CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-579

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-579
DRUG & DOSAGE FORM : Betamethasone Dipropionate Cream
SPONSOR : Clay Park
STRENGTH (s) : 0.05%
TYPE OF STUDY: SD SDF MULT OTHER Skin Blanching
STUDY SITE: CLINICAL : ANALYTICAL :

STUDY SUMMARY : The study was reviewed on consult to HFD-520

Parameter	test	ref	ratio	90% CI (log).
Cmax(ng/ml)				
AUC(0-T) ngxhr/ml				
AUC(0-Inf)ngxhr/ml				
Tmax hr				
Half-life hr				

N/A

DISSOLUTION :
Conditions

Time(min)	Test Mean(range)	Ref. Mean(range)
15		
30		
45		

N/A

Q =

PRIMARY REVIEWER : Andre J. Jackson BRANCH : I

INITIAL : /S/ DATE : 2/21/97

BRANCH CHIEF : T.C Huang BRANCH : I

INITIAL : /S/ DATE : 2/21/97

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : /S/ DATE : 2-28-97

~~DIRECTOR~~
OFFICE OF GENERIC DRUGS /S/, CDER

INITIAL : DATE :

ANDA 74-579

FEB 12 1996

Clay-Park Labs, Inc.
Attention: Jay Jadeja
1700 Bathgate Avenue
Bronx NY 10457

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Betamethasone Dipropionate Cream USP, 0.05% (base).

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

/S/

REQUEST FOR CONSULTATION

TO (Division/Office)		FROM:	
HFD-500(att:Z. Miguele)for review by HFD-~~520~~ 540		HFD-650/ Division of Bioequivalence	
DATE: 01/03/95	IND NO.	NDA NO.: ANDA 74-579	TYPE OF DOCUMENT: application
DATE OF DOCUMENT: 12/1/94			
NAME OF DRUG: Betamethasone Dip Crm	PRIORITY CONSIDERATION: Per Policy	CLASSIFICATION OF DRUG: Topical	DESIRED COMPLETION DATE: 04/95

NAME OF FIRM: Clay Park Labs INC.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

The firm has conducted a study that they claim demonstrates the bioequivalence of their product. Please review and provide comments. Thank You

y:\bostwick\74-529.fin

IF POSSIBLE PLEASE INCLUDE A COPY OF THE REVIEW ON COMPUTER DISK

1/5/96

PLEASE RETURN ATTENTION JASON A. GROSS (HFD-650) THROUGH THE DOCUMENT ROOM #150, METRO PARK NORTH II CONTACT CONCERNING QUESTIONS: JASON GROSS 594-2290

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
JASON A. GROSS, /S/	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

/S/

REQUEST FOR CONSULTATION

TO (Division/Office)			FROM:
HFD-500(att:Z. Miguele)for review by HFD-~~520~~ 540			HFD-650/ Division of Bioequivalence
DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT / DATE OF DOCUMENT
01/03/95		ANDA 74-579	application / 12/1/94
NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
etamethasone Dip Crm	Per Policy	Topical	04/95

NAME OF FIRM
Clay Park Labs INC.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
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- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

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- ☐ BIOAVAILABILITY STUDIES
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- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

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12/5/96

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SIGNATURE OF REQUES	METHOD OF DELIVERY *(Check one)*
ON A. GROSS, /S/	☐ MAIL ☐ HAND
TURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

FEB 6 1996

Betamethasone Dipropionate
0.05% Cream
ANDA # 74-579
Reviewer: Andre J. Jackson
WP #74579S.D94

Clay Park Laboratories
Bronx, New York
Submission Dated:
December 1, 1994

REVIEW OF TOPICAL CORTICOSTEROID BIOEQUIVALENCE STUDY

Background

In July of 1992, the Division of Bioequivalence issued an interim guidance "Topical Corticosteroids: In vivo Bioequivalence and in Vitro Release Methods". This document outlined the agency's proposed bioequivalence study design. The design involved 36 healthy subjects receiving of generic test formulation applied to circular, a diameter sites on one arm and reference formulation applied to sites on the contralateral arm. The sites were to be evaluated by both a chromameter and visually at 0.25, 0.5, 1, 2, 4, 8, 10 and 24 hours after removal of the formulation. In addition, a sixteen hour duration of application, with reading two hours after removal of formulation, was to be included. Following a washout, the study was to be repeated in the same subjects, using a second lot of the reference product and same test lot. Data analysis was to consist of fitting dose\response curves (Emax model) to the area under the response curves and maximum responses for the test and reference treatments in each subject.

On June 2, 1995, the Division of Bioequivalence issued a new guidance for the conduct of studies for topical corticosteroids which supercedes the July 1992 guidance. The current guidance is based upon the conduct of two studies by the firm- a pilot dose duration-response study and a pivotal in vivo bioequivalence study comparing test and reference products.

The current study did not meet the criteria related to evaluation by the E-max model per the 1992 guidance and it was completed and submitted prior to the issue of the 1995 guidance. Therefore, the study was evaluated via consult by David C. Bostwick, HFD-630.

