CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75042

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 75-042 APPLICANT: Taro Pharmaceuticals, USA

DRUG PRODUCT: Hydrocortisone Valerate Cream, 0.2%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA#: 75-042 **SPONSOR:** Taro
DOSAGE FORM: Hydrocortisone Valerate Cream
STRENGTHS(s): 0.2%.
TYPE OF STUDY: Pilot dose-response and pivotal bioequivalence studies.
STUDY SITE

STUDY SUMMARY: The sponsor submitted a pilot dose-response study and a pivotal bioequivalence study based on June 2, 1995, OGD guidance. The pilot study was conducted to determine population ED_{50} for the reference product, Westcort^R 0.2% cream (Westwood Squibb). The sponsor determined ED_{50} values of 34.2 and 43.2 minutes based on "naive pool" analyses of chromameter and visual assessments of skin blanching, respectively. It used a dose duration of 45 minutes for comparison of test and reference products in the pivotal study.

Comparison of test and reference products was based on the Area Under the Effect Curve (AUEC) using chromameter and visual assessments of vasoconstriction. Based on the chromameter data, 90% confidence intervals for the AUEC were within the acceptable range of 80-125%. Furthermore, the AUEC-90% confidence intervals based on visual scores data were also within the acceptable range of 80-125%. The results of the pivotal bioequivalence study demonstrate that Taro's hydrocortisone valerate is bioequivalent to the reference product, Westcort^R 0.2% cream, manufactured by Westwood and Squibb Pharmaceuticals.

***IN VITRO* RELEASE DATA:** The results of *in vitro* release testing indicated that the rates of hydrocortisone valerate release from the test and reference products were not comparable. Nonetheless, *in vitro* release data are not required to support product approval, based on the June 2, 1995 OGD guidance.

PRIMARY REVIEWER: Gur J.P. Singh, Ph.D. **BRANCH:** II

INITIAL /S/ DATE 7-2-97

TEAM LEADER: Shriniwas Nerurkar, Ph.D. **BRANCH:** II

INITIAL /S/ DATE 9/2/97

for **DIRECTOR, DIVISION OF BIOEQUIVALENCE:** Nicholas Fleischer, Ph.D.

INITIAL /S/ DATE 10/29/97

for **DIRECTOR, OFFICE OF GENERIC DRUGS**

INITIAL /S/ DATE 11/12/97

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Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 29 1997

Hydrocortisone Valerate

Topical cream, 0.2%
ANDA #75042
Reviewer: Gur J.P. Singh.
File #75042SI.D96

Taro

130 East Drive
Bramalea, Ontario.
Submission Date:
December 23, 1996.

Review of a pilot dose-response study, a pharmacodynamic bioequivalence study and in vitro *drug release data*

BACKGROUND

This application is based on the June 2, 1995, guidance for documentation of bioequivalence of topical dermatologic corticosteroids. This guidance recommended the use of dose duration method to study pharmacodynamic effects of topical corticosteroids manifested in the ability of these products to cause vasoconstriction of the skin micro-vasculature, leading to blanching of treated skin areas. In this method, vasoconstrictor responses of increasing durations of a formulation are measured as a function of time after treatment application. Because different dose durations represent different times for skin exposure to the test product, it has been assumed that increasing dose durations would results in correspondingly increasing amount of the drug available to penetrate the skin.

The guidance recommends the conduct of pilot dose-response study and a pivotal bioequivalence study. The dose-duration to be used in the bioequivalence study comparing the test and the reference product is based on the *population* ED_{50} value obtained from the pilot dose response study on the reference listed drug (RLD). The pivotal bioequivalence study also requires two calibrator dose durations D_1 and D_2, in addition to the ED_{50} value, where D_1 is approximately half of the bioequivalence study dose (ED_{50}) and D_2 is approximately 2 times of the bioequivalence study dose.

The methodology employed to determine the bioequivalence of Taro's hydrocortisone valerate 0.2% cream is consistent with the pilot-pivotal study concept recommended in the OGD guidance. Both pilot and pivotal studies are reviewed hereafter.

PILOT DOSE RESPONSE STUDY

OBJECTIVE: To determine the population ED_{50} for the vasoconstrictor response of (I) hydrocortisone valerate 0.2% cream (Westcort^R 0.2% cream) manufactured by Westwood Squibb Pharmaceuticals, and (II) fluocinonide 0.05% ointment (Lidex^R 0.02%) manufactured by Syntex. Products I and II were applied on separate arms. This

application contains only hydrocortisone valerate data; dose-response data for Lidex^R 0.05% cream is subject of another application (ANDA #75008) submitted by the sponsor.

STUDY SITE, PERSONNEL AND DATES: The vasoconstrictor pilot study was performed at the

Principal Investigator:
Bio-statistician:

Dosing Date: April 18, 1995.

Study Protocol and Informed Consent: The protocol used for this study (#9515030) and Informed Consent were approved by the d (pp 578, vol 1.2).

SUBJECT SELECTION: Potential subjects were screened for vasoconstrictor response to the RLD, Westcort^R 0.2% cream. One 10 μL application of the RLD was applied to the upper arm above the forearm and left in place for 2 to 4 hours. Skin blanching response was determined visually 6 to 8 hours after drug removal.

