0 to 1.09 suggesting equivalent antimicrobial activity by the two products as expected. With the *Enterobacteriaceae*, the ratio ranges from 0.62 to 1.46.

Reviewer's comments: Although the geometric mean MIC ratios favor Hibiclens over ChloraPrep One-Step, in reality both products contain chlorhexidine gluconate concentrations that are at least 100 fold greater than the highest MIC observed (200 µg/mL). The MIC studies provide insight into the potential spectrum of the test product. These types of studies do have limitations in that the concentration and duration of exposure are fixed and may not mimic what occurs under actual product use conditions. This limitation is important because most microbiologists would agree that antimicrobial activity is time and concentration dependent for antiseptics. The MIC studies show that at specified concentration and duration of exposure of 18-24 hours, CHG is at least bacteriostatic for the isolates tested. How this translates into actual product use requires time-kill kinetic and clinical simulation studies.

Time-Kill Kinetic Studies

The FR Notice requires that the applicant perform time-kill kinetic studies with the ATCC strains described in that document. It is realized that standardized methods 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 $\log_{10}$ reduction (99.9%) from the initial baseline. 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.

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 during hand washing with water. It is assumed that the test product will be diluted to a concentration of 1:10 with water during product use. The recommended time-kill time measurements described in the FR Notice are 0, 3, 6, 9, 12, 15, 20, and 30 minutes. The purpose of this study is to attempt to establish a relationship between the rates of kill in a test tube by the test product 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 reviewed when the submission was originally submitted on February 20, 1997. The information is provided again for convenience of the reader.

"Although the ChloraPrep *in vitro* spectrum of activity studies provide a description of the susceptibility bacterial populations likely to be encountered in healthcare settings, they do not provide information on how quickly the product is likely to achieve the antimicrobial action. This activity must be characterized through time-kill kinetic studies.

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. Thus 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 $\log_{10}$ reduction at 15 and 30 seconds as expected for all species except *Micrococcus lutea* (3.60 $\log_{10}$ reduction). Isopropanol produced almost identical results to the combination product.

Reviewer's Notes: The results of the 2% CHG were interesting. A 5.0 $\log_{10}$ reduction was produced at 30 seconds with most species. The exceptions were no effect for *Enterococcus faecium* (0.11 $\log_{10}$ reduction) and some effect for *Streptococcus pyogenes* (1.96 $\log_{10}$ reduction) at 30 seconds. Slightly better results were obtained with *Staphylococcus aureus* (1.92 $\log_{10}$ reduction) and *Staphylococcus saprophyticus* (3.81 $\log_{10}$ 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 (Table XII) of the organisms studied in the time-kill kinetics experiment do not support this supposition entirely. For example, *Enterococcus faecium* and *Streptococcus pyogenes* have the lowest CHG MICs (≤ 0.61 µg/mL) of the strains tested but had the lowest time-kill kinetic reductions of 0.11 $\log_{10}$ and 1.96 $\log_{10}$ 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 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 (scrub 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.

Clinical Simulation Studies

Review of the of the label (Volume 60 of 166, Appendices 1-5, January 13, 2000 submission) proposed for this product 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 first states:

Dry repeated back and forth strokes of the sponge
Completely wet the treatment area with antiseptic
Allow the area to air-dry for approximately 30) seconds. Do not blot or wipe away."

The second set of instructions state:

Moist repeated back and forth strokes of the sponge
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 final set of information describes the maximum surface area that can be prepped with the 3.0 mL applicator:

"The maximum treatment area for one applicator is approximately 130 cm^2.

Note: This reviewer bolded the text to be used in labeling in order to emphasize the information that needs to be derived from the studies. These sections will not be bolded in the product label.

Summary: Based on these instructions, the applicant is required to perform the preoperative skin prepping clinical simulation study with the drug/device combination using the directions and maximum surface area previously described.

Preoperative skin prepping clinical simulation study: The assessment of a product as an effective preoperative skin prep is described in the Tentative Final Monograph, [1] which 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 to whether they meet the groin portion or the abdomen portion or both. Once a subject 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 ≥2-log cfu/cm^2 reduction and for the groin a ≥3-log cfu/cm^2 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.

