CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73416

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

ANDA#: 73-416

Applicant: Desert Medical (Becton Dickinson AcuteCare)
Sandy, Utah

Name of Drug: E-Z Scrub 4% (Chlorhexidine Gluconate Scrub-Brush / Sponge)

Documents Reviewed: Bioequivalency Study Protocol 920402

Indication: Topical surgical scrub

Medical Input: Mr. David Bostwick, HFD-520

A. INTRODUCTION

The sponsor submitted a glove juice study in connection with a change in packaging of E-Z Scrub 4% CHG Surgical Brush/Sponge. Two test packaging systems, BDAC foil film packaging (test product 1) and can film packaging (test product 2) containing Hibiclens 4% chlorhexidine gluconate (CHG) solution were tested to the standard foil film package of CHG (control). The purpose of Protocol 920402 is to assess if the modified packagings of CHG is bioequivalent to the original formulation in terms of antimicrobial properties.

The study design featured a 5-day treatment period with applications at three and six hours apart. Sixty subjects were evaluated on day 1 before starting treatment and at days 2 and 5 of the treatment. Left and right hands were sampled at random. No post-therapy followup evaluation was reported.

The primary clinical response is antimicrobial equivalence. It will be measured in terms of immediate, persistent and residual properties. Immediate antimicrobial efficacy is a quantitative measurement of both mechanical removal and immediate inactivation of microorganisms residing on the skin surface. Persistent antimicrobial effectiveness is the product's ability to prevent microbial recolonization after application of the product by microbial inhibition or lethality. Residual efficacy is a measurement of product's cumulative antimicrobial properties repeated over time.

Baseline consistency:

It is noted that there are no significant differences between treatment groups with respect to baseline colony count (p-value =0.1357) or arms (p-value= 0.4145). No demographic information, namely age, gender or race of the subjects were

available.

B. EFFICACY EVALUATION

According to the Federal Register part 333.470(2)(b)(iii), the hand scrub drug products should must meet the following criteria when compared to the established baseline:

(1) Reduce the number of bacteria 1-$\log_{10}$ on each hand within 1 minute.
(2) The bacterial cell counts on each hand do not exceed the baseline within 6 hours on the first day.
(3) Produce a 2-$\log_{10}$ reduction of the microbial flora on each hand within 1 minute of product use by the end of the second day of enumeration.
(4) Produce a 3-$\log_{10}$ reduction of the microbial flora on each hand within 1 minute of product use by the end of the fifth day.

There is no specific regulation regarding reduction of microbial flora within 3 hours of application. According to a discussion with Dr. Albert Sheldon, the supervisory microbiologist in HFD-520, this timepoint is to note that there is a consistent reduction over time and that the colony counts do not exceed the baseline value within the critical initial six-hour time period.

Table 1 summarizes change in microbial flora from baseline for each hand.

Table 1: Change in Microbial Flora Count from Baseline

Day	Hour	Change from baseline					
		test product 1		test product 2		control	
		left	right	left	right	left	right
Day 1	0hours	-1.6500	-1.9814	-2.4340	-1.2100	-1.9933	-1.5280
	3hours	-1.5083	-1.4450	-0.9916	-1.1700	-1.0760	-1.0083
	6hours	-0.8971	-1.5650	-0.6320	-1.1700	-0.6366	-1.3866
Day 2	0hours	-3.0400	-2.7328	-3.0620	-2.1485	-2.6283	-1.8840
	3hours	-2.5850	-1.8516	-1.5216	-1.7825	-1.9060	-1.9016
	6hours	-1.2842	-2.2375	-1.2180	-1.6866	-1.4733	-1.9483
Day 5	0hours	-4.7920	-4.1471	-3.7100	-4.0257	-4.9866	-4.2800
	3hours	-2.9450	-3.4716	-3.2850	-2.6250	-3.5880	-2.8266
	6hours	-2.8300	-2.8325	-2.7940	-3.8883	-2.8766	-3.0400

It is noted that compared to the baseline, test product 1 for left hand is numerically worse than that of the control within 1 minute of application (0hrs) while test product 2 for right hand is numerically worse than that of the control within 1 minute of application (0hrs) on Day 1. It is expected that the reduction from baseline will be higher at 3 hours than at 6 hours, but the opposite is noted for right hand on test product 1 and control on Day 1 and Day 2, and test product 2 and control on Day 5. Note that 2-log reduction is not observed on the control product on the right hand for any timepoint on Day 2. 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.

A repeated measures analysis was performed to see if there is a statistically significant difference between drugs, hand or hour of application. In this type of analysis, it is assumed that every subject has several readings (left and right hand, a minute after scrub and after six hours), so there is a correlation structure between these observations. We look to see if there is any difference after taking this correlation structure into account.

Table 2: Repeated Measure Analysis of Variance for bacterial cell count

Source	df	Mean SS	F statistic	p-value (Prob > F)
drug	2	4.2220	5.24	0.0091*
hand	1	0.5089	0.63	0.4309
hour	2	16.8661	20.94	0.0001*
drug*hand	2	0.4196	0.52	0.5975
drug*hour	4	0.4952	0.61	0.6541

It is noted that there is a significant difference between ~~two~~ The drugs (p-value < 0.05). Significant reduction in bacterial cell count is noted between the hours of application (p-value < 0.05). There is no difference between two hands. No significant interaction exists between the drug and the hand on which it is applied or the drug and the hour of application. However, this reduction fails to meet the clinical acceptance criteria given above.

Statistical deficiencies:

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 test 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 serious concerns regarding validity of the test results and especially creates a strong impression that the clinical trial conducted is neither independent, nor well-controlled. 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 these data. Copies of the CRFs questioned are submitted in Attachment A.

B. SAFETY EVALUATION

No safety information was available in this submission.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

It is noted that compared to the baseline, there is a consistent reduction of bacterial cell counts according to the guidelines in CFR 333.470(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.

Several major statistical concerns are noted in this submission. Case report forms for subjects 15, 39 and 40 are missing. The test results were not read until after two days of performing the hand scrub. Severe violations of independence of patients and clinical monitoring personnel is noted. This raises serious concerns regarding validity of the test results. 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).

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