CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-090

Generic name: Permethrin Lotion, 1%

Sponsor: Clay-Park Labs, Inc.

Approval Date: December 20, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
76-090

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter	
ANDAs	
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-090

APPROVAL LETTER

4.1

ANDA 76-090

DEC 20 2001

Clay-Park Labs, Inc.
Attention: Candis Edwards
1700 Bathgate Avenue
Bronx, NY 10457

Dear Madam:

This is in reference to your abbreviated new drug application dated December 28, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Permethrin Lotion, 1%.

Reference is also made to your amendments dated July 5, 2001 and September 6, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted Over-The-Counter (OTC) labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Permethrin Lotion, 1%, to be bioequivalent to the listed drug (Nix® Crème Rinse, 1%, of Warner Lambert Co. Consumer Products Div.).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug..

Sincerely yours,

/S/

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

12/20/01

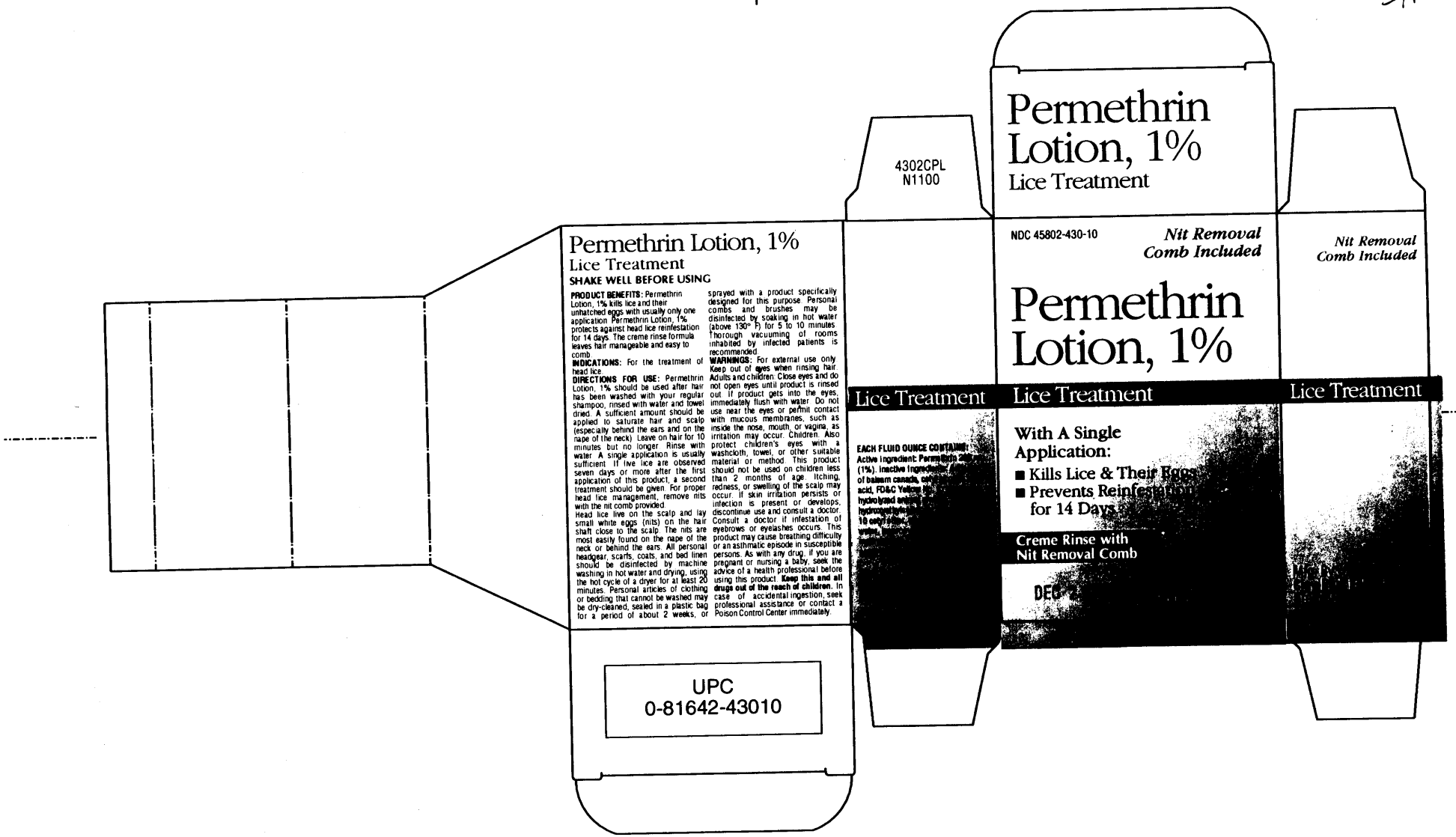
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-090

