

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-422 / S-032

MICROBIOLOGY REVIEW(S)

There appears to be a numbering error in the numbering of the microbiology reviews.

In this package are reviews numbered #3 and #4. Document room staff and staff in the Office of Nonprescription Products affirm no reviews are present numbered as #1 and #2.

Looking at the dates (of submissions and signoffs) in the reviews, it does appear that these are the only ones.

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 4
Consult

NDA # 19-422/S-032

Date Completed: October 10, 2002

Reviewer: Albert T. Sheldon, Jr. Ph.D.

Applicant (NDA):
Xttrium Laboratories, Inc.
415 West Pershing Road
Chicago, Illinois 60609

Chem/Ther. Type: Antimicrobial-antiseptic

Submissions Reviewed: Supplement - 032

Providing for: A change in the direction for use in the indications section when used as a surgical hand scrub. The current directions state that 5 milliliters of product should be used to scrub the hands for 3 minutes. These scrub directions are repeated twice. The applicant wishes to change the directions to wash with 8 milliliters of product for 1.5 minutes. These wash directions are also repeated twice.

Product Name(s):

Proprietary: Exidine Solution

Non-proprietary/USAN: chlorhexidine gluconate

Compendia: Chlorhexidine gluconate

Code name/number: 18472-51-0 (USP)

IND/NDA No.19-422/SE032
Exidine (2% Chlorhexidine gluconate)
Xttrium Laboratories, Inc

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Chemical name: 2,4,11,13-Tetraazatetradecanediiimidamide, N, N- β -bis (4-chlorophenyl)-3,12-diimino-, di-D-gluconate.

Structural formula: NA

Molecular formula: C₂₂H₃₀Cl₂N₁₀·2C₆H₁₂O₇

Dosage form(s): solution

Route(s) of administration: topical

Pharmacological Category: antiseptic

Dispensed: Rx _____ OTC X

Initial Submission Dates

Received by CDER: April 25, 1989
Received by Reviewer: May 10, 1989
Review Completed: June 5, 1989

Supplements: S-032

Dated January 10, 2002
Received by CDER: February 25, 2002
Received by Reviewer: March 1, 2002
Review Completed: October 10, 2002

Amendments:

Dated October 7, 2002
Received by CDER: October 7, 2002
Received by Reviewer: October 10, 2002
Review Completed: October 10, 2002

Related Documents:

NDA 19-125 Exidine (4% Chlorhexidine gluconate) Antiseptic
NDA 19-127 Exidine Foam (4% Chlorhexidine gluconate) Antiseptic
NDA 20-111 Dyna-Hex (0.75% Chlorhexidine gluconate) Health care personnel hand wash

Remarks:

The applicant submitted this supplemental application under the provision 21CFR 314.70 requesting approval of a new OTC label for Exidine (2% Chlorhexidine gluconate) Solution. Review of the of the proposed label provided January 10, 2002 suggests a change to the "Direction for Use" of the Exidine surgical hand scrub use product label. The changes include a reduction in the duration of scrub, an increase in volume of

product used, and a decrease in the rinse cycle of the hands. These product directions provide insight into the type(s) of clinical simulation studies and directions for use that will be required to demonstrate product efficacy. The current label directs the user to use the current surgical hand scrub directions.

"Wet Hands and forearms with water.

Scrub for 3 minutes with about 5 mL of product with wet brush, paying close attention to the nails, cuticles, and skin between the fingers.

A separate nail cleaner may be used.

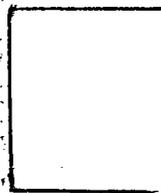
Rinse thoroughly.

Wash for an additional 3 minutes with about 5 mL of product and rinse under running water.

Dry thoroughly."

The proposed changes are provide with underlining used to emphasize segments to be modified and instructions that need to be used in the clinical simulation study:

"Wet Hands and forearms _____



Dry thoroughly."

