CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73416

MICROBIOLOGY REVIEW

Consult

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Clinical Microbiology

NDA #: 73-416 **MICRO.REVIEW #:** 01 **REVIEW DATE:** 26-Mar-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	04-May-93		10-May-96
AMENDMENT/AC	28-Aug-95	01-Sep-95	26-Sep-95

NAME & ADDRESS OF APPLICANT: Becton-Dickinson
AcuteCare
9450 South State Street
Sandy, Utah, 84072-3234

DRUG PRODUCT NAME

Proprietary: E-Z Scrub
Nonproprietary/USAN: Chlorhexidien gluconate
Code Names/#'s:
Chemical Type/
Therapeutic Class: **Antimicrobial**

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Antimicrobial

DOSAGE FORM: Topical
STRENGTHS: 4%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: ___x___ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See USAN 1996 page 147

SUPPORTING DOCUMENTS:

N/A

RELATED DOCUMENTS (if applicable):

N/A

CONSULTS:
This document is a consult from the Office of New Drug Chemistry/Division of Bioequivalence (HFD-650).

REMARKS/COMMENTS:

Historical Development:
On October 23, 1989 a consult was sent to the Division of Antiinfective Drug Products requesting an evaluation of a proposal by Deseret Medical, Inc. to waive the *in vivo* bioequivalence trial for a product they intend to market. They reasoned that the product is Hibiclens, an approved and marketed product which would contain their logo. The waiver was denied because insufficient information was provided to evaluate and verify the applicants statements regarding the similarity of the formulations (See Microbiological Review # 1 completed 11/7/89).

On January 2, 1990 the applicant responded to the deficiencies noted in the previous review. The information that was provided led this reviewer to conclude that if chemistry could verify that the same formulation, manufacturing and controls that were used in the formulation of Hibiclens were to remain in place during the manufacturing of the Deseret product, then the waiver should be granted (See Microbiological Review #2 dated 4/26/90).

Another consult was received on May 21, 1992 requesting review of a protocol designed to assess the efficacy of a product intended for surgical hand scrub use. The review was completed on July 7, 1992 and recommended changes to the protocol were made by this reviewer to assure compliance with established clinical simulation study protocols.

Current History:
The Office of New Drug Chemistry (formally the Office of Generic Drugs, CDER HFD-630) sent this consult for review on May 4, 1993. The document contains a surgical hand scrub study (# 920402) which was conducted by
for the indication of surgical hand scrub.

A cursor review was performed of the document and the raw data from this study was found to be absent. On June 22, 1995 an E-mail was sent to James Chaney and Janson Gross asking that additional information be provided (See appended E-mail dated 22-Jun-1995). The information was received on August 28, 1995 and was used for review of this ANDA.

In addition, since the test facility had been under intense investigation by the Division of Scientific Investigations (DSI) team of the FDA, I did not want to began the review of the submission until I had received clearance that the study was in compliance with good clinical practices (GLPs). Several studies had already been disqualified by the DSI team and I did not want to review a study that may eventually be disqualified. I received clearance from DSI on October 17, 1996 that they would be willing to accept this study as having been conducted under good laboratory practices.

In addition, the document was sent to the Division of Biometrics for statistical consult and that document, dated October 24, 1995, is appended.

The indication sought by the applicant of this ANDA is surgical hand scrub use. Therefore, the applicant is required to perform an adequate and well controlled clinical simulation study of the test product using the Tentative Final Monograph (TFM) surgical hand scrub protocol described in the Federal Register document (vol. 59, No. 116/ Friday, June 17, 1994 Pages 31445-31448). The requirements for the demonstration of efficacy as a surgical hand scrub are 1). that a sufficient number of panelists be used to demonstrate that the product produces ≥ 1 $\log_{10}$ reduction of the microbial flora per hand, one minute after product use, at the first surgical hand scrub when compared to the baseline ($\geq 1.0 \times 10^5$ CFU per hand). Additionally, the bacterial numbers after the first scrub must remain below the established baseline value by the end of the 6 hour test period. 2). The product must also produce ≥ 2 $\log_{10}$ reduction of the microbial flora per hand one minute after product use after the second (2^{nd}) surgical scrub. 3). The product must exhibit a further reduction of ≥ 3 $\log_{10}$ cfu per hand one minute after product use, at the eleventh (11^{th}) surgical scrub when compared to the original baseline. **The**

1 minute surgical hand scrub is defined as time zero when discussed below.

The applicant submitted final study report #920402 entitled "Single Blind Surgical Hand Scrub Evaluation (glove Juice) of Two Test Products and One Standard Control Product," conducted by in compliance with efficacy requirements established by the TFM.