Objective:

The aim of this study is to compare the relative vasoconstrictive effects of corresponding test and reference betamethasone topical cream formulations in asymptomatic subjects, and using the generic as a negative control The reference product is 0.05%

Diprosone cream manufactured by Schering Corporation.

Methods:

The study was conducted by under the direction of M.D. The study was done on the following dates: Period I, Group I-8-3-93
Period I, Group II-8-10-93
Period II, Group I-8-24-93
Period II, Group II-8-31-93

I. Characterization of Study Group:

A. Inclusion criteria

1. All volunteers selected for this study were female volunteers between the ages of 18 and 48 years. Weight range of the volunteers was within 30% of normal body weight relative to height and frame size as described in the "Table of Desirable Weights of Adults" published by the Metropolitan Life Insurance Company in 1983.

2. Good health, as determined by evaluation of a medical history prior to study initiation. Female subjects, who are not post-menopausal or surgically sterilized, will be tested for pregnancy prior to study initiation with blood or urine pregnancy test.

3. Known vasoconstrictor response to topical corticosteroids.

B. Exclusion Criteria:

1. History of allergy to betamethasone, to any corticosteroids, or to any creams, lotions, ointments, or cosmetics.

2. Volunteers with a history of alcohol or drug abuse.

3. History of serious gastrointestinal, renal, hepatic, cardiovascular or hematological diseases.

4. Any skin condition or coloration which would interfere with assessment of skin blanching.

5. Participation in a previous clinical trial within 28 days of dosing.

6. Use of any OTC medication on a regular basis.

7. Use of any systemic or topical corticosteroid within 30 days of dosing.

8. Pregnancy of any female subject at the time of the study.

Restrictions

1. Subjects were instructed to take no prescribed or OTC medication for at least 14 days prior to the initial dosing and throughout the study.

2. The subjects had to avoid contact with water on their arms, extremes of temperature and vigorous exercise during the study.

C. Informed Consent:
All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

The study was done in 40, healthy caucasian females.

A. Subjects were assigned to one of two treatment groups (See attached randomization scheme.) The locations of the test and reference creams were determined by random assignment. Seven circular application sites were designated on the flexor surface of the forearm between the wrist and the elbow. After baseline chromameter readings, an open washer was positioned over each site and taped to the forearm. The location of treated and untreated sites were done by random assignment. A application of the test and the reference creams was applied, using a ass syringe, to the remaining 5 sites on each arm.

At 0.5, 1,2,6 and 16 hours after application, one washer was removed from both a test and reference site and the residual surface cream was removed by gently wiping three times with a tissue. The washers at the untreated and vehicle sites were removed 6 hours after application and the sites were similarly wiped. Chromameter and visual assessments of the

blanching response at each site were made at 6, 8, 10, 12, 15, 18 and 24 hours post-application. After a 3-week washout, the same study procedures were followed except a second reference lot was applied to the opposite arm.

B. The products employed in the study were:

1. Test: 1 betamethasone dipropionate 0.05% cream, Lot # CPL P725.

2. Reference product: prosone^{R} 0.05% cream
Schering Corporation Lot # KGD 303(Period I)
Schering Corporation Lot # KGD 102(Period II)

There was a 3 week washout between doses.

C. The randomization scheme is presented in attachment 1.

The formulation for the test prduct is given in attachment 2.

Results:

The data from the study was analyzed by Dave Bostwick HFD-630. Results from the consult are appended to this review.

Recommendation:

1. The bioequivalence study conducted by Clay Park Laboratories on its betamethasone dipropionate 0.05% cream Lot No. CPL P 725, comparing it to Schering's Diprosone cream 0.05% Lot Numbers KGD 303 and KGD 102 has been found to be acceptable by the Division of Bioequivalence. Therefore, betamethasone dipropionate 0.05% cream manufactured by Clay Park Laboratories should be deemed bioequivalent to Diprosone cream 0.05% manufactured by g.