Final Printed Labeling

76-090
AP 12/20/0



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Clay Park Labs, Inc. Graphics Dept. (Ph 718 960-9967)

DIE# 20877B	COLORS: DEC 20 2001	PRODUCT NO: 430
CODE#	BK	MXC ARTIST: A A

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-090

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER 1

2. ANDA NUMBER 76-090 **[Permethrin Lotion, 1%]**

3. NAME AND ADDRESS OF APPLICANT

Clay-Park Labs, Inc.
Attention: Candis Edwards (Director of Regulatory Affairs)
1700 Bathgate Avenue, Brox, NY 10457
Phone: (718) 960-9976
Fax: (718) 960-0111

4. LEGAL BASIS for ANDA SUBMISSION

a. The basis for Clay-Park Labs, Inc.'s proposed ANDA for Permethrin Lotion, 1% is the approved, reference listed drug Nix® Creme Rinse (1%), the subject of NDA # 019918, approved May 02, 1990, held by Warner-Lambert Consumer Healthcare containing permethrin, 1%.

b. According to the information published in Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, current through October 2000 there is no unexpired marketing exclusivity for Nix® Creme Rinse (1%), under section 505 (j)(4)(D) of the Act.

The U.S. patent #4,024,163 (inventor: Elliott et. al.) expired on 05/17/1996. This patent claimed the active ingredient in the listed drug, pharmaceutical formulations containing the active ingredient, and the use of the active ingredient to control insect.

5. SUPPLEMENT(s) None.

6. NAME OF DRUG Permethrin Lotion

7. NONPROPRIETARY NAME Permethrin Lotion

8. SUPPLEMENT(s) PROVIDE(s) FOR None.

9. AMENDMENTS AND OTHER DATES

12/28/00	Original ANDA submission (received at OGD on 12/29/00).
12/29/00	Acceptable for filing
02/05/01	Submission of CMC ESD diskettes
02/06/01	FDA acknowledgment letter
03/05/01	Amendment (correction of discrepancies in hard copy)

10. PHARMACOLOGICAL CATEGORY Treatment of head lice (Ectoparasiticide)

11. HOW DISPENSED Over the counter

12. RELATED DMF/NDA/ANDA

Reference listed drug: Nix® Creme Rinse (1%), the subject of NDA # 019918, approved May 02, 1990, held by Warner-Lambert Consumer Healthcare.

OGD has approved the following ANDA for Permethrin Lotion, 1%

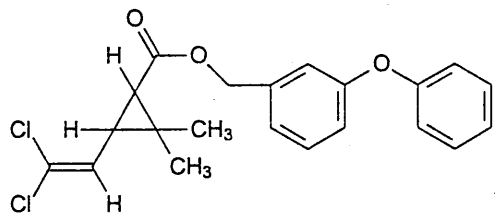
ANDA 75-014 (Alpharman U.S. Pharmaceuticasls Division): approved on 03/28/2000

13. DOSAGE FORM Lotion

14. POTENCY 1%

15. CHEMICAL NAME AND STRUCTURE

Permethrin. Cyclopropanecarboxylic acid, 3-(2,2-dichloroethyl)-2,2-dimethyl-, (3-phenoxyphenyl)methyl ester. $C_{21}H_{20}Cl_2O_3$. 391.29.
52645-53-1. Ectoparasiticide.



16. RECORDS AND REPORTS None.

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable (FAX amendment).