Fourteen (14) healthy, Caucasian, female volunteers screened above were enrolled for this study. The age of these subjects was in the range of 20 - 37 years (pp 557, vol 1.2). The weight range for these volunteers was 104-163 lbs. Subjects were selected based on acceptable medical history, negative pregnancy test, and they signed informed consent. The exclusion criteria used for this study were the following:

* History of allergy to hydrocortisone valerate, corticosteroids, creams, lotions, creams or cosmetics.
* Skin coloration which would interfere with assessment of skin blanching.
* Use of systemic corticosteroids within 30 days, pharmacological agents which may affect vasoconstrictor response within 28 days, prescription medicine within 7 days, over-the-counter medication with 72 hours, and alcohol and caffeine within 48 hours prior to dosing.
* Use of topical steroids on flexor surface of forearm within 30 days of dosing.
* Use of any creams, emollients or similar products on forearms within 24 hours of dosing.
* Use of tobacco products within 30 days.
* Drug or alcohol addiction requiring treatment within 12 months.
* Positive pregnancy test for female subjects.

STUDY DESIGN: The pilot study was conducted as a single period study. Hydrocortisone valerate cream used was Westcort^R 0.2% cream, lot #81G114, expiry date: 9/97 manufactured by Westwood Squibb Pharmaceuticals.

The cream was applied on the right arm. An untreated site was designated on each forearm. Eight (8) circular application sites (1.6 cm diameter) were designated on the flexor surface of the forearm between the wrist and the elbow. After baseline chromameter and visual readings, 10 μL portions of the cream were applied to assigned sites for 15, and 30 minutes, and 1, 1.5 2, 3 and 4 hours prior to removal. All applications were removed at the same time. Thus the procedure used for drug application and removal was the "Staggered application and synchronized removal" method given in the June 2, 1995 guidance. Skin blanching was evaluated at 2, 4, 6, 8, 10, 12, 20 and 24, 28 and 48 hours after drug removal.

ASSESSMENT OF VASOCONSTRICTION: Skin blanching was determined based on chromameter and visual assessment of designated skin sites. Visual Scoring used the following rating scale:

SCORE	SKIN SURFACE CONDITION
0	No Pallor; no change from surrounding.
1	Mild Pallor; slight or indistinct outline of application site.
2	Moderate pallor; discernable outline of application site.
3	Intense pallor; clean, distinct outline of application site.

HOUSING AND MEALS: All subjects checked in at least 12 hours before dosing. Meals were served at traditional times. Caffeine and alcohol were restricted. Water was provided *ad lib* throughout the study. The subjects were released on day 2, approximately 30 hours after the first drug application. Subjects were instructed to avoid contact with water on their arms, and extreme temperature, and avoid strenuous exercise during the study. Tight clothing on the forearm was not permitted.

DATA ANALYSIS: The chromameter data were normalized for baseline values and changes in the color of the untreated skin as recommended in the guidance. AUEC's were calculated for 2-24 hours after drug removal using the trapezoidal rule. Similarly AUEC values were calculated based on visual scores. AUEC values used by the sponsor were found to be accurate with the exception that the firm multiplied all chromameter AUEC values by -1. The pooled AUEC data as a function of the dose duration were fitted to the simple E_{max} model using PCNONLIN.

RESULTS: The sponsor reported chromameter data for 13 subjects, and visual scores data for 14 subjects. Chromameter-AUEC data for subject #1 was excluded from the analysis because it did not show skin blanching. The firm has used the software PCNONLIN to determine ED_{50} values for the visual and chromameter data. PCNONLIN is not a population modeling program. The technique used by the firm is known as the "naive pool" estimation of population ED_{50}, and this method does not keep track of the

individual subject data. Therefore the population estimates obtained using this method may not represent the entire population.

The accurate way of determining population parameters is the "nonlinear mixed effect modeling" approach using population modeling computer programs. PPHARM is one such program. The reviewer analyzed the chromameter- and visual-$AUEC_{2-24}$ data using this software. Pharmacodynamic parameter values based on sponsor's and reviewer's calculations are given below:

Data set	ED_{50}			E_{max}		
	Firm (A)	Rev. (B)	A/B	Firm ©	Rev.(D)	C/D
Chroma-meter	34.2 (19.8)	162.9 (141)	0.21	-38.7 (6)	-57.6 (73)	0.67
Visual	43.2 (13.2)	80.7 (116)	0.53	51.8 (5)	56.6 (23)	0.92

Parametric data are given as mean (%CV). Coefficient of variation on reviewer's estimates are much larger than those reported by the firm because reviewers analysis is based on mixed effect modeling which accounts for inter-subject as well as intra-subject variation in the pharmacodynamic response. Firms analysis is based on the "naive-pool" method where all data in the pool are considered to originate from the same source (subject).

The above analyses of both chromameter- and visual-AUEC data were based on the following simple E_{max} model:

$$AUEC = \frac{AUEC_{max} * Dose}{Dose + ED_{50}}$$

Where AUEC is the fitted value of $AUEC_{2-24}$. Dose refers to the "dose duration" and ED_{50} is the dose duration required to produce 50% of the $AUEC_{max}$.

However, recently some investigators have questioned the use of the above model for AUEC values based on visual scores data [P.H. Demana, E.W. Smith, R.B. Walker, J.M. Haigh and I. Kanfer. *Pharmaceutical Research*. **14**(3)303-307 (1997)]. Based on their "naive pool" analysis of vasoconstrictor data for two betamethasone valerate formulations,

these authors considered the following sigmoidal to be more appropriate for the analysis of visual scores data:

$$AUEC = \frac{AUEC_{max} * Dose^{H}}{Dose^{H} + ED_{50}{}^{H}}$$

where "H" is the sigmoidicity constant (Hill Coefficient) that influences slope in the region of ED_{50}.