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

/S/

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ Date: 2/5/96

Concur: /S/ Date: 2/6/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

HFD-
vision

Attachment I

BETAMETHASONE DIPROPIONATE .05% CREAM
STUDY NO. 9316902C

PERIOD 1
TREATMENT ASSIGNMENTS

SUBJ	LEFT ARM			RIGHT ARM		
	TREAT-MENT	VEHICLE POSITION	UNTREATED POSITION	TREAT-MENT	VEHICLE POSITION	UNTREATED POSITION
1	A	5	7	B	3	6
2	A	3	2	B	2	3
3	B	5	1	A	3	4
4	B	4	3	A	1	4
5	A	5	2	B	6	4
6	A	2	5	B	7	3
7	B	2	4	A	7	4
8	B	1	4	A	2	3
9	B	7	5	A	1	2
10	A	6	7	B	6	4
11	A	5	6	B	3	2
12	A	6	4	B	7	1
13	B	4	6	A	4	3
14	B	3	5	A	4	7
15	A	1	6	B	3	1
16	A	2	5	B	5	2
17	A	1	3	B	2	5
18	B	3	1	A	3	5
[illegible]	B	7	5	A	1	2
[illegible]	B	3	2	A	7	5
21	B	6	7	A	4	5
22	B	1	6	A	6	3
23	A	6	3	B	6	7
24	A	7	3	B	1	3
25	B	4	7	A	7	3
26	B	5	3	A	7	3
27	B	6	3	A	6	2
28	A	7	5	B	1	6
29	A	6	5	B	2	6
30	B	5	6	A	1	5
31	A	2	6	B	4	5
32	B	5	1	A	3	4
33	A	1	2	B	6	2
34	A	6	2	B	7	1
35	A	7	6	B	7	2
36	B	1	6	A	6	3
37	B	3	7	A	4	5
38	B	5	3	A	2	5
39	A	4	3	B	2	4
40	A	1	4	B	7	3

Attachment I

BETAMETHASONE DIPROPIONATE .05% CREAM
STUDY NO. 9316902C

PERIOD 2
TREATMENT ASSIGNMENTS

SUBJ	LEFT ARM			RIGHT ARM		
	TREAT-MENT	VEHICLE POSITION	UNTREATED POSITION	TREAT-MENT	VEHICLE POSITION	UNTREATED POSITION
1	B	2	3	A	5	3
2	B	1	5	A	6	7
3	A	2	6	B	4	1
4	A	4	7	B	7	5
5	B	5	4	A	3	5
6	B	5	4	A	3	4
7	A	2	3	B	6	3
8	A	4	3	B	3	1
9	A	5	6	B	2	4
10	B	2	7	A	6	3
11	B	4	1	A	5	7
12	B	7	3	A	4	2
13	A	2	1	B	3	1
14	A	7	3	B	7	1
15	B	1	5	A	4	5
16	B	7	3	A	2	6
17	B	7	4	A	2	1
18	A	5	7	B	4	6
19	A	1	4	B	2	6
[illegible]	A	4	7	B	7	6
	A	2	3	B	6	2
[illegible]2	A	1	3	B	1	4
23	B	6	5	A	3	1
24	B	6	3	A	2	6
25	A	6	3	B	4	5
26	A	7	2	B	7	1
27	A	1	2	B	5	3
28	B	4	2	A	5	3
29	B	2	4	A	1	2
30	A	3	7	B	6	3
31	B	7	5	A	6	4
32	A	7	5	B	1	4
33	B	1	3	A	6	5
34	B	1	6	A	3	2
35	B	6	2	A	4	3
36	A	2	4	B	6	3
37	A	1	7	B	2	3
38	A	6	5	B	7	1
39	B	5	3	A	1	3
40	B	5	4	A	5	7

Attachment II

12/14/94
/S/

COMPOSITION OF THE DRUG

lude the composition of the drug stating the name and amount of h ingredient whether active or not, contained in a stated ntity of the drug in the form in which it is distributed:

BETAMETHASONE DIPROPIONATE CREAM USP, 0.05%

GREDIENTS:	mg/g	Variations*
neral Oil USP XXII		within IIG range
ite Petrolatum USP XXII		within IIG range
tyl Alcohol,		other IIG range
osphoric Acid,		other IIG range
ieth-		other IIG range
nobasic Sodium Phosphate		within IIG range
ol ne Glycol, USP XXII		within IIG range
etamethasone Dipropionate USP XXII	0.066	0.66*** 3% excess
tearyl Alcohol,		other IIG range
hlorocresol		within IIG range
ater, Purified		

SECTION VI

NOTES:

* Excess is within allowable limits
** Brand of polyethylene Glycol Cetyl Ether (Ceteth
*** Equivalent to 0.05% of Betamethasone plus excess of 3% (0.0515%)

These amounts are accurate for each gram of material packaged in any size container.

Attachment III

BETAMETHASONE DIPROPIONATE
STUDY NO. 9316902C

TABLE C3: SUMMARY OF ADVERSE EVENTS

Duration:
Onset-End
H = Hours
D = Days
(If >24 Hours)

Severity (Sev):
1 = Mild
2 = Moderate
3 = Severe

Action Taken (Act):
1 = None
2 = Subject discontinued
3 = Other (see CRF)

Relationship (Rel):
1 = None
2 = Remote
3 = Possible
4 = Probable

Outcome (Out):
1 = Recovered
2 = AE continuing
3 = Subject lost to follow-up
4 = Other (see CRF)

Sub	Adverse Event	Onset (Per/Day)	Duration (Times)	Sev	Act	Rel	Out
01	Stuffy nose	I/14	0200-(29 H)	1	3	1	1
02	Headache	I/*	0600-1130	1	3	1	1
03	Multiple environmental allergies	I/18	1400-(53 H)	1	3	1	1
07	Headache	I/14	0200-(31 H)	1	3	1	1
09	Headache	I/19	1000-1100	2	3	1	1
14	Headache	I/19	0900-1000	1	3	1	1
15	Constipation	I/19	1200-(28 H)	1	3	1	1
	Headache	II/1	0330-1315	1	3	1	1
17	Cold symptoms	I/20	2030-(3 D)	1	3	1	1
20	Yeast infection	I/17	1400-(6 D)	2	3	1	1
26	Emesis x 3	II/1	1930-2055	1	3	1	1
38	Headache	I/1	1130-2200	1	3	1	1

* Adverse event began 2 hours prior to dosing in Period II.