Based on the proposed product label, the applicant needs to perform a surgical hand scrub clinical simulation study using the proposed protocol provided in the agencies Tentative Final Monograph for antiseptic Drug Products.¹

Conclusions/Recommendations:

- The applicants request to amend the product use direction for surgical hand scrub use is acceptable provided the Biostatistician confirms the analysis provided by the test laboratory.
- The new labeling directions proposed for this product suggest that the surgical scrub can be performed with or without a scrub brush. The clinical simulation study was performed without a scrub brush. It is assumed that use of a scrub brush will serve to augment the efficacy of the product. Thus, the clinical simulation study supports this request.
- The study was designed to show that the test product is effective when used as a surgical hand scrub. The directions for use require an increased volume of product, decreased duration of exposure, and rinsing of the hands for a shorter period of time (1 minute). These facts need to be included in the directions for use.

- The directions for use need to include the use of a nail pick to clean under the finger nails before the scrub is performed as requested. This is the manner in which the clinical simulation study was performed.
- Thus, the directions for surgical hand scrub use should instruct the user as follows:
Wet Hands and forearms _____

Scrub for 1.5 minutes with about 8 mL of product with or without a wet brush, paying close attention to the nails, cuticles, and skin between the fingers.

Wash for an additional 1.5 minutes with about 8 mL of product and rinse under running water for _____
Dry thoroughly
- The product is approved from the microbiological perspective.

Microbiology Executive Summary

The applicant requests a change to the directions for use of the surgical hand scrub product known as Exidine (2% Chlorhexidine gluconate Solution) or as described in the clinical simulations studies, Dyna-Hex (2% Chlorhexidine gluconate) Antimicrobial Skin Cleanser. The request is to decrease scrub time from two 3-minute scrubs to two 1.5-minute scrubs. Further, the directions propose an increase of product volume from 5.0 mLs per scrub, for a total exposure of 10.0 mLs, to 8.0 mLs per scrub for a total exposure of 16.0 mLs. The basis for approval is the clinical simulation study performed by _____ The study demonstrates that Exidine, when used as proposed, reduces the microbial flora of the hands as described in the agencies Tentative Final monograph for skin antiseptics. The applicant is not required to perform the *in vitro* spectrum of activity studies nor the *in vitro* time-kill kinetic studies because such information has already been provided in previous studies with this and other formulations.

**APPEARS THIS WAY
ON ORIGINAL**

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ON ORIGINAL**

INTRODUCTION

Hand washing to prevent the transmission of nosocomial pathogens is considered to be one of the most important and effective procedures performed by healthcare professionals in reducing the incidence of nosocomial infections. Hand washing is considered an important intervention strategy that incorporates both physical/mechanical action and chemical antimicrobial strategies to prevent the transmission of nosocomial pathogen by reducing or eliminating pathogens from the hands. The Food and Drug Administration recognizes this important strategy and supports the evaluation of products intended for such uses. In this regard, the agency published a FR Notice¹, which describes two indications that support the use of these chemical barrier intervention strategies when used as surgical hand scrubs, or health care personnel hand wash products. A third indication provides for the labeling of a product as a preoperative skin-prepping product that is used on the skin prior to invasive surgery. The latter indication is currently not applicable to the product described in this NDA.

The hand washing studies proposed in the FR Notice¹ have limitations in that they only allow assessment of product efficacy against the resident flora on the hands of test panelists or measurement of efficacy versus a surrogate marker. In reality, these test panelists are surrogates for healthcare personnel and probably do not carry, transiently, nor are they exposed to the same pathogens that healthcare professionals encounter during daily activities. Since the testing of these products has this inherent limitation, the agency must gather information on 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 characteristics desired for these products are dependent on the products intended use but in general we require that they be wide spectrum, fast acting, and persistent antimicrobials that are safe and effective for the intended uses as described within the TFM notice. The following studies are performed or were performed when the indications were first approved to assess these characteristics of the Exidine surgical hand scrub solution.

PRECLINICAL EFFICACY

In vitro

Antimicrobial Spectrum of Activity.

Antiseptic topical drug products (i.e. surgical hand scrubs) are used in health care settings such as hospitals and nursing homes where the likely hood of transmission of nosocomial and community acquired pathogens is high. The purpose of this study is to demonstrate that products intended for surgical hand scrub and/or health care personnel hand wash use have a satisfactory spectrum of activity against pathogens that are likely to be encountered in these health care setting. Thus, products used in these settings should be formulated with wide spectrum antimicrobials. The *in vitro* spectrum of activity studies are performed with organisms

that are know to be nosocomial pathogens¹ in order to assess whether the product is a wide spectrum antimicrobial.