19. REVIEWER AND DATE COMPLETED

Shing H. Liu, Ph.D. (completed on 04/30/01, revised on 05/31/01)

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OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER 2

2. ANDA NUMBER 76-090 **[Permethrin Lotion, 1%]**

3. NAME AND ADDRESS OF APPLICANT

Clay-Park Labs, Inc.
Attention: Candis Edwards (Director of Regulatory Affairs)
1700 Bathgate Avenue, Brox, NY 10457
Phone: (718) 960-9976 Fax: (718) 960-0111

4. LEGAL BASIS for ANDA SUBMISSION See Review #1

5. SUPPLEMENT(s) None.

6. NAME OF DRUG Permethrin Lotion

7. NONPROPRIETARY NAME Permethrin Lotion

8. SUPPLEMENT(s) PROVIDE(s) FOR None.

9. AMENDMENTS AND OTHER DATES (subject of this review cycle is marked by *)

12/28/00	Original ANDA submission (received at OGD on 12/29/00).
12/29/00	Acceptable for filing
02/05/01	Submission of CMC ESD diskettes
02/06/01	FDA acknowledgment letter
03/05/01	Amendment (correction of discrepancies in hard copy)
06/08/01	NA (FAX) letter (based on CMC Review #1 by Shing H, Liu, Ph.D.)
07/05/01	* Clay-Park's FAX amendment
09/06/01	* Informational amendment

10. PHARMACOLOGICAL CATEGORY Treatment of head lice (Ectoparasiticide)

11. HOW DISPENSED Over the counter

12. RELATED DMF/NDA/ANDA

Reference listed drug: Nix® Creme Rinse (1%), the subject of NDA # 019918, approved May 02, 1990, held by Warner-Lambert Consumer Healthcare. OGD has approved the following ANDA for Permethrin Lotion, 1%:

ANDA 75-014 (Alpharman U.S. Pharmaceuticasls Division): approved on 03/28/2000

13. DOSAGE FORM Lotion

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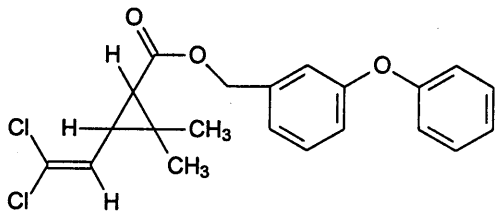

16. RECORDS AND REPORTS None.

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER AND DATE COMPLETED

Shing H. Liu, Ph.D. (completed on 07/24/01)
Revised on 12/13/01

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FAX AMENDMENT

ANDA 76-090

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN - 8 2001

TO: APPLICANT: Clay-Park Laboratories, Inc. TEL: 718-960-9976

ATTN: Candis Edwards FAX: 718-960-0111

FROM: Timothy Ames /S/ PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 28, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Permethrin Lotion, 1%.

Reference is also made to your amendment(s) dated: March 5, 2001.

Attached are 1 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FAX AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-090

MEDICAL REVIEW

MEDICAL OFFICER REVIEW
December 6, 2001

ANDA 76-090
Drug Product: Permethrin Crème Rinse, 1%
Sponsor: Clay-Park Laboratories, Inc.
Reference Listed Drug: Nix®, Permethrin crème rinse, Warner-Lambert

The statistical consult has been completed and reviewed. The statistician has reanalyzed the study with adjusted methods for analysis and evaluated not only the sponsor's Per Protocol (PP) population but also the modified PP populations defined in the Medical Officer's review. The generic product meets the bioequivalence crtiteria compared to the reference listed drug with all PP populations considered.

Conclusion:

This study establishes the bioequivalence of Clay-Park Labs, Inc.'s permethrin crème rinse, 1% and Warner-Lambert's Nix®.

/S/

Mary M. Fanning, MD, PhD
Associate Director for Medical Affairs
Office of Generic Drugs

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-090

STATISTICAL REVIEW(S)

Statistical Review: ANDA 76090, Permethrin Crème Rinse, 1%, Clay-Park Labs, Inc.