Date of Review: June 19, 1995

Consultative Review of Vasoconstrictor Assay - NDA 74-579
(Referred by Division of Bioequivalence, HFD-650).

Sponsor: Clay - Park Laboratories
Bronx, N.Y. 10457

Product: Betamethasone Dipropionate Cream, , 0.05%

Purpose of Submission: To establish the equivalency of the Clay - Park product to the similar Diprosone Cream marketed by Schering.

Date of Submission: December 1, 1994.

Investigator: }
} nces
}

Background: The vasoconstrictor assay has been used for some time as the test by which the relative potency of topical corticosteroid formulations is established. Because vasoconstrictor methodology was not standardized, and because questions have been raised about the ability of this methodology to detect differences in the potency of topical steroid products, the office of Generic Drugs (with consultation from this Division) has devised new methods to test the bioequivalency of topical steroids. An Interim Guidance for the performance of bioequivalence studies of topical steroids was issued on July 1, 1992. This application is the first which has been received which attempts to follows this guideline.

The Guidance was altered in late 1994. Since the study reviewed here was performed prior to issuance of the revised Guidance, the 1992 Guidance will be referred to in this document.

Formulations: The formulations of the Clay - Park and Schering products are similar.

Indication: These products are indicated for relief of the inflammatory and pruritic manifestations of corticosteroid - responsive dermatoses.

Method: This was a study of the relative vasoconstrictor effects of Clay - Park's 0.05% betamethasone dipropionate cream, the Clay - Park vehicle, and Schering's Diprosone Cream.

The following is an outline of the vasoconstrictor study proposed in the 1992 Guidance:

- 36 healthy subjects;
- Test formulation application to one arm; reference formulation to contralateral arm;
- of single strength of product applied over a diameter area with application area protected but unoccluded;
- Test and reference products removed after 0.25, 0.5, 1, 2 and 6 hours to provide five 'doses' (durations of application);
- Assessment of vasoconstrictor response at each site at 0.25, 0.5, 1, 2, 4, 6, 8, 10 and 24 hours, when applicable, after removal of the formulation;
- In addition, a sixteen hour duration of application, followed by a two hour reading post removal of the drug, should be included to correspond to pre-July 1992 requirements;
- Vasoconstrictor response assessed both visually and using the chromameter;
- Repeat study (replicate design) after suitable washout using second lot of reference product and switching arms for test and reference products;
- Application/measurement of suitable blanks (untreated skin and vehicle-only treatment skin) and calibrators to validate bioassay.

At each 'dose' (duration of application in the above example), the time course of response can yield the following variables: peak effect (E_{Peak}), time of this effect (T_{Peak}) and area under the effect/time curve from E_{0N} to the point at which the affect returns to E_0. Parameters describing the dose/response relationship (e.g., E_{Max}, EC_{50} and E_0) can be calculated for each subject and both test and reference formulations by fitting the peak response at each 'dose' to an appropriate pharmacodynamic model..

The following is an outline of the protocol performed by the test facility:

- 40 healthy female subjects
- Test formulation application to one arm; reference formulation to contralateral arm;
- of test products applied over diameter area with application area protected but unoccluded;

- Test and reference products removed after 0.5, 1, 2, 6 and 16 hours to provide five durations of application; (the test facility found that the 0.25 hour duration application did not provide a visually detectable blanching response);
- Assessment of vasoconstrictor response at each site at 6, 8, 10, 12, 15, 18 and 24 hours post-application; (the test facility found that the assessments prior to 6 hours post - application showed little if any blanching activity);
- Vasoconstrictor response assessed both visually and using the chromameter;
- After a 3 · week washout, the same study procedures were followed with a second lot of reference product applied to the opposite arm;
- The Clay - Park vehicle was used to validate the assay.

Visual scoring used the following scale:

0=No pallor; no change from surrounding area.
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.

Results:

A Chromameter

The post - application chromameter readings were first adjusted by subtracting the baseline reading. The test facility notes that there was extreme intra - subject variability in chromameter response. This variability led to low statistical power and wide 90% conference intervals, especially for the shorter deadlines of application. This is illustrated by the following tables, taken from the sponsors submission (the "test" product is Clay - Park's , while the "reference" is Diprosone):

Comparison of Test and Reference corrected baseline-adjusted chromameter (a-scale) results for different durations of application in Period I.