The FR Notice requires that *in vitro* spectrum of activity be assessed using standardized minimal inhibitory concentration (MICs) methods² against a selected panel of bacteria that are described in 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, the product vehicle to assess the contribution of the vehicle to the spectrum of activity, and to the active ingredient.

The applicant demonstrated the *in vitro* spectrum of Dyna-Hex Antimicrobial Skin Cleanser when other product lines were approved for use as a health care personnel hand wash (0.75% CHG) and as a preoperative skin prep (4% CHG). Thus, the *in vitro* spectrum of activity studies presented in those products will serve to fulfill the requirement for this product. We do so because the health care personnel hand wash contains 0.75% CHG which is lower than the 2.0% found in this product line.

Time-kill kinetic Studies.

I stated previously that one of the desired characteristics of a surgical hand scrubs include that they must be fast acting. The agency has concluded that this characteristic can be assessed by the conduct of an *in vitro* time-kill kinetic study as described in the TFM.¹ This information was submitted and found acceptable when other product lines were approved for use as a health care personnel hand wash (0.75% CHG) and as a preoperative skin prep (4.0% CHG). Thus, the *in vitro* spectrum of activity studies presented in those products will serve to fulfill the requirement for this product.

CLINICAL EFFICACY

Staphylococcal mediated prosthetic valve endocarditis and postoperative wound infections in patients undergoing cardiac surgery has been documented.^{3 4} However, few reports actually address common source epidemics of staphylococci infections in such patients.⁵ Several papers have been published which conclusively establish surgeons as the source of outbreaks in some cases.^{6 7} Control measures instituted at one facility included hand washing with a chlorhexidine-based product.¹¹ This resulted in the

elimination of *Staphylococcus epidermidis* from the hands of a surgeon identified as the carrier whose patients had a higher incidence of postoperative infections than that of other surgeons.

Surgical hand scrubbing is performed to remove transient bacteria and reduce the resident flora of the hands of surgeons and health care personnel involved in surgical suites. The product is also designed to have a persistent effect in case the physical integrity of surgical glove is compromised. It is assumed that the persistence effect will prevent the multiplication of resident flora in the surgical glove occluded hand thus preventing contamination of the surgical field. The typical duration of surgical scrubbing in the United States is usually 5 minutes.⁶

The Food and Drug Administration supports the practices of hand washing and encourages the development of these products for the intended use by establishing efficacy requirements. The surgical hand scrub protocol described in the FR Notice is designed to mimic, microbiologically, the conditions and use of the product in the clinical setting. Thus, the applicant is required to perform a surgical hand scrub simulation study as described in the FR Notice.¹

The randomized, parallel design study is performed by establishing a test panel to represent the surgeon or health care professional. Inclusion criteria require that the hands of panelists contain numerable baselines $\geq 1.5 \times 10^5$ cfu/hand. Panelist are randomized into groups of 6 as described in Table 1 to maximize the information obtained from this study design. Thus, by randomizing 30 subjects per study arm, we can obtain 5 groups of 6 subjects each which will provide a total of 20 observations per time point. On days 2, 3 and 4, surgical scrubs are performed at hourly intervals as described in Table 2.

Table 1. Randomization of Subjects for the Surgical hand scrub effectiveness study.

Subjects	Enumeration times (Hours)		
	1/60	3	6
A	R*	L	-
B	L	-	R
C	-	L	R
D	L	R	-
E	R	-	L
F	-	R	L
Total observations	4	4	4

* R= right hand and L= left hand

Table 2. Surgical hand scrub and enumerations scheme.

Scrub Interval	Days of test				
	1	2	3	4	5
1	X*	X*	X	X	X*
2		X	X	X	
3		X	X	X	

*After the surgical scrub is performed, enumerations of the hands are performed on this day. Enumerations are performed five minutes after product use and after 3 and 6 hours as described in the scheme presented in Table 3.