Material reviewed:
1. Material from ANDA 76-090
2. July 24, 2001 Medical Officer Review by Mary Fanning, M.D, Ph.D., Associate Director for Medical Affairs, Office of Generic Drugs.
3. Received the package on September 26, 2001

Introduction

Permethrin is a synthetic pyrethroid that is used to treat head pediculosis as a 1% application. The sponsor reported that permethrin cream product 1% over-the-counter offers the highest cure rate (>95%) of any agents tested. The sponsor submitted a clinical bioequivalence study to compare their generic product, Permethrin crème rinse, 1% (Clay-Park Labs, Inc. – Test Product), to the reference listed drug product, NIX® Permethrin crème rinse, 1% (Warner-Lambert – Reference Product).

Study Objectives

The objective of this study was to evaluate the clinical equivalence of the Test Product versus the Reference Product in the treatment of patients with head lice in order to establish bioequivalence.

Study Design

The experimental design for this bioequivalence study was a double-blinded, randomized, multi-centered and parallel group study. The study enrolled 283 patients. All the patients were children diagnosed with head lice, male or female, between the ages of 2 and 18 years. 142 patients were randomized to the Test Product group and 141 were randomized to the Reference group. The two treatments were:

1. Test Product – Permethrin crème rinse, 1% - Clay-Park Labs, Inc.

2. Reference Product - Permethrin crème rinse, 1% - NIX®, Warner-Lambert

Patients would receive either Test Product or Reference Product at visit 1 (Day 0, baseline) and then were examined at visit 2 (Day 2, within the visit window[1]) and visit 3 (Day 14, within the visit window[2]) after the treatment at visit 1. Each patient received only one treatment during the study.

[1] If Day 2 falls on a weekend or holiday, the patient must come in the day after the weekend/holiday, but no later than Day 5.

[2] If a patient was unable to return on day 14, the visit must be completed no earlier than day 13, and no later than day 18 after the treatment.

Endpoints

The primary endpoint was the cure rate. The cure was defined as absence of live lice at 14 days after treatment application. The failure was defined as presence of live lice at 2 or 14 days after treatment application. Failures at day 2 will be carried forward as failures at day 14.

There were no secondary efficacy variables in the sponsor's protocol. In this statistical review, we also examined the other three binary endpoints: (1) nits detected at day 14 (yes/no) (2) itching occurred at day 14 (yes/no) and (3) erythema occurred at day 14 (yes/no). These three endpoints can be viewed as the secondary efficacy variables.

Analysis Populations

The sponsor analyzed two data sets, the Intent to Treat (ITT) population and the Per Protocol (PP) population.

The ITT population consisted of all the 283 patients who completed informed consents and received study treatments. 283 patients were randomized into two groups, 142 with the Test Product and 141 with the Reference Product.

The PP population consisted of 228 patients, 114 in each treatment arm. A PP patient was one who satisfied: (1) inclusion/exclusion criteria, (2) received the study treatment, (3) had no study protocol violations, and (4) had been assessed for cure/failure at Day 14, or defined as a failure at Day 2. Among the 55 patients excluded from the PP population, 16 subjects were out of the visit window (10 subjects from the Test group, 6 subjects from the Reference group); 23 subjects were lost to follow-up (13 from the Test group, 10 from the Reference group); 15 subjects were excluded from the study because of protocol violation (5 from the Test group and 10 from the Reference group); and 1 subject was not included in the study (from the Reference group) because of withdraw of consent.

In the Medical Officer's review, two other data sets, namely, Medical Officer Listing 1 (PP population plus 3 patients from the Test group) and Medical Officer Listing 2 (PP population plus 5 patients from the Test group and 10 from the Reference group) were considered.

In Medical Officer Listing 1, 3 patients in the Test group (patient #136, #11 and #319) excluded by the sponsor were included in this data set. Patient #136 used Nix and baby oil on the 2nd day of the study before the return visit. Patient #11 was out of the day 14 visit window by one day according to the sponsor's protocol.[3] Patient #319 used pediculocide before the day 2 visit. These 3 patients were counted as failures and were included in Medical Officer Listing 1.

In Medical Officer Listing 2, 15 patients taking non-study pediculocide treatment during the course of study were included in this data set as failures instead of excluded as protocol

[3] In the Medical Officer's review, #11 was reported to be out of the day 2 visit window by one day.

violations by the sponsors. 5 patients were in the Test group and 10 patients were in the Reference group.