Duration	Least Squares Means		Observed Diff. (%) *	90% Conf. Intervals (%)		
	Test	Reference		Power	Lower	Upper
Area						
0.5 hour	18.76	16.44	14.14	0.23	-12.8	41.0
1.0 hour	21.66	19.18	12.94	0.26	-11.7	37.6
2.0 hour	26.25	25.82	1.67	0.48	-15.6	19.0
6.0 hour	29.82	28.44	4.83	0.57	-10.5	20.2
Maximum						
0.5 hour	1.928	1.736	11.03	0.32	-10.8	32.9
1.0 hour	2.026	1.965	3.10	0.39	-16.3	22.5
2.0 hour	2.425	2.528	-4.06	0.61	-18.8	10.7
6.0 hour	2.685	2.706	-0.79	0.72	-13.7	12.1

Chromameter results for the 16- hour duration of application in Period I.

Reading	Least Squares Means		Observed Diff. (%)*	90% conf. Intervals (%)		
	Test	Reference		Power	Lower	Upper
18 hour	1.905	1.905	-0.01	0.39	-19.5	19.5

*None of the differences was detected as statistically significant by ANOVA (a = 0.05.)

Comparison of Test Reference corrected baseline-adjusted chromameter (a-scale) results for different durations of application in Period II.

	Least Squares Means		Observed Diff.	90% Conf. Intervals (%)		
Duration	Test	Reference	(%) *	Power	Lower	Upper
Area						
0.5 hour	16.73	15.90	5.18	0.18	-26.2	36.5
1.0 hour	18.09	17.46	3.65	0.37	-16.4	23.7
2.0 hour	22.11	20.52	7.75	0.44	-10.4	25.9
6.0 hour	23.72	26.29	-9.78	0.41	-28.7	9.1
Maximum						
0.5 hour	1.679	1.661	1.05	0.30	-22.0	24.1
1.0 hour	1.856	1.780	4.24	0.45	-13.7	22.2
2.0 hour	2.096	2.012	4.15	0.57	-11.3	19.6
6.0 hour	2.265	2.479	-8.62	0.64	- 22.8	5.6

Chromameter results for the 16 -hour duration of application in Period II.

	Least Squares Means		Observed Diff.	90% Conf. Interval (%)		
Reading	Test	Reference	(%)*	Power	Lower	Upper
18 hour	1.723	1.571	9.66	0.28	-14.0	33.3

* None of the differences was detected as statistically significant by ANOVA (a = 0.05).

Comments: It can be seen from these results that although the means of the chromameter readings at the various time points are reasonably similar, the variability of the data is so great that the 90% confidence intervals are consistently greater that 20%. These results are not unexpected, given reports of difficulty by other investigators in achieving consistent results with the chromameter.

B. Visual evaluation

The following tables give the numbers of patients who exhibited the noted visual blanching scores by duration of application and by hour of assessment after drug removal: Those tables which do not have columns for scores of 2 or 3 indicate that no patients exhibited vasoconstriction scores of 2 or 3 during the time period being evaluated. Also, it should be noted that there were two separate scoring periods (1 and 2).

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCO		
Frequency			Total
REF			36
TEST			36
VEHCL			72
Total	132	12	144

---------- DURATION=0.5 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	36	0.06
TEST	36	0.03
VEHCL	72	0.13

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=8 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				36
TEST				36
VEHCL				72
Total	119	24	1	144

---------- DURATION=0.5 HOUR=8 ----------

TRTMNT	N Obs	Mean
REF	36	0.22
TEST	36	0.36
VEHCL	72	0.07

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=10 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				36
TEST				36
VEHCL				72
Total	113	29	2	144

---------- DURATION=0.5 HOUR=10 ----------

TRTMNT	N Obs	Mean
REF	36	0.28
TEST	36	0.44
VEHCL	72	0.10

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=0.5 HOUR=12

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				36
TEST				36
VEHCL				72
Total	118	24	2	144

DURATION=0.5 HOUR=12

TRTMNT	N Obs	Mean
REF	36	0.25
TEST	36	0.42
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=0.5 HOUR=15

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				36
TEST				36
VEHCL				71
Total	107	35	1	143

Frequency Missing = 1

DURATION=0.5 HOUR=15

TRTMNT	N Obs	Mean
REF	36	0.39
TEST	36	0.53
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				36
TEST				36
VEHCL				72
Total	118	25	1	144

---------- DURATION=0.5 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	0.31
TEST	36	0.42
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCO				
Frequency					Total
REF					36
TEST					36
VEHCL					72
Total	127	15	1	1	144

---------- DURATION=0.5 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	36	0.19
TEST	36	0.33
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE		
Frequency			Total
REF			36
TEST			36
VEHCL			72
Total	122	22	144

---------- DURATION=1 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	36	0.17
TEST	36	0.19
VEHCL	72	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=1 HOUR=8

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency	0			Total
REF				36
TEST				36
VEHCL				72
Total	106	29	9	144

DURATION=1 HOUR=8

TRTMNT	N Obs	Mean
REF	36	0.56
TEST	36	0.61
VEHCL	72	0.07

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=1 HOUR=10

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				36
TEST				36
VEHCL				72
Total	95	33	16	144