Panelists are required to use the volume of drug and surgical scrub time recommended in the product label in performing the simulated surgical hand scrub. Then they don sterile surgical gloves and at the time intervals specified in Table 1, sampling solution is instilled into the glove, the hands are massaged for three minutes and an aliquot removed for enumeration. The time from aliquot removal to placement of this sample in neutralizer containing dilution blanks is critical for accurate enumeration. The efficacy requirements for surgical hand scrub are a 1- \log_{10} reduction per hand from the established baseline approximately five minutes after product use on day 1 (1st wash). Regrowth of the resident flora must not supercede the established baseline by the 6-hour enumeration time frame. On day two (2nd wash), the product should produce a 2- \log_{10} reduction of the microbial flora per hand and on the 5th day (11th wash), the product should produce a 3- \log_{10} per hand. In no test day where the hands are enumerated should regrowth of the microbial flora supercede the established baseline.

Xttrium Pivotal Clinical Simulation Surgical Hand Scrub Study

Xttrium Laboratories, Inc submitted a surgical hand scrub study that was conducted by _____ The surgical hand scrub study is titled "SURGICAL SCRUB EVALUATION OF A 2% CHLORHEXIDINE GLUCONATE SOLUTION USED WITHOUT A SCRUB BRUSH PROCEDURE" (Final Report #010206-102 dated May 18, 2001). _____ provides a statement that methods used are "based on the Food and Drug Administration's Tentative Final Monograph for *Effectiveness Testing of a Surgical Hand Scrub* (Tentative Final Monograph for Health Care Antiseptic Drug Products, FR 59:116, 17 June 94)". Thus the methods and materials are reviewed to assess compliance with the TFM.

The study design provided by _____ followed the trial design previously described in Tables 1 and 2. Approximately 90 intent to treat (ITT) panelists meeting the desired entry/exclusion criteria were enrolled in the study to obtain 60 per protocol (PP) panelists, which are randomized equally into two arms; 30 for the test product and 30 for the control product. Using the sampling scheme suggested in Table 1, 60 observations are obtained from the 30 panelists per arm. These 60 observations are equally allocated to the immediate, 3-hour and 6-hour sampling time frames. Baseline determinations are obtained three times over a one week period after an appropriate two week washout period in which no antimicrobial containing products are used.

The test week constituted the week immediately following the 7 day baseline week. Products are assigned to panelists and they are instructed to use the product 11 times; once on day 1; three times on days 2, 3, and 4; and once on day 5 as previously described in Table 2. The use directions for the control product and test product were evaluated to assure that products are used according to approved directions (Hibiclens) or to desired directions (Dyna-Hex). For the Hibiclens product, two 1.5 minutes surgical scrubs are performed with a sterile scrub/brush and 5.0 mLs of product. The Dyna-Hex product is

used in two 1.5 minute scrubs with 8.0 mL of product per scrub (Total exposure is 16 mLs of product). The test product was used according to the proposed labeling directions. Enumeration was performed on days 1, the first scrub on day 2, and on day 5 using the glove juice technique as outlined in Table 2. Samples are obtained immediately after product use and at 3 hours and 6 hours based on the randomization scheme previously described in Table 1. Skin stripping fluid, free of neutralizers, is used to obtain the sample. The sample is placed, immediately after acquisition, into the first dilution tube containing the appropriate phosphate buffer and neutralizer(s), serially diluted, and plated. The results of the study are presented in Tables 3 and 4 for control and test product, respectively.

Table 3. Statistical summary of the lob10 recovery values for the test product, HIBICLENS-Lot # 4562C and 4723B.