Hence, in Medical Officer Listing 1, 117 subjects were in the Test group and 114 in the Reference group. In Medical Officer Listing 2, 119 subjects were in the Test group and 124 subjects in the Reference group.[4]

The sponsor reported the results based on the ITT and PP populations. In this statistical review, we analyzed all the four data sets mentioned above: (1) ITT population, (2) PP population, (3) Medical Officer Listing 1 and (4) Medical Officer Listing 2.

Sponsor's Statistical Methods

The clinical bioequivalence of the Test Product to the Reference Product was based on the cure rates at Day 14, and was established if the 90% confidence interval for the difference in their cure rates was contained within the interval –20% to 20%. The ±20% rule with the 90% confidence interval has been used for the clinical assessment of bioequivalence for generic drugs.

Suppose p_{T_j} and p_{R_j} are the cure rates for the Test and Reference Product for center j, respectively. The standard error for $p_{T_j} - p_{R_j}$ is

$$SE_j = \sqrt{\frac{p_{T_j}(1-p_{T_j})}{n_{T_j}} + \frac{p_{R_j}(1-p_{R_j})}{n_{R_j}}} \qquad \text{(I)}$$

where n_{T_j} and n_{R_j} are the sample sizes for the Test Product and the Reference Product in center j, respectively.

The difference of the two cure rates can be estimated by

$$\theta = \frac{\sum w_j (p_{T_j} - p_{R_j})}{\sum w_j} \qquad \text{(II)}$$

Where $w_j = \frac{1}{SE_j^2}$. The standard error for θ is:

$$SE = \left[\frac{1}{\sum (1/SE_j^2)} \right]^{1/2}.$$

[4] These numbers reported here are slightly different from the numbers reported in Table I in the Medical Officer's review. However, they are consistent with the numbers reported in Table V in the Medical Officer's review.

The sponsor cited (II) from Huque and Dubey (1990). This formula requires that the standard error of the difference in cure rates at center j not equal to zero. If this was the case for center j, the sponsor proposed a modified formula for the standard error, which is:

$$\tilde{SE}_j = \sqrt{\frac{n_{Rj}-1}{n_{Rj}^3} + \frac{n_{Tj}-1}{n_{Tj}^3}} \qquad \text{(III)}$$

Then a two-sided 90% confidence interval for θ was computed as

$$\theta \pm 1.645\,\tilde{SE}.$$

Statistical reviewer's comments:

1. (II) is valid only under the condition that there is no serious treatment by center interaction. The sponsor did not check this assumption. In this statistical report, we used a logistic regression model to study the interaction between center and the treatment. Even though the parameter of interest here is the difference of the two rates, testing the homogeneity of the odds ratio and rate difference across the centers should be equivalent if we assume that the cure rates of the Reference Product for different centers are approximately the same; and this is a reasonable assumption since we know that the cure rate was above 95% for the Reference Product.

2. We recommend using the Wald's Method with Yate's continuity correction to calculate the confidence interval for the rate difference for testing bioequivalence, provided there is no serious treatment by center interaction. We do not recommend using the sponsor's suggested modified formula (III) for calculating the standard error. This formula can lead to arbitrary results, as we now argue:

Assume that n_{Tj}^C and n_{Tj}^F are the numbers of cures and failures in the Test group for center j, and similarly, n_{Rj}^C and n_{Rj}^F are the numbers of cures and failures in the Reference group for center j. Then equation (I) can be rewritten as

$$SE_j = \sqrt{\frac{n_{Tj}^C n_{Tj}^F}{n_{Tj}^3} + \frac{n_{Rj}^C n_{Rj}^F}{n_{Rj}^3}}.$$