Two pivotal studies were provided in compliance with the TFM. MicroBioTest, Inc of Sterling Virginia and Hill Top Research, Inc. of Miamiville, Ohio performed the two studies according to protocol # 990326.MBT and 990326.HTR, respectively, using The studies were designed as randomized, active-controlled, open label evaluations of ChloraPrep One Step (lot #905083) versus 70% isopropyl alcohol (lot # 905105) and 2% chlorhexidine gluconate (lot # 905106). The protocols were evaluated for compliance with the TFM recommendations and the studies appear to be compliant. Minor modifications were made in the study design that should not influence the outcome of the study. The time intervals evaluated included 10 minutes, 6 hours, and 24 hours post product use.

Reviewer's comments: There are two modifications that were made to the protocols that may be problematic. The first 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, the agency required $\geq 3\text{-log}_{10}$ cfu/cm^2 on the abdomen and $\geq 5\text{-log}_{10}$ cfu/cm^2 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/cm^2 and a $\geq 3\text{-log}_{10}$ reduction/cm^2 at the 10-minute time interval for the abdomen and inguinal areas, I agreed to let companies use $\geq 2.5\text{-log}_{10}$ cfu/cm^2 and $\geq 4\text{-log}_{10}$ cfu/cm^2 as the minimum bacterial load requirements for the abdomen and inguinal test sites, respectively. This change should 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/cm^2 (≥ 300 cfu/cm^2) to $\geq 2.2\text{-log}_{10}$ cfu/cm^2 (≥ 158 cfu/cm^2) for the abdomen. The significance of this change in not clear and may be moot if the bacterial populations actually studied supercede the acceptable baseline of $\geq 2.5\text{-log}_{10}$ cfu/cm^2 (≥ 300 cfu/cm^2). Review of the data will be performed with this thought in mind (see Table 2 below).

The second and more problematic issue is the design of the pivotal clinical simulation study, which does not include a marketed 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 study in the hands of the investigators performing the study. Since the indication is preoperative skin prepping, the positive control should have been Hibiclens 4% chlorhexidine gluconate. In this instance, the applicant designed a 3-arm study that includes the test product, a 70% vehicle control, and a 2% aqueous formulation of chlorhexidine gluconate control. The two vehicle control arms are required because this product is formulated with two active ingredients. Since the study is not adequately controlled, it can not be accepted as a pivotal trial.

Deficiency: The pivotal clinical simulation protocols (protocol # 990326.HTR and # 990326.MBT) were 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 is going to be an effective preoperative skin prepping product. The issue that we face is a regulatory issue. Will the agency accept an aqueous 2% CHG arm as an appropriate positive control? A 2% CHG product is currently approved for preoperative skin prepping and it may be logical to extrapolate that the 2% CHG aqueous control would be a reasonable product to validate the study. This regulatory issue will require further discussion by the team.

MicroBioTest Research, Inc clinical simulations study: The protocol used in this study was evaluated to assess compliance with the protocol described in the TFM. Evaluation indicates that methods and materials were for the most part followed with minor modifications that should not have a bearing on results. Of particular interest is the proportion of panelists that contained cfu/cm^2 below the recommended value of $\geq 2.5\text{-log}_{10}$ cfu/cm^2 and the use of $\geq 2.2\text{-log}10$ cfu/cm^2 and 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.

The number of panelist qualified for statistical evaluation for the clinical simulation studies performed by MicroBioTest are present in Table 1. According to pre-study statistical analysis, at least 40 panelists were to be included for each of the 3 arms of the study. Clearly this was not achieved in some instances and the statistician will need to address this issue.

Table 1. The number of subjects statistically evaluable by each test facility for each of the three arms and test sites.

Test Facility	Product tested	Groin (40)*	Abdomen (40)*
Hill Top Research, Inc.	ChloraPrep One Step	26	42
	70% IPA	28	42
	2% CHG	20	43
MicroBioTest, Inc	ChloraPrep One Step	36	39
	70% IPA	39	41
	2% CHG	45	40

* Pre study statistical calculations suggest that approximately 40 panelists must complete the study to assure statistical meaningful analysis and conclusions to be reached.

The baseline data was evaluated to determine how many subjects actually had baseline counts that were below the required minimum of ≥ 2.5 $\log_{10}$ cfu/cm^2. Especially since the applicant changed this requirement from the previously mentioned value to an entry value of ≥ 2.2 $\log_{10}$ cfu/cm^2. The data presented in Table 2 suggests that the percent of subjects having values below the required minimal entry criteria ranges from 12 to 28 percent in Hill Top study and from 0.0 to 7.7 percent in the MicroBioTest study. However, the actual differences are not great since some of the subjects that had entry values less then required were close to the required entry level (See double asterisks below). The impact of these individuals on the statistical mean baseline value was not considered influential. However, it is interesting that the difference between the two test facilities is greater than anticipated. Perhaps the differences may be due to the geographic location of the two test facilities. Irrespective of the reason, the data will be accepted for analysis.