In view of the above publication the reviewer also analyzed visual-AUEC data using above sigmoidal E_{max} model; chromameter data could not be fitted with this model due the presence of negative data which prevented convergence, probably by interfering with some of the steps algorithms uses in fitting these data. Visual scores data permitted the use of the sigmoidal model. Results of analyses of these data based on both mixed effect modeling (MEM) and the "naive pool (NP)" method are given below:

Method	ED_{50}	E_{max}	Hill Coefficient
MEM	64.1 (42)	100.3 (86)	3.5 (114)
NP	48.9 (4)	37.9 (44)	1.1 (5)

Parametric data are given as mean (%CV).

Based on "naive pool" analyses ED_{50} values using simple and sigmoidal E_{max} model were 43.2 and 48.9 respectively, and these values were not significantly different. Furthermore, the fitted "H" value of 1.1 based on the sigmoidal model is approximately same as the fixed value of unity used in the simple E_{max} model.

Based on mixed effect modeling, ED_{50} (64.1) value calculated using the sigmoidal model was 79% of the ED_{50} (80.7) based on the simple E_{max} model. Of these two ED_{50} values the reviewer has limited confidence in the estimate based on the sigmoidal model, because some of the Bayesian estimates of individual subject's "H" values were not realistic. For subjects 1, 7, 10 and 11, "H" values were 9.7, 5.66, 11.9 and 9.1 respectively. Such high values of "H" are indicative of very steep dose-response which may be inconsistent with the action of low potency corticosteroids. In addition, such high values of gamma are rare. A survey of literature indicates that the average value of the

sigmoidicity constant may be approximately 2 [S. Dutta, Y. Matsumoto and W.F. Ebling. *J Pharm Sci.* **85**: 232-239 (1996)].

The *population* ED_{50} values for both chromameter and visual assessment of skin blanching were larger in magnitude using the mixed effect modeling approach. The sponsor selected an ED_{50} value of 45 minutes for the pivotal study, and it was smaller than the *population* ED_{50} values based on either method of assessment of skin blanching. Implications of using pivotal study dose < ED_{50} are discussed in the Comments section of this review.

PIVOTAL BIOEQUIVALENCE STUDY

OBJECTIVE: To study the relative vasoconstrictor effects of the test and reference topical hydrocortisone valerate creams. The sponsor has studied the effect of its hydrocortisone valerate 0.2% cream and two reference product preparations, i.e. Westcort^R 0.2% cream approved in USA (Reference 1) and Westcort^R 0.2% cream approved in Canada (Reference 2). Electronic files submitted with this application contained data for comparison of the test product with the US RLD. This review will focus on comparisons of vasoconstrictor effects of the test product and the US RLD (Westcort^R 0.2% cream).

STUDY SITE, PERSONNEL AND DATES: The vasoconstrictor study was performed at the

Principal Investigator:
Bio-statistician:

Dosing Dates:

Group 1 (Subject #1-20):	September 20, 1996,
Group 2 (Subject #21-36):	October 26, 1996, and
Group 3 (Subject #37-43):	November 10, 1996.

Study Protocol and Informed Consent: The protocol used for this study (#9615064, September 3, 1996) and Informed Consent were approved by the

SUBJECT SELECTION: Potential subjects were screened for vasoconstrictor response to the reference listed drug Westcort^R 0.2% cream as mentioned for the pilot study. All subjects were selected based on a demonstrated skin blanching response. Forty three(43) healthy, non-tobacco using female volunteers screened above were enrolled for this study. All subjects were Caucasians (pp 128, vol. 1.1). The age of these subjects was in the range of 18 - 39 years. The weight range for these volunteers was 110-159 lbs. These subjects were enrolled based on acceptable medical history, negative pregnancy

test and a signed informed consent. Criteria used for subject exclusion were the same as those mentioned above for the pilot study.

STUDY DESIGN: The pivotal study was conducted as a one-period/group study involving randomized applications of the test formulations to both arms along with the replicate applications of the calibrator doses (D_1 and D_2) of the reference product. There was an untreated control site on each arm. The treatment randomization provided complementary applications on left and right arm as given below:

ANTECUBITAL FOSSA

Right Arm		Left Arm	
Site	Treatment	Site	Treatment
9	D2	18	D1
8	REF-USA	17	Test
7	REF-CAN	16	REF-CAN
6	Test	15	REF-USA
5	Untreated	14	Untreated
4	REF-USA	13	Test
3	D1	12	D2
2	REF-CAN	11	REF-CAN
1	Test	10	REF-USA

WRIST

Where:

Test: Hydrocortisone valerate 0.2% cream, Taro Pharmaceuticals, Inc., (Lot #S133-5592, Lot size: expiry date: not known) applied for dose duration of 45 minutes.

REF-USA: Westcort^R topical cream 0.2% (Lot #81H48, expiry date: 9/98) manufactured by Westwood Squibb Pharmaceuticals (USA), applied for dose duration of 45 minutes.

REF-CAN: Westcort^R topical cream 0.2% (Lot #5270, expiry date: 7/99) manufactured by Westwood Squibb Pharmaceuticals (Canada) applied for dose duration of 45 minutes.