The protocol stated that approximately 60 panelists were to be entered into the 3 arm study and were to be randomly allocated to either test product # 1 (BDAC packing foil film), test product # 2 packaging; film), or control product (Hibiclens). Eighteen subjects (36 hands) were incorporated into each arm; thus 56 of the 60 subjects had to be evaluable to be included in the study. The 36 hands per product were divided into 3 groups of 12 by random allocation of right and left hands which were sampled at specified time periods after product use. The control product is incorporated into the study to validate the study results obtained with the test product.

The test panelists were all required to have entry criteria of $\geq 1 \times 10^5$ cfu per hand after they washed their hands with a bland soap for 30 seconds. This procedure is implemented to assist in the removal of transient bacteria from the hands so that product efficacy can be based on enumeration of resident bacterial flora only. The glove juice technique was used in the enumeration procedure.

The surgical hand scrub must be performed according to labeling directions for the control product. The test products must be labeled according to product use directions used in the simulated clinical trial since that is how efficacy was assessed. Generally, they MUST follow the innovators directions for use.

A total of 11 surgical hand scrubs are performed by all panel members over a period of 5 days. The first scrub is performed on day one and three additional scrubs are performed on the second, third and fourth days of the study. A final surgical hand scrub is conducted on the fifth day. Emunerations are performed after the first, second and

eleventh scrubs at times O hour, 3 hours or 6 hours depending on the randomization scheme.

The accuracy of the calculations and transformation of the surgical hand scrub raw data was been performed by this reviewer and found to be accurate. This was accomplished by tabulation of the data (tabulations not shown). Eighteen (18) subjects (36 hands) were randomly assigned to 3 groups of 12 hands as described in the protocol. In essence, one person used the same product for the duration of the study but enumeration of the hands was performed by allocation to either time zero, 3 hours or 6 hours after product use for all three enumeration periods.

The results of the study are presented below for each arm of the study. The tabulated data represent the statistical mean log reductions achieved by each product for the designated day and time. Thus the binomial approach was used in this evaluation. That is, did it meet the efficacy requirements ofr did it not. The data was calculated to obtain an estimation of the comparability of the outcomes for each product. Further analysis will be conducted by the biostatistican and that information should be consulted also.

The standard deviation is the "n-1 sample weighted" SD.

Table 1. **Test Product #1:** Statistical mean $\log_{10}$ reductions ± SD achieved by scrub and time of enumeration.

Scrub Number	Enumerations performed at:		
	Zero hour	3 hours	6 Hours
1	1.78±1.01	1.48±0.74	1.76±1.61
2	2.92±1.17	2.27±0.75	1.64±0.86
11	4.42±1.50	3.10±0.72	3.19±1.49

Table 2. **Test Product #2:** Statistical mean $\log_{10}$ reductions achieved by time and day of enumeration.

Scrub Number	Enumerations performed at:		
	Zero hour	3 hours	6 Hours
1	1.80±1.11	0.97±0.65	0.84±0.92
2	2.53±1.26	1.53±0.54	1.30±0.77
11	3.89±1.65	2.97±1.05	3.29±1.68

Table 3. **Control Product:** Statistical mean $\log_{10}$ reductions achieved by time and day of enumeration.

Scrub Number	Enumerations performed at:		
	Zero hour	3 hours	6 Hours
1	1.89±0.83	1.09±0.67	1.02±0.55
2	2.36±0.84	1.83±0.96	1.61±0.64
11	4.50±1.16	3.01±1.30	3.27±1.72

Evaluation of the data present in the three tables reveals that all three products produced the required ≥1 $\log_{10}$ cfu per hand one minute after product use after the first scrub ($time_{-0}$) as required. Also, the bacterial flora of the hands did not exceed the established baseline at the end of the 6 hour time frame. Evaluation of the raw data supports this conclusion for test product # 1 and the control product. However, 3 of the 12 hands (subjects 11, 14, and 20) tested with test product # 2 showed that the microbial flora of the hand actually exceeded the established baseline for that hand. However, the product managed to meet the standard irrespective of these observations. In summary, all three products met this efficacy requirement for surgical hand scrub use.

All products are required to meet ≥2 $\log_{10}$ reductions at the 2nd scrub and ≥3 $\log_{10}$ reduction after the 11th scrub and that is what was observed for all three products. Further, it can be seen that as the frequency of use of the product increases, the reduction of the bacterial populations on the hands increase suggesting a cumulative effect of the products resulting in a corresponding effect on the microbial flora of the hand. This is defined as the desired cumulative or persistence effect of the product on the hands.

All previous conclusions are based on the statistical mean reductions achieved by each product and compliance of these results with the requirements of the test.

The exclusion criteria for the non-evaluable panelist had not been provided and it is not known why particular individuals were excluded from the study. This information was requested June 22, 1995 and it was provided in the August 28, 1995 submission. Three test subjects were lost to follow up and three did not return to start the study.