Sample	Sample size	Mean	± SD	95% CI	Log ₁₀ reduction
Baseline	60	5.96	0.35	5.87 to 6.05	NA
Day 1, Immediate	20	4.14	0.82	3.75 to 4.52	1.82
Day 1, 3- hour	20	5.21	0.59	4.94 to 5.49	0.75
Day 1, 6-hour	20	5.19	0.62	4.89 to 5.48	0.77
Day 2, Immediate	20	3.52	0.75	3.16 to 3.87	2.44
Day 2, 3- hour	20	4.53	0.80	4.15 to 4.90	1.43
Day 2, 6-hour	20	4.44	0.70	4.11 to 4.76	1.52
Day 5, Immediate	20	2.43	0.30	2.29 to 2.58	3.53
Day 5, 3- hour	20	3.04	0.68	2.72 to 3.35	2.92
Day 5, 6-hour	20	3.23	0.77	2.87 to 3.59	2.73

Table 4. Statistical summary of the lob10 recovery values for the test product, Dyna-Hex Antimicrobial Skin Cleanser-Lot # 007-1021-661.

Sample	Sample size	Mean	± SD	95% CI	Log ₁₀ reduction
Baseline	60	5.90	0.43	5.79 to 6.01	NA
Day 1, Immediate	20	4.34	0.97	3.89 to 4.80	1.56
Day 1, 3- hour	20	5.14	0.53	4.89 to 5.39	0.76
Day 1, 6-hour	20	5.35	0.69	5.03 to 5.67	0.55
Day 2, Immediate	20	3.73	0.96	3.28 to 4.18	2.17
Day 2, 3- hour	20	4.62	0.66	4.31 to 4.93	1.28
Day 2, 6-hour	20	5.03	0.66	4.72 to 5.34	0.87
Day 5, Immediate	20	2.62	0.55	2.36 to 2.88	3.28
Day 5, 3- hour	20	3.36	0.80	2.99 to 3.74	2.54
Day 5, 6-hour	20	3.85	0.88	3.44 to 4.26	2.05

Reviewers Comments for control product: Evaluation of the Hibiclens control data presented in Table 3 shows that the mean (±SD) baseline values per hand are 5.96 (±0.35) and this baseline meets the entry criteria of 1.5×10^5 cfu per hand (5.18 log₁₀ per

hand). Statistical evaluation suggests that the lower limit of the 95% CI is above the baseline value required per hand. If we also look at the stem-leaf plot of the control baseline data, we see that all of the 60 observations have baseline values greater than 5.18 \log_{10} per hand. This data is provided in volume 1 of 2 (page 1025) and is a plot of the average cfu/hand for days 1,3, and 5 for Hibiclens,

The requirements for a surgical hand scrub are a 1- \log_{10} reductions on day 1 after the 1st wash, a 2- \log_{10} on day after the 2nd wash, and a 3- \log_{10} reduction on day 5 after the 11th wash. It is clear that Hibiclens meets the efficacy requirements by producing 1.82 \log_{10} reduction at the 1st wash, a 2.44 \log_{10} reduction at the 2nd wash, and a 3.53 \log_{10} reduction at the 11th wash. The data also demonstrates that as the wash frequency increases from wash 1 to wash 11, the efficacy of the product increases as demonstrated by increasing \log_{10} reductions. That is, as the product is used over the 5 day study period, the \log_{10} reductions increase with time. This also suggests that a substantive residue of CHG is present on the hands of users immediately after product use. In addition, evaluation at the 6-hour time frame demonstrates that the regrowth of the resident flora does not supercede the previously established baseline. Again, the residue of CHG on the hands appears to have a suppressive affect since the resident flora remains 2- \log_{10} (>99%) below the original baseline at the 6 hour time frame of the 11th wash. An alternate hypothesis is that the carry over of CHG is greater than the concentration used to perform the neutralization validation and we are seeing kill (efficacy) *in situ*. This was examined when evaluating the validation of neutralized data. The applicant tested 1:10 and 1:100 dilutions of test and control product and all were successfully neutralized.

Reviewers comment for test product: Evaluation of the test data presented in Table 4 shows that the mean (\pm SD) baseline values per hand are (5.90 \pm 0.43) and we accept this as meeting the entry criteria of 1.5×10^5 cfu per hand (5.18 \log_{10} per hand). Again the 95% CI analysis shows that the baseline is within the expected range. If we look at the stem-leaf plot provided in volume 1 of 2 (page 1008), which is a plot of the average cfu/hand for days 1,3, and 5 for Dyna-Hex, we see that only 3 of the 60 possible observations have baseline values less than 5.18 \log_{10} per hand. Those values were examined and found to be 5.0, 5.1 and 5.1 \log_{10} per hand. These results are not deemed to influence or bias the baseline results.