D_1: Westcort^R topical cream 0.2% (Lot #81H48, expiry date: 9/98) manufactured by Westwood Squibb Pharmaceuticals (USA), applied for dose duration of 20 minutes.

D_2: Westcort^R topical cream 0.2% (Lot #81H48, expiry date: 9/98) manufactured by Westwood Squibb Pharmaceuticals (USA), applied for dose duration of 90 minutes.

TREATMENT ADMINISTRATION: Subjects were treated in three groups. The forearm of each subject was washed with mild soap and gently dried within two hours prior to dosing. Nine (9) circular application sites (approximate diameter 1.6 cm) were designated on the flexor surface of each arm. Using a 250 μL Hamilton syringe, 10 μL application of active drug were applied to eight (8) sites on each arm as shown in the schematics above. The actual randomization for various treatments is given on pages 129-131 (vol 1.1) The products were evenly spread within each site using the conical tip of a 1.5 mL polypropylene microcentrifuge tube. All sites were kept unoccluded throughout the study.

The application of active treatments was staggered. Consistent with the pilot study, all treatments were removed at the same time following the "staggered application and synchronized removal" scheme recommended in the June 2, 1995 OGD guidance.

At the end of the treatment period, all sites (including the untreated spots) were gently wiped several times with a cotton ball. Skin blanching assessments were performed at 0, 2, 4, 6, 8, 10, 12, 21 and 24 hours after drug removal.

HOUSING AND MEALS: Same as that given for the pilot study.

ASSESSMENT OF VASOCONSTRICTION: Same as that given for the pilot study.

METHOD VALIDATION: Prior to the pivotal study, precision of chromameter operators (%CV) was evaluated from replicate evaluations of five readings/site taken at least three minutes apart. For this method validation three subjects were studied, and four untreated sites were on each arm of these subjects were evaluated. Results of method validation are summarized on page 272-353 (vol 1.1). Intra-site %CV was in the range of 5.4%-7.5%, and inter-site %CV was in the range of 9.3%-14.9%.

DATA ANALYSIS: Chromameter data was transformed and AUEC's were calculated as mentioned in the pilot study. The $AUEC_{0\text{-}24}$ values for visual assessment of skin blanching were calculated directly from the raw blanching scores.

The ratio of mean $AUEC_{0-24}$ value (average of left and right arm values) for D_2/D_1 was calculated for each subject. Subjects whose D_2/D_1 ratios were ≥ 1.25 were considered to be "evaluable subjects" (see below) and included in the statistical analyses.

The $AUEC_{0-24}$ data for evaluable subjects, based on visual and chromameter readings, were used to calculate the 90% confidence intervals using Locke's method, as recommended in the OGD guidance.

RESULTS

Clinical Conduct of the Study: All forty three (43) subjects dosed in this study completed the two days of evaluation. No adverse events were reported.

Accuracy of Pharmacodynamic Metric Data: Vasoconstrictor responses of test and reference products were compared based on the chromameter assessment and visual scoring. The reviewer has verified the correction of the chromameter raw data for the baseline and changes that occurred in the untreated skin. The corrected data were used for calculation of the pharmacodynamic metric, $AUEC_{0-24}$. For the presentation of chromameter AUEC data the sponsor reversed the sign from negative to positive. The reversal of sign, in this manner, poses problems in selection of "evaluable subjects" in the manner described in the June 2, 1995 guidance. Therefore, all chromameter AUEC were multiplied by "-1". The resulting $AUEC_{0-24}$ data showed values identical to those calculated by the reviewer (see table 1, attachment). The visual- score AUEC's reported by the sponsor were also found to be accurate. Nonetheless, bioequivalence data presented in this review are based on reviewer's calculations.

It is noted that, the sponsor employed an ED_{50} determined based on $AUEC_{2-24}$, and in the pivotal study the metric used for comparisons of test and reference product is $AUEC_{0-24}$. In reviewer's experience estimates of ED_{50} based on $AUEC_{0-24}$ may not be significantly different from those obtained using $AUEC_{2-24}$ data. Furthermore, since determination of "evaluable" subjects was based on $AUEC_{0-24}$ data, the use of $AUEC_{2-24}$ in the pilot study should not affect bioequivalence evaluations in the pivotal study.

Evaluable Subjects: Based on the OGD guidance "evaluable subjects" are those which exhibit AUEC-D_2/AUEC-D_1 ratio of ≥ 1.25, and this guidance recommends the inclusion of only evaluable subjects' data in statistical analyses for documentation of bioequivalence. There were 19 and 32 such subjects based on chromameter and visual assessment, respectively (Tables 2 and 3, attachment). There were some subjects which qualified for bioequivalence evaluation based on both methods of assessment (visual and chromameter) whereas the others were qualified by one or the other method.

Based on the chromameter data the sponsor qualified 22 subjects for bioequivalence comparisons, instead of 19 determined by the reviewer. The discrepancy between these numbers is because of subject #34, 41 and 42 which, based on the OGD guidance, did

not qualify as evaluable subjects, because one of the treatments (D_1) did not show skin blanching. The guidance accepts a ratio of ≥1.25 if both D_1 and D_2 treatments demonstrate measurable vasoconstriction. The reviewer has examined if the above three subjects may be considered as "Evaluable subjects" and the impact of inclusion of these subjects is discussed below (see Evaluation of Bioequivalence). The number of "evaluable subjects" for the visual assessment of skin blanching were the same based on reviewer's and sponsor's calculations.