If $SE_j=0$, there are only 4 possibilities, either (1) $n_{Tj}^C=0$ and $n_{Rj}^F=0$, or (2) $n_{Tj}^C=0$ and $n_{Rj}^C=0$, or (3) $n_{Tj}^F=0$ and $n_{Rj}^C=0$ or (4) $n_{Tj}^F=0$ and $n_{Rj}^F=0$. Let us consider (1), which is the situation in the ITT population for center 210, where there is 0 cure in a total of 2 patients in the Test Product ($n_{Tj}^C=0$) and 1 cure in a total of 1 patient in the Reference Product ($n_{Rj}^F=0$ or $n_{Rj}^C=1$) (see Table 1). Then the sponsor proposed to replace both n_{Tj}^C and n_{Rj}^F by 1, which will lead to (III). There was no

explanation in the protocol why this should be done. Why can we not keep $n_{Tj}^{C}=0$ as it was and replace n_{Rj}^{F} by a small number since n_{Rj}^{F} is zero? For example, if we assume $n_{Rj}^{F}=0.0001$ then 90% CI for the difference of two rates is –72% to 63.9%, which is outside the boundaries of bioequivalence interval while the reported result by the sponsor was -7.19% to 9.93 (see Table 3). We will have infinite results by choosing different n_{Rj}^{F} s in this situation. The same arguments can be applied to the other three cases.

Statistical Results

Sponsor's Results: Primary Endpoint

Tables 1-3 are the results reported by the sponsor. The numbers of cures and failures for each center are listed in Table 1 and Table 2 for the ITT and PP population, respectively. For the ITT patients, the sponsor used (III) to modify the SE for center 210 and the centers 202, 204, and 208 were collapsed for the analysis. For PP patients, the sponsor used (III) to modify the SE for center 214. After collapsing centers 204, 208, 210, the sponsor used (III) again to compute the SE for the combined center since the cure rate was 0% for both treatment groups. Table 3 summarized the reported results for both ITT and the PP population.

Table 1
Distribution of Cure/Failure by Study Center for the ITT Patients (from the sponsor's report)

Center Number		Permethrin Crème Rinse, 1% (N=142)	Nix® Crème Rinse (1%) (N=141)
201	Cure	5	5
	Failure	3	1
202	Cure	1	0
	Failure	0	0
203	Cure	3	5
	Failure	5	5
204	Cure	0	1
	Failure	1	0
205	Cure	9	8
	Failure	0	1
207	Cure	4	7
	Failure	2	0
208	Cure	0	0
	Failure	0	1
209	Cure	1	1
	Failure	2	1
210	Cure	0	1
	Failure	2	0
211	Cure	17	16

	Failure	5	5
212	Cure	28	27
	Failure	12	13
213	Cure	22	17
	Failure	8	14
214	Cure	11	11
	Failure	1	1

Table 2
Distribution of Cure/Failure by Study Center for PP Patients (from the sponsor's report)

Center Number		Permethrin Crème Rinse, 1% (N=142)	Nix® Crème Rinse (1%) (N=141)
201	Cure	2	3
	Failure	1	1
202	Cure	0	0
	Failure	0	0
203	Cure	3	4
	Failure	5	4
204	Cure	0	0
	Failure	1	0
205	Cure	7	5
	Failure	0	1
207	Cure	3	5
	Failure	2	0
208	Cure	0	0
	Failure	0	0
209	Cure	0	1
	Failure	1	1
210	Cure	0	0
	Failure	2	0
211	Cure	12	9
	Failure	3	3
212	Success	26	26
	Failure	11	13
213	Success	18	15
	Failure	6	13
214	Success	11	9
	Failure	0	0

Table 3
Bioequivalence for the ITT and PP Patients (from the sponsor's report)

Population		Permethrin Crème Rinse (N=142)	Nix® Crème Rinse (1%) (N=141)	90% CI of Bioequivalence
ITT	Cure	101	99	-7.19% to 7.93%
	Failure	41	42	
PP	Cure	82	77	-5.93% to 11.65%
	Failure	32	37	

We verified these results and our calculation (based on their method) agrees with the sponsor's.

Statistical Reviewer's Results: Primary Endpoint

We used SAS PROC LOGISTIC to test the treatment effect, center effect and the treatment-center interaction effect using the PP population (the same analyses can be performed with other data sets). Three models were considered: (1) a logistic model with only treatment included, (2) a logistic model with treatment and center included, and (3) a logistic model with treatment, center and the treatment-center interaction included. There was not enough evidence to show the treatment effect (from all three models), which was consistent with the sponsor's result. There was also not enough evidence to show the center effect (from model (2) and (3)) and the treatment by center interaction effect. We decided to pool the data over centers for assessing the cure rates.