DURATION=1 HOUR=10

TRTMNT	N Obs	Mean
REF	36	0.81
TEST	36	0.81
VEHCL	72	0.10

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT Frequency	SCORE			3	Total
REF					36
TEST					36
VEHCL					72
Total	96	35	12	1	144

---------- DURATION=1 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	36	0.78
TEST	36	0.83
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / Frequency	SCORE				Total
REF					36
TEST					36
VEHCL					71
Total	90	35	16	2	143

Frequency Missing = 1

---------- DURATION=1 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	36	0.92
TEST	36	1.00
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCOR				
Frequency					Total
REF					36
TEST					36
VEHCL					72
Total	103	25	15	1	144

---------- DURATION=1 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	0.83
TEST	36	0.75
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / Frequency	SCORE			Total
REF				36
TEST				36
VEHCL				72
Total	113	23	8	144

---------- DURATION=1 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	36	0.56
TEST	36	0.50
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=6

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency	0			Total
REF				36
TEST				36
VEHCL				72
Total	125	18	1	144

DURATION=2 HOUR=6

TRTMNT	N Obs	Mean
REF	36	0.14
TEST	36	0.17
VEHCL	72	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=8

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					36
TEST					36
VEHCL					72
Total	96	34	13	1	144

DURATION=2 HOUR=8

TRTMNT	N Obs	Mean
REF	36	0.86
TEST	36	0.75
VEHCL	72	0.07

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=10 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					36
TEST					36
VEHCL					72
Total	83	35	24	2	144

---------- DURATION=2 HOUR=10 ----------

TRTMNT	N Obs	Mean
REF	36	1.19
TEST	36	1.08
VEHCL	72	0.10

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					5
TEST					5
VEHCL					2
Total	92	28	19	5	144

---------- DURATION=2 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	36	1.03
TEST	36	1.11
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					36
TEST					36
VEHCL					71
Total	87	20	29	7	143

Frequency Missing = 1

---------- DURATION=2 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	36	1.28
TEST	36	1.36
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					36
TEST					36
VEHCL					72
Total	93	24	20	7	144

---------- DURATION=2 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	1.22
TEST	36	1.11
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=24

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency			2	Total
REF				36
TEST				36
VEHCL				72
Total	109	23	12	144

DURATION=2 HOUR=24

TRTMNT	N Obs	Mean
REF	36	0.67
TEST	36	0.61
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				36
TEST				36
VEHCL				72
Total	101	38	5	144

---------- DURATION=6 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	36	0.44
TEST	36	0.64
VEHCL	72	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=8

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE					
Frequency				3	Total
REF					36
TEST					36
VEHCL					72
Total	90	35	15	4	144

DURATION=6 HOUR=8

TRTMNT	N Obs	Mean
REF	36	0.97
TEST	36	1.03
VEHCL	72	0.07

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=10 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					36
TEST					36
VEHCL					72
Total	82	29	28	5	144

---------- DURATION=6 HOUR=10 ----------

TRTMNT	N Obs	Mean
REF	36	1.25
TEST	36	1.33
VEHCL	72	0.10

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=12

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					36
TEST					36
VEHCL					72
Total	81	26	28	9	144

DURATION=6 HOUR=12

TRTMNT	N Obs	Mean
REF	36	1.42
TEST	36	1.50
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=15

TABLE OF TRTMNT BY SCORE

TRTMNT SCORE

Frequency					Total
REF					36
TEST					36
VEHCL					71
Total	75	22	29	17	143

Frequency Missing = 1

DURATION=6 HOUR=15

TRTMNT	N Obs	Mean
REF	36	1.72
TEST	36	1.81
VEHCL	72	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					36
TEST					36
VEHCL					72
Total	86	14	33	11	144

---------- DURATION=6 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	1.56
TEST	36	1.56
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=24

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE	3	Total
Frequency		
REF		36
TEST		36
VEHC	0	72
Total	1	144

DURATION=6 HOUR=24

TRTMNT	N Obs	Mean
REF	36	0.94
TEST	36	1.19
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=16 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					36
TEST					36
VEHCL					72
Total	77	21	29	17	144

---------- DURATION=16 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	36	1.83
TEST	36	1.75
VEHCL	72	0.01

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 1

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=16 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					36
TEST					36
VEHCL					72
Total	90	30	22	2	144

---------- DURATION=16 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	36	1.03
TEST	36	1.17
VEHCL	72	0.01

STUDY NO. 9316902C

VISUAL SCORING IN

PERIOD II

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				40
TEST				40
VEHCL				80
Total	108	42	10	160

---------- DURATION=0.5 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	40	0.20
TEST	40	0.25
VEHCL	80	0.55

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=8 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE					
Frequency				3	Total
REF					40
TEST					40
VEHCL					80
Total	132	21	6	1	160

---------- DURATION=0.5 HOUR=8 ----------

TRTMNT	N Obs	Mean
REF	40	0.25
TEST	40	0.53
VEHCL	80	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=10 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					40
TEST					40
VEHCL					80
Total	128	24	5	3	160