With regard to the steepness of the dose response for this study, based on all 40 subjects' chromameter data, mean AUEC-D_2 was 74% greater than the mean AUEC-D_1. The difference between the pharmacodynamic responses of D_1 and D_2 based on visual scores was 118%.

Evaluation of Bioequivalence: .

$AUEC_{0-24}$ data for chromameter and visual assessment of skin blanching are given in tables 4 and 5 (attachment). The presence of both positive and negative AUEC values in the chromameter data set precludes the use of log-transformation and the standard two-sided t-test procedure for calculation of the 90% confidence intervals. Instead, the OGD guidance recommends the use of Locke's method *(J. Pharmac. Biopharm.*, 12:649-65, 1984).

The bioequivalence data based on reviewer's calculation of confidence intervals using $AUEC_{0-24}$ data for evaluable subjects and Locke's method are given below:

Assessment Method	Test (A)	Reference (B)	A/B	90% CI
Chromameter (n = 19)	-14.67 (61)	-15.51 (69)	0.95	79-115[a]
(n= 22)	-14.33 (58)	-14.90 (68)	0.96	82-115
Visual (n = 32)	20.77 (63)	22.31 (49)	0.93	83-103

Data are given as Mean(%CV)
[a]*Outside the convectional bioequivalence interval of 80-125%.*

Based on AUEC data for the 19 "evaluable subjects" determined by the reviewer, 90% confidence intervals are outside the conventional range of 80-125%. On the other hand if the AUEC data for subjects #34, 41 and 42 are included, the number of "evaluable subjects rises to 22. Based on the AUEC data for these 22 subjects, 90% confidence intervals fall within the acceptable range of 80-125%. Therefore, it is of interest to determine if the inclusion of data for the above for subjects is scientifically justified.

The objective of using a dose duration equal to the RLD ED_{50} along with D_1 and D_2 is to make sure that (a) the subjects can discriminate between pharmacodynamic effects of a known low (D_1) and a known high (D_2) dose durations, and (b) the comparison of the test and reference products is made at a dose duration (ED_{50}), the vasoconstrictor effect of which lies between those of D_1 and D_2. AUEC values of above three subjects for these dose durations are given in table 6 (attachment). For these subjects the effect of D_1 was not strong enough to produce negative AUEC values. However, all these subjects demonstrated ability to discriminate between D_1 and D_2 and the effects of the RLD ED_{50} were sandwiched between D_1 and D_2. They also exhibited a gradual increase in skin blanching as the dose duration was increased from D_1 to D_2. The inability of these three subjects to demonstrate skin blanching at D_1 may partly be due to the selection of D_1 value based on "naive pool" analysis of the pilot study data. If the selection was based on proper analysis (mixed effect modeling), the value of D_1 (81 minutes, one half of the population ED_{50} of 162.9 minutes) would have been even greater than the RLD ED_{50} (45 minutes) used in the pivotal study; these three subjects would have exhibited measurable skin blanching at that dose duration. Therefore, the AUEC data for these subjects may be included for documentation of bioequivalence. Based on the 22 subjects' chromameter AUEC data the test product is bioequivalent to the reference product.

Based on the visual assessment the 90% confidence intervals comparing the test and the reference product were within the acceptable range of 80-125%.

IN VITRO RELEASE PROFILES

The June 2, 1995, OGD guidance does not require *in vitro* release data to support product approval. However the guidance states that " Following future recommendations of the Scale-Up and Post Approval Changes for Semisolid (SUPAC-SS), OGD may recommend the submission of *in vitro* release data to support waiver of *in vivo* bioequivalence of the lower strength(s) of topical corticosteroid products...."

The sponsor has submitted *in vitro* release data for its hydrocortisone valerate 0.2% cream and the reference product (pp 1010-1036, vol 1.2). A review of the summary data (pp 1022 vol 1.2) indicates that, on average, the *in vitro* release rates of the test product was 27% of that of the reference product. The reviewer also analyzed these data using the method recommended in Agency's SUPAC-SS guidance (see table 7, attachment). Based on this analysis the 90% confidence intervals comparing the test and reference products were in the range of 25-30%.

Note that the reviewer has performed the SUPAC-SS analysis for completeness of a summary of all scientific data given in this application. However, the results of this analysis should not affect the outcome of the study as these data are not required for product approval; such analyses are required for scale up and post approval changes in formulations.

PRODUCT COMPOSITION (NOT TO BE RELEASED UNDER FOI):

Compositions of Taro's hydrocortisone valerate 0.2% cream and Westcort[R] 0.2% Cream (Reference product, NDA 17950-001). Ingredient strengths are given as percent concentrations in finished products.

Ingredient	TEST	REF
Hydrocortisone Valerate	0.2%	0.2%
Petrolatum, White		
Stearyl Alcohol		
Streareth-		
Steareth-		
Propylene Glycol		
Amphoteric-		
Carbomer		
Sodium Phosphate, Dried		
Sodium Phosphate, Dibasic		
Sodium Lauryl Sulfate		
Sorbic Acid		
Water		

With respect to the inactive ingredients, the composition of the test product is qualitatively and quantitatively different from that of the reference product. However, based on Agency's *Inactive Ingredient Guide (January 1996),* potencies of all inactive ingredients used in the test product are within the range used for topical dermatologic products.