It is clear that Dyna-Hex also meets the efficacy requirements for a surgical hand scrub since it produces a 1.56 \log_{10} reduction on day 1 after the 1st wash, a 2.17 \log_{10} reduction on day 2 after the 2nd wash, and a 3.28 reduction on day 5 after the 11th wash. We conclude that Dyna-Hex meets the efficacy requirements for a surgical hand scrub when used as directed.

During the preliminary review of the submission, the following was requested of the applicant to help understand the investigators response to issues described below. The following were conveyed to the applicant:

1. Section 12.11.7 states for the test product that "Subjects performed a final rinse under running tap water maintained at 40° \pm 2°C such that each hand and forearm was rinsed for thirty (30) seconds (for a total rinse time of one (1) minute). In Section 12.11.19,

it states for the control product ""Subjects performed a final rinse under running tap water such that each hand and forearm was rinsed for one (1) minute (for a total rinse time of one (2) minute). This difference introduces a bias in favor of the test product. Please explain why this difference in rinsing regimen needed to be implemented?

The applicant responded that the 30 second total rinse per hand is what is to be proposed in the label. Thus they wanted to conduct the study as they will propose the product is to be used in the product label. The test product was rinsed for two minutes because that is what it states in the TFM.

Reviewers response: Although I agree that the control product should be used with a 2 minute rinse, I am more concerned by the proposal that the test product is rinsed for only 30 seconds per hand (total of 1 minute). The reason for this concern is that the hands of individuals are exposed to 60% (10 versus 16 mLs) more antiseptic and the hands are rinsed for shorter durations of time. It is possible that the shortened duration of exposure during the surgical scrub will not lead to hands that are red or irritated. The medical reviewer should be consulted to determine whether this is considered a potential problem.

2. Three "Protocol and/or SOP deviation recording forms" were submitted to the agency that requires additional explanation.

In the first form it states that 3 stacks of baseline plates had to be incubated for 113 hours as opposed to the protocol specified 72 hours. Please explain why it was necessary to do so and any follow-up investigations that were made to explain the observation.

The applicant responded that the added incubation time was due to technical error and would serve to provide a worst case scenario since additional organisms would grow.

The reviewer agrees with this assessment.

Did the plates represent the test or control product?

The applicant stated that the plates represented the second of three baseline samplings.

The reviewer concludes that this will not negatively impact the baseline determination.

What subjects were these samples taken from? Was this data used in the final analysis?

The data was taken from subjects 88, 89, and 90. The data was used in the mean baseline calculation.

The reviewer concludes that this will not negatively impact the baseline determination.

In the second form it is stated that some samples were taken at times prior to 6 and 3 hours post-scrub and at times that exceeded 3 and 6 hours post scrub. Please identify the subjects in which this occurred and whether the noted samples times represent test and/or control drug product? Also provide the actual times that sampling occurred and whether the data was used in the analysis?

The applicant responds with a tabulation presenting the study subjects identified for which samples were obtained prior to 3 and 6 hours or after 3 and 6 hours.

The reviewer evaluated the tabular information and concludes that the time differences are not significant enough to influence the outcomes for test or control products.

In the third form, it is stated that there were three occurrence where washes occurred prior to the protocol defined one hour time. Please identify the subject in which this occurred and whether they represent the test or control product.

The applicant states that all sequential washes were less than 60 minutes apart for only 5 subjects and all represented the control. Product. The lapse occurred between wash 1 and 23 subjects and between washes 2 and 3 in two subjects.

The reviewer concludes that the data will not influence the outcome of the study.

Reviewer comment: The applicant provided the specific details of each question.. The responses are all satisfactory. In addition, the ability of the applicant to response to these individual questions demonstrates that they have the ability to find and retrieve minute details of the study.

Validation of the Neutralization system

The test laboratory validated the neutralizers used in this clinical simulation study by using the American Society for Testing and Materials *Standard Practices for Evaluating Inactivators on Antimicrobial Agents Used in Disinfectant, Sanitizer, Antiseptic, or Preserved Products (ASTM 1054-91)*.