Let p_T and p_R be the rates for the Test and Reference Product, respectively, then a 90% confidence interval for $p_T - p_R$ can be used to test the hypothesis

H_0: $p_T - p_R \leq -.20$ or $p_T - p_R \geq .20$

H_1: $-.20 < p_T - p_R < .20$.

Let n_T and n_R be the sample sizes for the Test and Reference Product respectively, and

$$SE=\sqrt{\frac{p_T(1-p_T)}{n_T}+\frac{p_R(1-p_R)}{n_R}}.$$

Then using the Wald's method with Yates' correction, we have

$$L=(\hat{p}_T-\hat{p}_R) - 1.645SE - 0.5*(1/n_T + 1/n_R)$$

$$U=(\hat{p}_T-\hat{p}_R) + 1.645SE + 0.5*(1/n_T + 1/n_R)$$

We reject H_0 if $L>-.20$ and $U<.20$.

We will use the above method to compute the 90% confidence intervals in this report.

In the Medical Officer's review, the 90% Confidence Intervals for $p_T - p_R$ were reported for the PP population, Medical Officer Listings 1 and 2 [5]. These results re-summarized in Table 4 here. Using the Wald's method with Yates' correction, our calculation matches Medical Officer's results for the three populations. We also calculated the 90% CI for the ITT population and the result is listed in Table 4 also.

Table 4
90% CI for the Four Data Sets (ITT, PP, Medical Officer Listing 1 & 2)

	Test (n)	Reference (n)	90% CI
PP			
Cure	82	77	-6.49; 15.25
Failure	32	37	
Total	114	114	
Medical Officer 1			
Cure	82	77	-8.35;13.43
Failure	35	37	
Total	117	114	
Medical Officer 2			
Cure	82	77	-4.02;17.64
Failure	37	47	
Total	119	124	
ITT			
Cure	101	99	-8.7;10.52
Failure	41	42	
Total	142	141	

Since all the 90% Confidence Intervals for the four populations are within (-20%, +20%), we conclude that clinically, the two products are bioequivalent for the primary endpoint. Our findings agree with the sponsor's results.

Statistical Reviewer's Results: Secondary Endpoints

Endpoint: Nits Detected at Day 14

Populations	Nits Detected	Test Product	Reference Product	90% C.I. for Bioequivalence of Two Products
PP	No	44	45	- 14.03% to 14.31%[6]

[5] I think there was a typo in Table V in Medical Officer's review. It should be 90% instead of 95% Confidence Intervals.
[6] Missing values were not included when calculating the 90% C.I. for the difference of two rates.

	Yes	35	36	
	Missing	35	33	
	Total	114	114	
Medical Officer Listing 1	No	44	45	- 14.03 to 14.31%[6]
	Yes	35	36	
	Missing	38	33	
	Total	117	114	
Medical Officer Listing 2	No	45	46	- 13.16 to 14.75%[6]
	Yes	36	38	
	Missing	38	40	
	Total	119	124	
ITT	No	49	50	- 13.97 to 12.97%[6]
	Yes	38	38	
	Missing	55	53	
	Total	142	141	

The 90% confidence intervals based on the four populations for $p_T - p_R$ are all within (-20%, 20%) interval.

Endpoint: Itching Occurred at Day 14

Populations	Itching Occurred	Test Product	Reference Product	90% C.I. for Bioequivalence of Two Products
PP	No	59	68	- 21.71% to 2.54%[6]
	Yes	42	32	
	Missing	13	14	
	Total	114	114	
Medical Officer Listing 1	No	59	68	- 21.71 to 2.54%[6]
	Yes	42	32	
	Missing	16	14	
	Total	117	114	
Medical Officer Listing 2	No	61	74	- 21.63 to 1.90%[6]
	Yes	43	34	
	Missing	15	16	
	Total	119	124	
ITT	No	69	80	- 20.32 to 2.09%[6]
	Yes	44	34	
	Missing	29	27	
	Total	142	141	

All the four 90% confidence intervals for $p_T - p_R$ are outside the (-20%, 20%) interval.