---------- DURATION=0.5 HOUR=10 ----------

TRTMNT	N Obs	Mean
REF	40	0.30
TEST	40	0.53
VEHCL	80	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					40
TEST				2	40
VEHCL				0	80
Total	123	28	6	3	160

---------- DURATION=0.5 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	40	0.40
TEST	40	0.68
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					40
TEST					40
VEHCL					79
Total	127	22	5	5	159

Frequency Missing = 1

---------- DURATION=0.5 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	40	0.33
TEST	40	0.70
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					40
TEST					40
VEHCL					80
Total	137	17	2	4	160

---------- DURATION=0.5 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	40	0.25
TEST	40	0.50
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=0.5 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					40
TEST					40
VEHCL					80
Total	134	19	6	1	160

---------- DURATION=0.5 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	40	0.25
TEST	40	0.50
VEHCL	80	0.05

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=6 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				40
TEST				40
VEHCL				80
Total	102	42	16	160

---------- DURATION=1 HOUR=6 ----------

TRTMNT	N Obs	Mean
REF	40	0.40
TEST	40	0.35
VEHCL	80	0.55

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=8 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE					
Frequency				3	Total
REF					40
TEST					40
VEHCL					80
Total	118	29	11	2	160

---------- DURATION=1 HOUR=8 ----------

TRTMNT	N Obs	Mean
REF	40	0.65
TEST	40	0.65
VEHCL	80	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=10 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					40
TEST					40
VEHCL					80
Total	108	35	10	7	160

---------- DURATION=1 HOUR=10 ----------

TRTMNT	N Obs	Mean
REF	40	0.75
TEST	40	0.90
VEHCL	80	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency				3	Total
REF					40
TEST					40
VEHCL					80
Total	111	27	14	8	160

---------- DURATION=1 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	40	0.90
TEST	40	0.93
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=1 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE					
Frequency					Total
REF					40
TEST					40
VEHCL					79
Total	103	29	22	5	159

Frequency Missing = 1

---------- DURATION=1 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	40	0.95
TEST	40	1.10
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=1 HOUR=18

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					40
TEST					40
VEHCL					80
Total	108	32	16	4	160

DURATION=1 HOUR=18

TRTMNT	N Obs	Mean
REF	40	0.85
TEST	40	0.98
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=1 HOUR=24

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				40
TEST				40
VEHCL				80
Total	119	31	10	160

DURATION=1 HOUR=2

TRTMNT	N Obs	Mean
REF	40	0.55
TEST	40	0.63
VEHCL	80	0.05

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=6

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				40
TEST				40
VEHCL				80
Total	93	52	15	160

DURATION=2 HOUR=6

TRTMNT	N Obs	Mean
REF	40	0.48
TEST	40	0.48
VEHCL	80	0.55

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=8

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE					
Frequency				3	Total
REF					40
TEST					40
VEHCL					80
Total	102	36	18	4	160

DURATION=2 HOUR=8

TRTMNT	N Obs	Mean
REF	40	1.00
TEST	40	0.98
VEHCL	80	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=10

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0				Total
REF					40
TEST					40
VEHCL					80
Total	91	36	20	13	160

DURATION=2 HOUR=10

TRTMNT	N Obs	Mean
REF	40	1.35
TEST	40	1.28
VEHCL	80	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					40
TEST					40
VEHCL					80
Total	88	35	24	13	160

---------- DURATION=2 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	40	1.50
TEST	40	1.40
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					40
TEST				7	40
VEHCL				0	79
Total	86	27	32	14	159

Frequency Missing = 1

---------- DURATION=2 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	40	1.58
TEST	40	1.60
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=2 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					40
TEST					40
VEHCL					80
Total	96	27	22	15	160

---------- DURATION=2 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	40	1.40
TEST	40	1.43
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=2 HOUR=24

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE			
Frequency				Total
REF				40
TEST				40
VEHCL				80
Total	111	31	18	160

DURATION=2 HOUR=24

TRTMNT	N Obs	Mean
REF	40	0.90
TEST	40	0.68
VEHCL	80	0.05

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=6

TABLE OF TRTMNT BY SCORE

TRTMNT / Frequency	0	Total
REF		40
TEST		40
VEHCL		80
Total	62 61 36 1	160

DURATION=6 HOUR=6

TRTMNT	N Obs	Mean
REF	40	1.25
TEST	40	1.05
VEHCL	80	0.55

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=8

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE					
Frequency					Total
REF					40
TEST					40
VEHCL					80
Total	89	36	26	9	160

DURATION=6 HOUR=8

TRTMNT	N Obs	Mean
REF	40	1.53
TEST	40	1.23
VEHCL	80	0.06

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=10

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE					
Frequency					Total
REF					40
TEST					40
VEHCL					80
Total	80	33	25	22	160

DURATION=6 HOUR=10

TRTMNT	N Obs	Mean
REF	40	1.88
TEST	40	1.60
VEHCL	80	0.13

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=12 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					40
TES					40
VEH					80
Total	77	23	35	25	160