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

Test Facility	Product tested	Abdomen Proportion*	Percent (%)
Hill Top Research, Inc.	ChloraPrep One Step	5/42	11.9**
	70% IPA	12/42	28.6**
	2% CHG	8/43	18.6***
MicroBioTest, Inc	ChloraPrep One Step	3/39	7.7
	70% IPA	0/41	0.0
	2% CHG	2/40	5.0

* Number of subjects with values <2.5-log10 cfu/cm^2/number of subjects with values ≥ 2.5 $\log_{10}$ cfu/cm^2.

** Four of the subjects had baseline values >2.4 cfu/cm^2

*** Two of the subjects had baseline values >2.4 cfu/cm^2

The results of the preoperative skin prepping study performed by MicroBioTest are presented in Table 3. These data show that ChloraPrep (lot # 905083), Isopropyl alcohol (IPA, lot # 905105), and 2% chlorhexidine gluconate (CHG, lot # 905106) produced the required reduction of ≥ 2-$\log_{10}$ reduction/cm^2 and a ≥ 3-$\log_{10}$ reduction/cm^2 at the 10-minute time interval for the abdomen and inguinal areas, 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 24 hours after product use and demonstrated continued suppression of the flora with ChloraPrep and 2% CHG at both tests sites.

The applicant performed statistical analysis of the data generated in this study and demonstrate that there were no statistically significant differences (ANOV, p-value >0.50) between the baselines of the three product groups for the abdomen and the inguinal fold test sites. Further within-treatment t-test analysis for the abdomen and inguinal fold versus the established baseline revealed, as expected, statistically significant difference (p-value 0.0001) at the three time intervals measured for all three products suggesting that all

produced significant antimicrobial reductions. Between treatment analysis were also performed but they are not necessary to gain approval of the product under investigation. So this information will not be evaluated.

Reviewer's note: The FDA statistician should validate the statistical analysis that are relevant for approval of this NDA and include analysis of within treatment comparisons.

Table 3. MicroBioTest preoperative skin prepping bacterial reductions (log_{10}±SD) achieved with the ChloraPrep One-Step, 70% isopropyl alcohol (IPA) and 2% chlorhexidine gluconate (CHG) at the designated enumeration time frames.

Body site	Enumeration	ChloraPrep	IPA	2% CHG
	Baseline	3.2426±0.8002	3.2342±0.6827	3.3080±.07370
Abdomen	1/60 hour	2.5616±0.9906	2.8382±0.7849	2.3723±1.1647
	6.0 hours	2.1503±1.2906	2.0764±1.2879	1.8032±1.3076
	24 hours	2.1807±1.1501	1.8622±1.2601	2.1045±1.4102
Groin	Baseline	4.9409±0.7001	4.8137±0.6316	4.8167±0.6246
	1/60 hour	4.1999±1.3018	3.9601±1.2410	3.8635±1.2937
	6.0 hours	3.4952±1.4511	3.1376±1.5326	3.3459±1.6603
	24 hours	2.6685±1.5577	2.5358±1.8246	2.8583±1.8372

Reviewer's comments: From the Microbiological perspective, the results of the MicroBioTest clinical simulation preoperative skin prepping study are accepted. The test laboratory used an appropriate trial design in the conduct of study, they employed acceptable techniques as described in the TFM, and used appropriate efficacy requirements as described in the TFM. The FDA statistician should validate the statistical analysis performed and results concluded by the applicant for this study. The review team needs to assess whether they will allow the use of the 2% CHG aqueous formulation as an acceptable control.

[redacted]

Deficiency: The neutralizer validation information provided by MicroBioTest 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 have not identified the indicator organisms used in the study, nor have they provided the proper controls required in the ASTM reference. In addition, the applicant allowed the use of two different techniques to validate the neutralizers without providing the scientific rational for doing so.

Applicants Response to deficiency: On July 6, 2000 the applicant submitted the complete protocol, identifying the time frames used for all steps of the procedure, the two microorganisms used to validate the neutralizer and the toxicity study control. The response is satisfactory.

Hill Top Research, Inc clinical simulations study: The Hill Top study was performed using the identical trial design, conducts of study, techniques employed and efficacy requirements as the first study. The results of the Hill Top study (# 990326.HTR) are very similar to the previous study results in that appropriate baseline values and required reductions were achieved at the desired time interval for the ChloraPrep. This data is presented in Table 5 below.