According to the information provided in the study report, it would appear that the three products tested were all 4% chlorhexidine gluconate manufactured according to the same formulation. The report identifies Test product #1 as BDAC Packing (foil film) containing Hibiclens (Lot #02122234E), Test Product #2 as _ containing Hibiclens (Lot # 02122245X), and Control product as BDAC Hibiclens packaged in foil film for (Lot # . Thus it appears that the product was tested against itself. A review of the original Microbiological Reviews suggested that a waiver be given to the applicant since they were using the Hibiclens formulation to market this product. That is, the product marketed by Becton Dickinson was in fact the Hibiclens formulation. However, it appeared that the applicant wanted to label this product without reference to the Hibiclens manufacture and wanted to manufacture the product independently of the originator. This may be why the applicant had to conduct the study.

Note: The Reviewing chemist assigned to this ANDA should compare the formulation (components and composition) of the product which is the subject of this ANDA with the formulation of the Stuart Pharmaceuticals product known as

Hibiclens. According to the information conveyed in this study (Section 6. TEST MATERIAL), it is suggested that Becton-Dickinson packages this 4% CHG product for and apparently also packages the same product for its own use.

Neutralization Validation:

CONCLUSIONS & RECOMMENDATIONS:

It is this reviewers opinion that the two test formulations manufactured by Becton-Dickinson AcuteCare are capable of producing equivalent efficacy results when compared to the control product Hibiclens. All three products are manufactured according to the same formulation and the efficacy expected of all three formulations is bioequivalence. All three products contain 4% chlorhexidien gluconate (CHG) and it has been this reviewers opinion that formulations containing this volume of CHG provide an over abundance of the antimicrobial for the intended use. I would recommend that the products be approved.

The surgical hand scrub must be performed according to labeling directions for the control product. The test products must be labeled according to product use directions used in the simulated clinical trial since that is how efficacy was assessed. Generally, they MUST follow the innovators directions for use.

/S/ 3/28/97

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

AS 4/1/97

Consultation Microbiological Review 1

November 1, 1989

ANDA No. 73-416
Deseret Medical, Inc.
9450 South State Street
Sandy, Utah 84070

On October 23, 1989 the Division of Anti-Infective Drug Products (HFD 520) received for review an Abbreviated New Drug Application (ANDA) for a Chlorhexidine Gluconate (4%) Surgical Brush/Sponge. This ANDA is dated September 25,1989 and contains information on "the analytical methods and descriptive information needed to perform testing of the bulk 4% chlorhexidine gluconate solution received from and the finished dosage form". The ANDA also requests " a waiver of the in vivo bioequivalency study requirements under 21CFR320.22 (2) on the basis that the drug is a topically applied preparation intended for local theraputic effect".

It is the opinion of this reviewer that the waiver of the in vivo bioequivalancy requirement be denied. The denial is based on the following facts:

1). By definition, the word therapeutic implies a curative effect. In deed, the word therapeutic implies that it is an agent that is capable of curing an illness or eliminating an infection. However, surgical handscrub products are not indicated as therapeutics but as fast acting antimicrobials that are designed to kill and/or eliminate transient and resident microbes from the hands of a surgeon prior to surgery. The product must also demonstrate a persistent effect by suppressing the transcient and resident microbial flora of the hands for a specified time period of approximately 6 hours. No claim of clinical theraputic efficacy is made for surgical handscrub products.

Thus, the sponsors comment that the product is topically applied and intended for local theraputic effect is not consistent with the actual use of the product.

2) The in vivo bioequivalency requirement is designed to demonstrate that a generic version of a product performs in a manner that is considered to be statistically equivalent to the inovators product. Thus, the study is not only an examination of the finished dosage form, but, by design is an examination of the generic companies manufacturing expertise in reproducing an equivalent form of the inovators product.

If the generic firm was to obtain the finished dosage form (i.e. sponges containing 4% CHG packaged in identical packaging material) from the inovator and the inovator was placing the generic firms proprietary name on the product, it would not be necessary to perform the in vivo bioequivalency study provided the product had the same indications. However, in this case Deseret Medical, Inc. is purchasing bulk 4% chlorhexidine gluconate solution as a starting material for the manufacture of their finished dosage form. The 4% CHG is injected (volume unknown relative to the inovators product) into a sponge (characteristics unknown relative to inovators product) and the package sealed to produce the finished dosage form. In addition it is not known whether the instructors for use are identical for the genric version and the inovators product.

In conclusion, the sponsor must conduct the in vivo bioequivalency study in order to demonstrate that they are capable of manufacturing a product that is equivalent to the inovators product as measured by the surgical handscrub study.

