CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73416

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE
SIGN-OFF FORM

ANDA: 73-416 SPONSOR: Becton Dickinson
DRUG & DOSAGE FORM : Chlorhexidine Gluconate 4% Scrub-Brush/Sponge

TYPE OF STUDY: Clinical Study
STUDY: ☑Acceptable

REVIEWER: Hoainhon Nguyen BRANCH: I
INITIAL: HN DATE : 3/3/99

TEAMLEADER: Yih-Chain Huang, Ph.D. BRANCH : I
INITIAL : YCH DATE : 3/3/99

DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE
INITIAL : DPC DATE : 3/3/99

MAY 16 1997

Chlorhexidine Gluconate 4% Scrub-Brush/Sponge
ANDA # 73-416
Reviewer: Hoainhon Nguyen

Becton Dickinson
Sandy, Utah
Submission Date:
August 28, 1995
May 4, 1993

Review of Clinical and Statistical Consult and Inspection Reports on a Bioequivalence Study (with Amendment)

The firm has submitted additional information on the clinical study for the test product in response to the deficiency comments by the Division of Bioequivalence on its original submission (in the letter dated July 14, 1995).

The original clinical trial results and the amendment were reviewed by the Division of Anti-Infective Drug Products and the Division of Biometrics. The clinical end point was reduction of the microbial flora per hand, one minute after product use, at the first, second and eleventh surgical hand scrub when compared to the baseline. The study #920402 entitled "Single Blind Surgical Hand Scrub Evaluation (Glove Juice) of Two Test Products and One Standard Control Product" used 60 panelists who were randomly allocated to one of the 3 arms of the study: Test product #1, Becton Dickinson AcuteCare Packaging (foil film) containing Hibiclens® (4% Chlorhexidine Gluconate, Lot #02122234E), Test product #2, containing Hibiclens® (Lot #02122245X), or Reference product as Hibiclens® packaged in foil film for (Lot #02122227H). The study was conducted by

Dr. Albert Sheldon of the Division of Anti-Infective Drug Products was the medical reviewer of the clinical data. Dr. Sheldon further consulted Dr. Alaka G. Chakravarty of the Division of Biometrics for assessment of the statistical method used and the study results based on this method. Between the statistical consult (completed October 23, 1995) and the medical consult (completed April 1, 1997) was the inspection of the conducted by the Division of Scientific Investigations (June 3 and 7, 1996) as *"a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on*

which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected."

According to the medical reviewer, he had delayed his review of the clinical data until October 17, 1996 for the following reason: *"...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 begin 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."***

As seen below, the statistical consult had found several major statistical deficiencies which concerned deviations from Good Clinial Trial practices, such as *"violations of independence of patients and clinical monitoring personnel"*, and recommended that the study results *"be independently verified by Office of Scientific Investigations before accepting the data submitted"*. According to the inspection report by the DSI for the protocol #920402 (See the DSI correspondence to the laboratory dated October 30, 1996, and the summary of the inspection attached to this review), the inspectors, Ms. V. Teres Speer and Mr. Andrew J. Bound, confirmed the above-mentioned violations and cited others such as the lack of *"SOPs for patient participation, subject enrollment, laboratory operations"*. However, as indicated by the medical officer, despite of all the findings in the laboratory inspection by the DSI, the DSI gave him *"the clearance"* to go ahead with his review of the clinical data.

The Biometrics, DAIDP and DSI consult recommendations are given at verbatim below.

I. <u>Biometric Consult Deficiency Comments and Recommendations:</u>

"<u>Statistical deficiencies:</u>

Several major statistical concerns are noted in this submission. They are as follows:

- *It appears that all evaluations on Subject #s 15, 39 and 40 and the post-baseline*

evaluation for Subject #20 are missing.