This standard suggests conceptual aspects that are to be considered during the validation process. The inactivator studies must be validated with the target microorganism which is

specific for the particular antiseptic test method. In this instances, *Staphylococcus epidermidis* (ATCC#12228) was used to confirm the adequacy of the neutralizers. The standard also requires that the neutralizer system used is not in and of its self toxic to the marker organism used in the validation . Finally, the neutralizer must demonstrate that it is capable of neutralizing the chlorhexidine gluconate used in this product formulation.

Reviewers response: The data for the neutralization validation is provided in Addendum VII of volume 3 of 3. A review of this addendum finds the neutralization evaluation data, the neutralization evaluation forms (Form no. 91-L-013) and data generated, the inoculum preparation tracking form and data, project notes, and Neutralization statistics. No formal report was provided so this reviewer evaluated the existing information to determine whether the neutralization system was adequate.

- Appropriate growth controls for skin stripping fluid, phosphate buffer with and without neutralizers were tested and found satisfactory. That is, no toxicity was demonstrated by the neutralizer concentrations used with the *S. epidermidis* marker relative to the neutralizer free control.
- Neutralization of glove juice fluid obtained for a panelist and a 1:10 and 1:100 dilutions of test and control product were also used to assess the neutralization of CHG immediately and at 30 minutes neutralization exposure. The data demonstrate survival of the marker organism suggesting appropriate neutralization of the glove sample and know volumes/concentrations of CHG for both test and control products.
- Appropriate growth and sterility controls were run concurrently and were satisfactory. Growth was seen in inoculated tubes and the sterility control had no growth.
- It is concluded that validation of the neutralization system is demonstrated and the clinical simulations study is accepted as proof of efficacy.

**APPEARS THIS WAY
ON ORIGINAL**

Albert T. Sheldon, Jr. Ph.D.

Microbiology Reviewer and Team Leader

Cc: Original NDA No. 19-422
Microbiologist, HFD-520
File name: N19-422_S032_R#4.doc

SMicro/ATSheldon

DepDir/LGavrilovich

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

² 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.

³ Archer GL, Armstrong BC. (1983) Alterations of staphylococcal flora in cardiac surgery patients receiving antibiotic prophylaxis. J. Inf. Dis. 147:642-649.

⁴ Karchmer, AW, Archer GL, Dismukes WE. (1983) Prosthetic valve endocarditis: microbiologic and clinical observations as guides to therapy. Ann. Inter. Med, 98:447-455.

⁵ Archer GL, Vishniavsky N, Stiver HG. (1982) Plasmid pattern analysis of *Staphylococcus epidermidis* isolates from patients with prosthetic valve endocarditis. Infect Immun 35:627-632.

⁶ van Den Broek PJ, Lampe AS, et. al. (1985) Epidemic of prosthetic valve endocarditis caused by *Staphylococcus epidermidis*. Br. Med. J {Clin Res} 291:949-950.

⁷ Boyce JM, Potter-Byone G, et. al. (1990) A Common Source Outbreak of *Staphylococcus epidermidis* Infections among patients undergoing cardiac surgery. JID. 161:493-499.

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/s/

Albert Sheldon
10/9/02 02:58:24 PM
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10/11/02 03:39:52 PM
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Division of Anti-Infective Drug Products
Clinical Microbiological Review # 3
Consult

NDA # 19-422/S-032

Date Completed: August 16, 2002

Reviewer: Albert T. Sheldon, Jr. Ph.D.

Sponsor (IND)/Applicant (NDA):

Xttrium Laboratories, Inc.
415 West Pershing Road
Chicago, Illinois 60609

Chem/Ther. Type: Antimicrobial-antiseptic

Submissions Reviewed: Supplement - 032

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Exidine (2% Chlorhexidine gluconate)
Xttrium Laboratories, Inc

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Chemical name: 2,4,11,13-Tetraazatetradecanediimidamide, N, N β -bis (4-chlorophenyl)-3,12-diimino-, di-D-gluconate.