/S/ 11/7/89

Albert T.Sheldon
Supervisor Microbiology
HFD-520

CC; ANDA 73-416
HFD-230 C.C.E. 12/1/89
HFD-520 11/7/89
HFD-520/ASheldon/PWynston 11/2/89
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CONSULTATION

Microbiology Review # 2
Division of Anti-Infective Drug Products

ANDA # 73-416 **Date Completed:** April 26,1990

Applicant: Deseret Medical
9450 South State Street
Sandy, Utah 84070

Product Names
Proprietary: E-Z Scrub 106

Non-Proprietary: chlorhexidine gluconate

USAN: chlorhexidine gluconate

Dosage Form(s) and Route(s) of Administration: Four(4)% chlorhexidine gluconate topical solution

Pharmacological Category and/or Principle Indication: antimicrobial for surgical handscrub use.

Initial Submission: January 2, 1990
Received by Reviewer: February 28, 1990
Review Initiated: March 5, 1990
Review Completed: April 28, 1990

Remarks: On October 23, 1989 the Division of Anti-Infective Drug Products received for review an Abbreviated New Drug application for a Chlorhexidine Gluconate (4%) Surgical Brush/Sponge. This document was reviewed (See Microbiological Review completed November 1, 1989) and based on the information submitted for review, it was concluded that the request for wavier of the vivo bioequivalency requirement not be granted as requested by the sponsor. The reasons for the denial are presented in the initial review. In summary, it was concluded that insufficient manufacturing information was submitted to the reviewer by the sponsor which would have allowed him to assess whether the wavier should be granted. Therefore and based on the information reviewed, the wavier was denied.

On March 5, 1990 a review of additional information submitted to the ANDA was initiated. The information conveyed in the cover letter stated that "whomever in the Anti-Infective Drug Division reviewed the request for a wavier of (the) in vivo bioequivalence did not have access to our submission in its entirety". This is indeed the case because the information conveyed in this submission provides clarification of the issues raised in the first review. According to the information supplied, the sponsor is currently packaging and distributing, as a contract packager, a 4% chlorhexidine gluconate solution for . That is, has an approved NDA (#18-423) to market a 4% chlorhexidine gluconate solution (Hibiclens) for surgical handscrub use. The bulk dosage form is sent in gallon drums to , who in turn inject the solution into scrub brushes and complete packaging of the product. In essence, is a contract packager and distributor of Hibiclens for . However, some (approximately 65%) of this product is also sold on the market by Deseret Medical as E-Z Scrub 106 and according to 21CFR/201.1 of the code, it must state on the label that the product is manufactured for by .

Consequently, it is the intent of Deseret to gain approval of an ANDA thus allowing them to market the E-Z Scrub 106 product as the without having to reference manufacture even though the bulk finished dosage form of the product will still be manufactured and supplied by . It is stated by the sponsor's representative that this action will result only in minor labeling changes but these changes are not identified. Therefore, the reviewing chemist should be cognizant of Deseret's intentions and should assess whether the sponsor of the ANDA must reveal, in it's product labeling, that the product is manufactured by . The intentions of the sponsor regarding this aspect of the labeling may be false and/or misleading.

Also included in the January 2, 1990 submission was a surgical handscrub study (#8704-09-001D) in support of the efficacy of the product when used as a surgical handscrub. However it was noticed that this same study was also submitted to the Division of Anti-Infective Drug Products (HFD-520) in a New Drug Application (#20-039) which provides for an entirely different formulation. In order to clarify the discrepency, a call was placed to the sponsor (Mr. Charles Welle) and the question was asked "Was this study conducted with the formulation described in the NDA or that in the ANDA?" The sponsor's response was that the study represented both products. That is, the two (test) products tested in the aforementioned surgical handscrub study were manufactured using the formula described in the NDA and the control product (Hibiclens) represented the product formula described in the ANDA. The sponsor sent a letter (See attached correspondence dated March 21,1990) to the NDA clarifying this confusion.

Since the product to be marketed under this ANDA by Deseret Medical, Inc. is, in fact, the same Hibiclens product that is

currently being marketed by Stuart Pharmaceuticals, the waiver should be granted. However, the reviewing chemist should verify that the same manufacturing and controls procedures will remain in place when Deseret manufactures this product under its own ANDA. Specifically, the quality control program (oversight) currently provided by Stuart Pharmaceuticals should remain in tact.

Conclusions and/or Recommendations:
The request for waiver of the in vivo bioequivalency requirements should be granted. This conclusion is based on the facts presented by the sponsor regarding the product's history and the fact that the product they intend to market is the same product currently being marketed by Stuart Pharmaceuticals. Stuart's product, Hibiclens, is approved for surgical handscrub use.

/S/ 4/26/90

Albert T. Sheldon
Supervisory Microbiologist
HFD-520

mml 4/27/90