COMMENTS:

1. The sponsor performed a pilot dose-response study based on the OGD guidance. Based on the "Naive pool" analysis of the dose response data (chromameter), it calculated an ED_{50} of approximately 45 minutes. The reviewer also determined approximately same value of ED_{50} using the "naive pool" method. However as mentioned above the naive pool analysis may not provide an ED_{50} representative of the population as the predicted and observed data did not show any correlation. Therefore, the reviewer calculated population ED_{50} using the "nonlinear mixed effect modeling" approach. The population ED_{50} values for the chromameter and visual data were found to be 162.9 and 80.7 minutes, respectively.

   Bioequivalence data used for product evaluation in the pivotal study are based on an ED_{50} of 45 minutes. Since this value is approximately one third of the population ED_{50}, it is important to consider how this may affect bioequivalence evaluation. The premise of the pilot-pivotal study concept endorsed by GDAC was to make sure that the test and reference products are compared on the sensitive region of the dose-response curve, *i.e.*, in the region of 20% to 80% of the E_{max}, based on the E_{max} model. This range of pharmacodynamic response extrapolates (on the dose axis) to dose range from one fourth of ED_{50} to four times ED_{50}. Comparisons of products at doses > ED_{50} is not recommended because pharmacodynamic responses become insensitive to doses that differ over an order of magnitude.

   The research performed by the Agency has indicated that the intra-subject variability in pharmacodynamic response of dermatologic corticosteroids is greatest at doses below the ED_{50} and it decreases as the administered dose increases with respect to the ED_{50} (Singh et al,,1995, *Clinical Pharmacology and Therapeutics.* **57**:181). The same study also indicated that the width of the 90% confidence intervals was greatest at doses below the ED_{50} and it became smaller as the dose was increased. The confidence interval width became insensitive to doses >ED_{80}. These results suggest that if a sponsor used a dose duration < ED_{50}, the products are compared at much more steeper portion of the dose response curve. As a results, it may be harder for the sponsor to meet the bioequivalence intervals when the pivotal study dose < ED_{50}, than when it is equal to the ED_{50}, as the pharmacodynamic assay may probably be more sensitive to differences in drug delivery from the test and reference products at doses of smaller magnitude. Therefore, a dose less than the population ED_{50} used for bioequivalence comparisons is acceptable.

2. All forty three (43) subjects dosed for this study competed the evaluations. For bioequivalence evaluation there were 22 and 32 evaluable subjects based on the chromameter and visual assessment of vasoconstriction.

3. Based on the both chromameter and visual evaluation of skin blanching, 90% confidence intervals comparing these products were within the acceptable limit of 80-125%.

4. Based on both chromameter and visual assessments of skin blanching, the test product is bioequivalent to the reference product.

5. The reviewer calculated the correlation between the AUEC values based on chromameter and visual data. The results of these analyses shown in figure 1 (attachment) indicate that these data are poorly correlated. These data are presented for completeness of information, and these observations should not affect the outcome of the biostudy reviewed henceforth.

RECOMMENDATIONS

1. The *in vivo* bioequivalence study conducted by Taro Pharmaceuticals comparing its hydrocortisone valerate 0.2% cream (lot #S133-5592) to the reference product, Westcort[R] 0.2% cream (lot #81H48) has been found to be acceptable to the Division of Bioequivalence. The results of this vasoconstrictor study demonstrate that Taro's hydrocortisone valerate 0.2% cream is bioequivalent to the reference product, Westcort[R] 0.2% cream manufactured by Westwood Squibb Pharmaceutical.

2. The *in vitro* release data submitted by Taro Pharmaceuticals's on its hydrocortisone valerate 0.2% cream are acknowledged. The *in vitro* release testing should be incorporated in firms's manufacturing and quality control programs.

Gur J.P. Singh, Ph.D. /S/
Review branch II, Division of Bioequivalence.

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR: /S/ 9/2/1997

CONCUR: /S/ DATE 10/29/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence.

GJP SINGH 7-2-97 75042SI.D96
cc. ANDA # 75042, original, HFD-650 (Division Director), HFD-630 (OGD), HFC-130 (Jallen), HFD-600 (Hare), HFD-655 (Nerurkar, Singh), Drug file, Division file.

ATTACHMENTS

Page(s) 11

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

raw data

Table 2: AUEC-D2/AUEC-D1 ratios based on chromameter data and reviewer's calculations (ANDA #75042)

SUB	AUEC (0-24) D1	D2	D2/D1	SUB	AUEC (0-24) D1	D2	D2/D1
1				22			
2				23			
3				24			
4				25			
5				26			
6				27			
7				28			
8				29			
9				30			
10				31			
11				32			
12				33			
13				34			
14				35			
15				36			
16				37			
17				38			
18				39			
19				40			
20				41			
21				42			
				43			

The individual subject AUEC(0-24) data represent average value of the left and right arm replicates.

Highlighted cells indicate evaluable subjects with D2/D1 ratio of 1.25 or greater.

Mean	-11.29	-19.71
%CV	130	71
n	43	43
Mean	-11.92	-26.00
%CV	74	51.82
n	19	19

Table 3: AUEC-D2/AUEC-D1 ratios based on visual scores and reviewer's calculations (ANDA #75042)

SUB	AUEC (0-24) D1	D2	D2/D1	SUB	AUEC (0-24) D1	D2	D2/D1
1				21			
2				22			
3				23			
4				24			
5				25			
6				26			
7				27			
8				28			
9				29			
10				30			
11				31			
12				32			
13				33			
14				34			
15				35			
16				36			
17				37			
18				38			
19				39			
20				40			
				41			
				42			
				43			

The individual subject AUEC(0-24) data represent average value of the left and right arm replicates.