● *The test results were not read until after two days of performing the hand scrub. Due to nature of the experiment, serious questions arise concerning validity of the test results (vide Attachment A).*

● *Severe violations of independence of patients and clinical monitoring personnel is noted. Some of them are:*

i) was test subject #30. She is also the person responsible for recording, calculating and reviewing her own test results, along with others. She was also test subject #52, recording, calculating and reviewing her own results. She was evaluated on test product 2 as subject #32 on dates 11-2-92, 11-3-92 and 11-6-92 and evaluated on test product 1 as subject #52 on identical dates. This is impossible from a practical standpoint.

ii) was test subject #14. She also the person responsible for recording, calculating and reviewing her own test results.

iii) was test subject #29. She was also the Project Monitor and approving official of her own test results.

iv) was test subject#38. She was also the reviewer of some of the case report forms.

v) was test subject #43. He was also the person responsible for recording his own test results.

This raises concerns regarding validity of the test results and especially creates a strong impression that the clinical trial conducted is neither independent, nor well-controlled."

In addition, other significant findings are noted:

" It is noted that compared to the baseline, there is a consistent reduction of bacterial cell counts according to the guidelines in CFR333.470(2)(b)(iii) for each hand on BDAC foil film and can film packaging than standard packaging implying that

the modified packaging may have better immediate antimicrobial properties. However, the stipulated reduction often does not persist six hours after antimicrobial scrub application for both test products, leading to the inference that they do not have superior persistent antimicrobial efficacy compared to the control. (Table 1).

Significant difference between two drugs and the hour of application is noted with respect to reduction of bacterial cell count (p-value<0.05) by repeated measures analysis. There is no difference between two hands or any significant interaction between the drugs and the hand on which it is applied or the drug and the hour of application (Table 2). However, this reduction fails to meet the established clinically significant reduction values."

The consult report concluded that: *"Until results can be verified and audited, the statistical reviewer has reservations on accepting the bioequivalency study as adequate or well-controlled. It is strongly suggested that the results must be independently verified by Office of Scientific Investigations before accepting the data submitted (vide Attachment A)."*

II. DSI Inspection Report Recommendations:

"In summary, the data submitted to the FDA was verifiable. However, there are several critical aspects of this study that cannot be verified, which includes the impact of study personnel who may not have been well qualified to carry out such studies, and who have had a history of "fixing-up" data. The consideration that this is a topical solution, and will be used in a low concentration, could make the use of this data to support the NDA less problematic."

III. DAIDP Consult Recommendations:

"It is this reviewer's 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% chlorhexidine gluconate (CHG) and it has been this reviewer's 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."

DBE Comments :

1. The statistical consult findings that (a) the test products *"do not have superior persistent antimicrobial efficacy compared to the control"* and (b) the *"significant difference between two drugs and the hour of application... with respect to reduction of bacterial cell count" "fails to meet the established clinically significant reduction values"* do not contradict the finding by the medical review that the two test formulations are equivalent to the control product Hibiclens.

2. The acceptability of the clinical data (with respect to clinical trial practice deviations) is confirmed as the *"clearance from DSI"* received by the medical reviewer on October 17, 1996 *" that they would be willing to accept this study as having been conducted under good laboratory practices"* following the DSI inspection of

DBE Recommendation:

Based on the recommendations by the Biometrics, the DSI, and the DAIDP medical consults, the bioequivalence study, Single Blind Surgical Hand Scrub Evaluation (Glove Juice) study #920402 conducted by Becton Dickinson comparing the Test product #1, Becton Dickinson AcuteCare Packaging (foil film) containing Hibiclens® (4% Chlorhexidine Gluconate, Lot #02122234E), and the Test product #2, , containing Hibiclens® (Lot #02122245X), with Reference product as Hibiclens® packaged in foil film for (Lot #02122227H), has been found acceptable. The study demonstrates that the Test products, Becton Dickinson AcuteCare Packaging (foil film) containing 4% Chlorhexidine Gluconate) and , containing 4%

Chlorhexidine Gluconate are bioequivalent to BDAC Hibiclens® packaged in foil film for

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 5/15/97

Concur: /S/ Date: 5/16/97
for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 73-416 (original, duplicate), HFD-652 (Huang, Nguyen), HFD-650(Director), Drug File, Division File