---------- DURATION=6 HOUR=12 ----------

TRTMNT	N Obs	Mean
REF	40	2.10
TEST	40	1.95
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=15 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					40
TEST					40
VEHCL					79
Total	74	24	31	30	159

Frequency Missing = 1

---------- DURATION=6 HOUR=15 ----------

TRTMNT	N Obs	Mean
REF	40	2.13
TEST	40	2.13
VEHCL	80	0.08

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=6 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency					Total
REF					40
TEST					40
VEHCL					80
Total	83	30	23	24	160

---------- DURATION=6 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	40	1.83
TEST	40	1.80
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

DURATION=6 HOUR=24

TABLE OF TRTMNT BY SCORE

TRTMNT / SCORE Frequency				Total
REF				40
TEST				40
VEHCL				80
Total	101	39	20	160

DURATION=6 HOUR=24

TRTMNT	N Obs	Mean
REF	40	0.98
TEST	40	0.90
VEHCL	80	0.05

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=16 HOUR=18 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	0				Total
REF					40
TEST					40
VEHCL					80
Total	84	21	26	29	160

---------- DURATION=16 HOUR=18 ----------

TRTMNT	N Obs	Mean
REF	40	1.93
TEST	40	2.00
VEHCL	80	0.04

STUDY 9316902C: RESULTS OF VISUAL SCORING IN PERIOD 2

FREQUENCY OF SCORES FOR EACH DURATION OF APPLICATION AT EACH ASSESSMENT HOUR READ

---------- DURATION=16 HOUR=24 ----------

TABLE OF TRTMNT BY SCORE

TRTMNT	SCORE				
Frequency	C				Total
REF					40
TEST					40
VEHCL					80
Total	95	36	25	4	160

---------- DURATION=16 HOUR=24 ----------

TRTMNT	N Obs	Mean
REF	40	1.10
TEST	40	1.25
VEHCL	80	0.05

Comment: Little visual vasoconstriction was seen for the 0.5 hour duration of application. However, betamethasone dipropionate cream 0.05% and Diprosone Cream 0.05% are comparable in their vasoconstrictor activity. If the totals of the mean scores for all evaluations are taken by time period, the following is seen:

Scoring Period #1

Test Product	Mean Total
Clay - Park betamethasone dipropionate	23.39
Diprosone Cream	23.88
Clay- Park Vehicle	1.78

Scoring Period #2

Test Product	Mean Total
Clay-Park betamethasome Dipropionate	30.99
Diprosone Cream	29.97
Clay -Park Vehicle	4.05

Thus, the Clay-Park product achieved 106.3% of the mean total vasoconstriction of Diprosone during scoring period #1, and 103.4% of this total during scoring period #2. Both products were superior to the Clay-park vehicle.

Conclusions and Recommendation: This ANDA may be approved on the basis of bioequivalence in that the vasoconstrictor activity of the test and reference products are not significantly different. The chromameter results suggest comparability, but the variance in the data causes wide confidence intervals in the statistical analysis.

Because of reported difficulties in achieving consistent chromameter results, the July 1, 1992 Guidance under which this study was performed has been superseded by another guidance dated December 1, 1994. The new guidance recommends a pilot vasoconstrictor study be done in order to validate chromameter readings in a selected group of "good" responders. In any event, there is no reason to refuse to approve this application on the basis of inconsistent chromameter readings, since no one has been able to achieve consistent results using the old guidance.

/S/
David C. Bostwick

/S/ 11/27/95
Jonathan Wilkin, M.D.

(revised :- HFD-540 - 11/95)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74-579

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #1

November 5, 1997

A. 1. ANDA: **74-579**

APPLICANT: Clay-Park Labs, Inc.
Attention: Giabriel Lebovic
1700 Bathgate ave.
Bronx, NY 10457

2. PRODUCT NAME: **Betamethasone Dipropionate Cream, 0.05%, USP**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: synthetic corticosteroid

B. 1. DATE OF INITIAL SUBMISSION:
2. DATE OF AMENDMENT: **September 12, 1997.- Subject of this review.**
3. RELATED DOCUMENTS:
4. ASSIGNED FOR REVIEW: November 5, 1997.

C. REMARKS: Review of Antimicrobial Preservative Effectiveness testing at 0%, 50%, 80% and 100% preservative concentrations.

D. CONCLUSIONS: The submission is are recommended for approval on the basis of antimicrobial preservative activity. Specific comments are provided in "E. Review Notes".

/S/

James L. McVey

initialed by R. Patel

cc:

E. REVIEW NOTES:

Antimicrobial Preservative-Effectiveness Test. The USP <51> method was used to evaluate product with 0%, 50%, 80% and 100% of the label preservative content (Chlorocresol) against the 5 recommended organism. All test samples were effective according to the USP criteria including the unpreserved sample. This test is signed on 2/21/97. An earlier study, dated 11/18/92, done by for Clay Park, shows that a product tested by a USP method with the addition of isolated molds also passes USP criteria.

Acceptable