Highlighted cells indicate evaluable subjects with D2/D1 ratio of 1.25 or greater.

Mean	13.58	29.66
%CV	85.33	48.11
n	43	43
Mean	14.11	32.62
%CV	69.88	37.92
n	32	32

Table 4: AUEC (0-24) for test and reference products based on chromameter data and reviewer's calculations (ANDA #75042)

AUEC (0-24)

All Subjects				Evaluable Subjects			
SUB	TEST	REF	TEST/REF	SUB	TEST	REF	TEST/REF
1				1			
2				2			
3				3			
4				7			
5				13			
6				14			
7				15			
8				16			
9				18			
10				20			
11				22			
12				23			
13				24			
14				26			
15				29			
16				33			
17				39			
18				40			
19				43			
20							
21							
22							
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32							
33							
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37							
38							
39							
40							
41							
42							
43							
Mean	-13.85	-14.55	0.97	Mean	-14.67	-15.51	1.14
%CV	82	74	120	%CV	61	69	96
n	43	43	43	n	19	19	19
				Mean	-14.33	-14.90	1.14
				%CV	58	68	89
				n	22	22	22

The individual subject AUEC(0-24) data represent average values of left and right arm replicates.

Shaded cells at the left indicate test and reference product AUEC's for "evaluable subjects (right hand data set)"used for bioequivalence determination, as these subjects (n= 19) showed D2/D1 ratios of 1.25 or greater.

Mean and %CV values for n = 22 is includes subjects 34, 41 and 42 (see the review for details)

Table 5: AUEC (0-24) for test and reference products based on visual scores and reviewer's calculations (ANDA #75042)

AUEC (0-24)						
All Subjects				Evaluable Subjects		
SUB	TEST	REF	TEST/REF	SUB	TEST	REF	TEST/REF
1				2			
2				3			
3				4			
4				5			
5				8			
6				10			
7				12			
8				13			
9				15			
10				16			
11				17			
12				20			
13				22			
14				23			
15				24			
16				25			
17				26			
18				27			
19				29			
20				31			
21				32			
22				33			
23				34			
24				35			
25				36			
26				37			
27				38			
28				39			
29				40			
30				41			
31				42			
32				43			
33							
34							
35							
36							
37							
38							
39							
40							
41							
42							
43							
Mean	19.00	20.12	0.99	Mean	20.77	22.31	0.95
%CV	69	55	58	%CV	63	49	52
n	43	43	43	n	32	32	32

The individual subject AUEC(0-24) data represent average values of left and right arm replicates.

Shaded cells at the left indicate test and reference product AUEC's for "evaluable subjects (right hand data set)"used for bioequivalence determination, as these subjects (n= 32) showed D2/D1 ratios of 1.25 or greater.

Table 6

Chromameter AUEC(0-24) data for subjects 34, 41 and 42

Dose Duration	Mutiple of ED50	SUBJECT 34	41	42
D1	0.5	5.07	8.29	1.88
ED50	1	-10.82	-13.55	-8.75
D2	2	-21.55	-25.25	-20.97