It should be recalled that the entry criteria for the abdomen was somewhat lower than required and that larger proportions of subjects were included with the lower number as described in Table 2. The baseline values presented in Table 5 and the standard deviations provided suggest that this abdomen and inguinal data set is acceptable since those individuals not having the desired baseline did not influence the baseline substantially. Statistical analysis to assess differences between baseline populations for the three study arms reveal that there is no statistical difference between the three baseline arms (p-value >0.50). Within treatment statistical analysis was also performed to determine whether ChloraPrep produced significant reductions in bacterial counts versus its baseline. The analysis reveals that ChloraPrep and other control arms produce statistically significant reductions (p-value <0.0001) for all three arms at all three-time points evaluated. This study confirms the results of the MicroBioTest study and provides the scientific evidence of efficacy required to recommend approval.

Table 5. Hill Top, Inc. preoperative skin prepping bacterial reductions (log_{10} ±SD) achieved with the ChloraPrep One-Step, 70% isopropyl alcohol (IPA) and 2% chlorhexidine gluconate (CHG) at the designated enumeration time frames.

Body site	Enumeration	ChloraPrep	IPA	2% CHG
	Baseline*	3.0290±0.4487	2.9595±0.4384	2.9804±0.3801
Abdomen	1/60 hour	2.4889±0.7516	2.5779±0.5592	2.3392±0.8712
	6.0 hours	2.3385±0.8688	2.2739±0.9201	2.4368±0.6348
	24 hours	2.6627±0.6098	1.8312±1.5462	2.1563±1.0122
Groin	Baseline*	5.2246±0.6169	5.1806±.05687	5.2173±0.6163
	1/60 hour	3.7239±1.0736	3.4814±1.4318	2.9957±1.1230
	6.0 hours	3.9248±1.3073	3.5167±1.3913	3.9336±1.5010
	24 hours	4.0024±1.1486	2.8334±2.2647	3.9166±1.5701

* Baseline was calculated as the average of two-baseline enumeration's that were performed one week apart.

Reviewer's comments: From the Microbiological perspective, the results of the Hill Top clinical simulation preoperative skin prepping study are accepted. The test laboratory used an appropriate trial design in the conduct of study; they employed acceptable techniques as described in the TFM, and used appropriate efficacy requirements as described in the TFM. The FDA statistician must validate the statistical analysis performed and results concluded by the applicant for this study.

Validation of the Neutralization system: Validation of the neutralization system used by Hill Top Laboratories is presented in Volume 2 of 11, Protocol # 990326.HTR, appendix VIII. It should be noted that this protocol reference number is identical to that used in the MicroBioTest study thus suggesting that both study protocols are identical. This was confirmed by evaluation of the protocols. Thus, the neutralization materials which are described more clearly in the Hill Top section would also describe the materials used in the MicroBioTest study. In fact, the information presented in Volume 5 of 11 (appendix IV) for MicroBioTest and in volume 2 of 11 (appendix IV) provides the components and composition of the stripping sampling solution with neutralizers used in both facilities and they are the same. At least this answers the question of the composition of the neutralizer used by MicroBioTest Research, Inc.

Validation of the neutralization system used by Hill Top Research was performed by a method that differs from that used by MicroBioTest Research. Hill Top took an approach that mimics actual product use in the clinical setting. The forearm of an individual was treated with the test and control products, allowed to air dry for the appropriate duration, and sampled and plated according to the study enumeration protocol. Thus the skin stripping solution used in the [redacted] technique already contained the neutralizers. The [redacted]

Article	Time	Plate counts		Avg. cfu/mL	% Recovery
# Control	30 seconds	49	50	5.0×10^1	NA*
	30 minutes	46	39	5.0×10^1	NA
Toxicity control	30 seconds	67	50	5.0×10^1	116
	30 minutes	55	65	5.0×10^1	143
ChloraPrep	30 seconds	59	55	5.0×10^1	114
	30 minutes	54	52	5.0×10^1	126
70% IPA	30 seconds	61	52	5.0×10^1	112
	30 minutes	59	70	5.0×10^1	152
2% CHG	30 seconds	50	42	5.0×10^1	92
	30 minutes	53	64	5.0×10^1	138

* Not Applicable

/S/ 7/11/00

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Cc: Original NDA No. xxx-xxx
Microbiologist, HFD-520
File name:

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DepDir/LGavrilovich 7/12/00

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HFD-520/Micro
HFD-520/MO/
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HFD-520/Chem/
[redacted]
HFD-520
HFD-502