Structural formula: NA

Molecular formula: C₂₂H₃₀Cl₂N₁₀·2C₆H₁₂O₇

Dosage form(s):

Route(s) of administration:

Pharmacological Category:

Dispensed: Rx _____ OTC X

Initial Submission Dates

Received by CDER:

Received by Reviewer:

Review Completed:

Supplements/Amendments: January 10, 2002

Received by CDER:

Received by Reviewer:

Review Completed: October 7, 2002

Related Documents: NA

Remarks:

The applicant submitted this supplemental application under the provision 21CFR 314.70 requesting approval of a new OTC label for Exidine (2% Chlorhexidine gluconate Solution (CHG)). Review of the of the proposed label provided January 10, 2002 suggests a change to the "Direction for Use" of the Exidine surgical hand scrub product label. The changes include a reduction in the duration of scrub and an increase in volume of product used. These product directions provide 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 current surgical hand scrub directions.

"Wet Hands and forearms with water.

Scrub for 3 minutes with about 5 mL of product with wet brush, paying close attention to the nails, cuticles, and skin between the fingers.

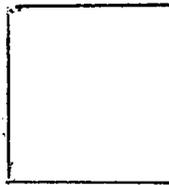
A separate nail cleaner may be used.

Rinse thoroughly.

Wash for an additional 3 minutes with about 5 mL of product and rinse under running water.
Dry thoroughly."

The proposed changes are provide with underlining used to emphasize segments to be modified:

"Wet Hands and forearms _____



Dry thoroughly."

Based on the proposed product label, the applicant needs to perform a surgical hand scrub clinical simulation study according to the directions provided in the agencies Tentative Final Monograph for antiseptic Drug Products.¹

Conclusions/Recommendations:

A cursory review of the final report (#010206-102) has been completed and several questions arose as a result of this evaluation. These questions or issues need to be conveyed to the applicant for consideration. It is necessary to address these questions or issues to assure completed evaluation of the information submitted. The applicant provided their own interpretation of the consequences of these issues without providing further explanation of the issues. The agency needs to make their own conclusions based on the changes noted.

The following should be conveyed to the applicant:

1. Section 12.11.7 states for the test product that "Subjects performed a final rinse under running tap water maintained at $40^{\circ} \pm 2^{\circ}\text{C}$ such that each hand and forearm was rinsed for thirty (30) seconds (for a total rinse time of one (1) minute). In Section 12.11.19, it states for the control product ""Subjects performed a final rinse under running tap water such that each hand and forearm was rinsed for one (1) minute (for a total rinse time of one (2) minute). This difference introduces a bias in favor of the test product. Please explain why this difference in rinsing regimen needed to be implemented?
2. Three "Protocol and/or SOP deviation recording forms" were submitted to the agency that requires additional explanation.

In the first form it states that 3 stacks of baseline plates had to be incubated for 113 hours as opposed to the protocol specified 72 hours. Please explain why it was necessary to do so and any follow-up investigations that were made to explain the observation. Did the plates represent the test or control product? What subjects were these samples taken from? Was this data used in the final analysis?

In the second form it is stated that some samples were taken at times prior to 6 and 3 hours post-scrub and at times that exceeded 3 and 6 hours post scrub. Please identify the subjects in which this occurred and whether the noted samples times represent test and/or control drug product? Also provide the actual times that sampling occurred and whether the data was used in the analysis?

In the third form, it is stated that there were three occurrence where washes occurred prior to the protocol defined one hour time. Please identify the subject in which this occurred and whether they represent the test or control product.

Additional; comments may be required for the neutralization validation experiments and/or the clinical simulations study upon completion of in-depth review.

Albert T. Sheldon, Jr. Ph.D.

Microbiology Reviewer and Team Leader

Cc: Original NDA No. 19-422
Microbiologist, HFD-520
File name: N19-422_S032_deficinicies

SMicro/ATSheldon

DepDir/LGavrilovich

Cc:
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-520/SMicro/ATSheldon
HFD-520/Micro
HFD-520/MO/
HFD-520/Pharm/
HFD-520/Chem/
HFD-520/CSO/
HFD-520
HFD-502
HFD-635

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

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/s/

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