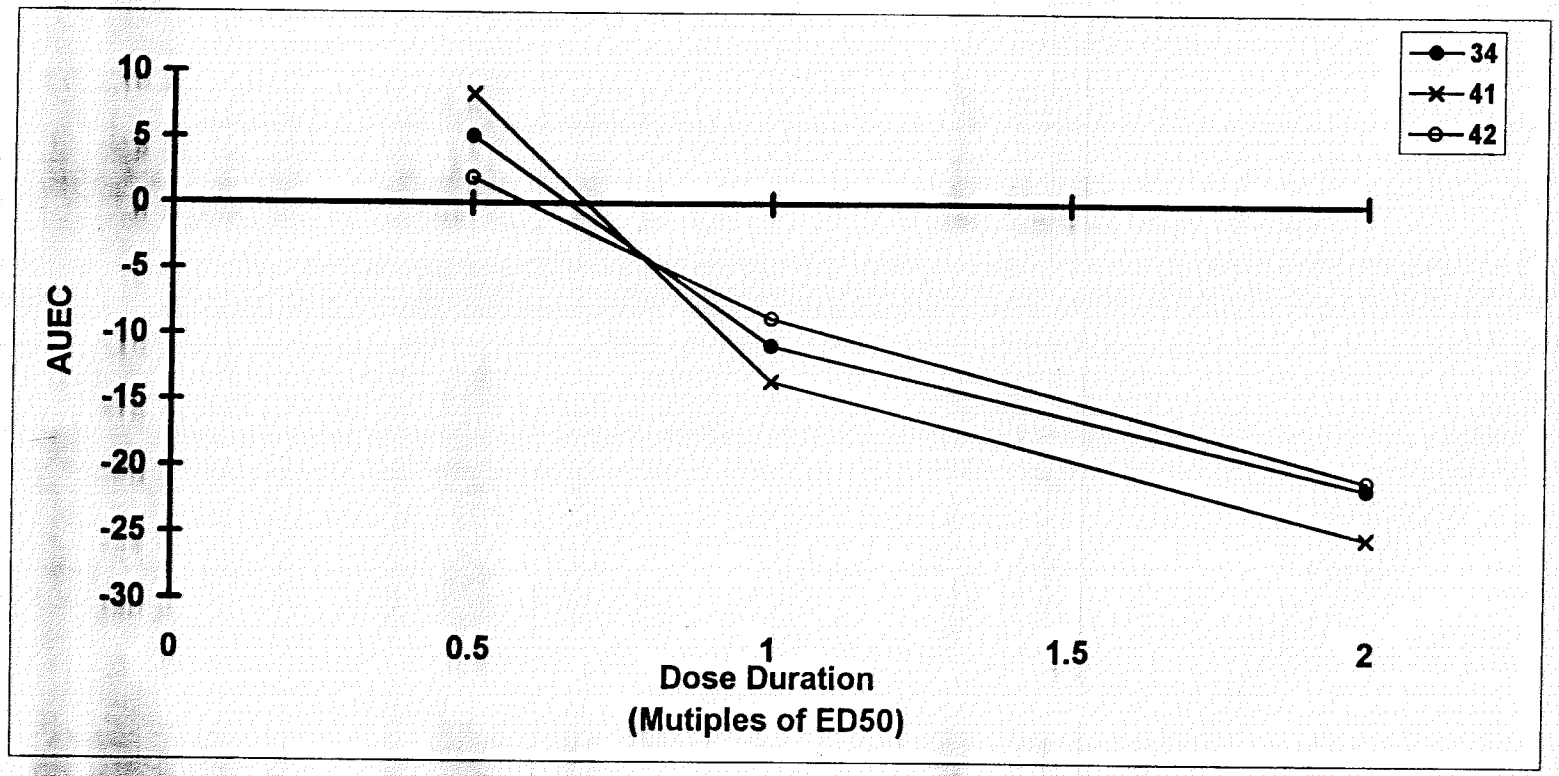
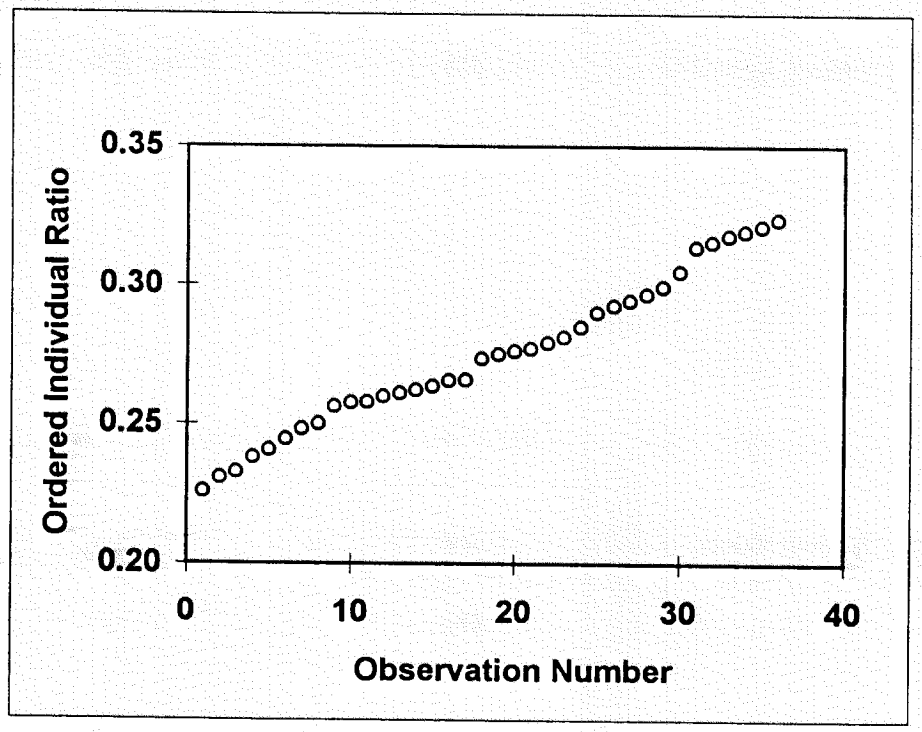


Table 7

Analysis of the *in vitro* release data (ANDA #75042) based on methodology recommended in the SUPAC-SS guidance

		TEST					
		1.43	1.37	1.34	1.53	1.67	1.64
REF	5.23	0.27	0.26	0.26	0.29	0.32	0.31
	5.76	0.25	0.24	0.23	0.27	0.29	0.28
	5.48	0.26	0.25	0.24	0.28	0.30	0.30
	5.16	0.28	0.27	0.26	0.30	0.32	0.32
	5.20	0.28	0.26	0.26	0.29	0.32	0.32
	5.94	0.24	0.23	0.23	0.26	0.28	0.28



Obs.	Ratio
1	0.23
2	0.23
3	0.23
4	0.24
5	0.24
6	0.24
7	0.25
8	0.25
9	0.26
10	0.26
11	0.26
12	0.26
13	0.26
14	0.26
15	0.26
16	0.27
17	0.27
18	0.27
19	0.28
20	0.28
21	0.28
22	0.28
23	0.28
24	0.28
25	0.29
26	0.29
27	0.29
28	0.30
29	0.30
30	0.30
31	0.31
32	0.32
33	0.32
34	0.32
35	0.32
36	0.32

90% Confidence intervals: 25-30%

Figure 1
Correlation between AUEC (0-24) values
based on chromameter and visual assessment of skin blanching