Endpoint: Erythema Occurred at Day 14

Populations	Erythema Occurred	Test Product	Reference Product	90% C.I. for Bioequivalence of Two Products
PP	No	90	94	-12.31% to 2.53%[6]
	Yes	11	36	
	Missing	13	14	
	Total	114	114	
Medical Officer Listing 1	No	90	94	- 12.31 to 2.53%[6]
	Yes	11	6	
	Missing	16	14	
	Total	117	114	
Medical Officer Listing 2	No	92	100	- 12.31 to 2.53%[6]
	Yes	12	8	
	Missing	15	16	
	Total	119	124	
ITT	No	101	106	- 10.67 to 3.46%[6]
	Yes	12	8	
	Missing	29	27	
	Total	142	141	

All the four 90% confidence intervals for $p_T - p_R$ are within the (-20%, 20%) interval.

Summary

1. For this multi-center clinical trial, the sponsor simply assumed homogeneity of treatment effects across centers and applied a standard method (weighted average) to compute the difference of two treatment cure rates. Since the parameter of interest is the difference of two rates, the homogeneity study across centers needs to be further explored. In this review, we used a logistic regression to examine the homogeneity under the assumption that the cure rates for the Reference Product are the same across the centers.

3. We recommend using the Wald method with Yates continuity correction. We are aware that other methods are available for the study of bioequivalence if we cannot assume homogeneity in a multi-center trial. For example, Huque and Dubey (1990) proposed a method using a mixed-effect model. However, as pointed by Huque and Dubey (1990), "much work needs to be done to clearly understand the implications of the estimates and confidence intervals derived through a mixed-effects model."

4. For the primary endpoint (cure rate), our findings agreed with the sponsor's results for all the four populations considered in this statistical review.

5. For the secondary endpoints (the sponsor did not consider the secondary endpoints), Nits Detected at Day 14 and Erythema Occurred at Day 14, all the 90% confidence intervals for $p_T - p_R$ are within (-20%, 20%) interval based on the four populations considered in this review.

6. For the secondary endpoint, Itching Occurred at Day 14, all the four 90% confidence intervals for $p_T - p_R$ fall outside (-20%, 20%) interval based on the four populations considered in this review. The results are more favorable for the Reference Product.

/S/ 11/27/01

Joanne (Juan) Zhang, Ph.D.
Mathematical Statistician
Quantitative Methods & Research Staff
OB/CDER

/S/ 11/27/01

Concur: Stella Machado, Ph.D.
Director
Quantitative Methods & Research Staff
OB/CDER

cc:
Original ANDA 76-090

HFD-600	Mary M. Fanning
HFD-650	Dale P. Conner
HFD-615	Harvey A Greenberg
HFD-705	Joanne (Juan) Zhang
HFD-705	Stella G. Machado

References

Huque MF, Dubey SD, "Design and Analyses for Therapeutic Equivalence Clinical Trials with a Binary Clinical Endpoint." American Statistical Associations Proceedings of Biopharmaceutical Sections 91-98, 1990.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-090

BIOEQUIVALENCE REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-090 SPONSOR : Clay-Park Laboratories, Inc.

DRUG AND DOSAGE FORM : Permethrin Crème Rinse, 1%.

STRENGTH(S) : 1%

TYPES OF STUDIES : Clinical end point study

CLINICAL STUDY SITE(S) : [redacted]

ANALYTICAL SITE(S) :

STUDY SUMMARY : Clinical End Point Study.

DISSOLUTION :

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _NO____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Mary Fanning, MD BRANCH : II

INITIAL : /S/ DATE : 12/10/01

TEAM LEADER : Rabindra Patnaik, Ph.D. BRANCH :

INITIAL : /S/ DATE : 12/10/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 12/10/01

A1.1 Ack

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-090 APPLICANT: Clay-Park Laboratories, Inc.

DRUG PRODUCT: Permethrin Crème Rinse, 1%.

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/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-090 SPONSOR : Clay-Park Laboratories, Inc.

DRUG AND DOSAGE FORM : Permethrin Crème Rinse, 1%.

STRENGTH(S) : 1%

TYPES OF STUDIES : Clinical end point study

CLINICAL STUDY SITE(S) : ~~~~~~~~~~~~~~~~~~~~

ANALYTICAL SITE(S) :

STUDY SUMMARY : Clinical End Point Study.

DISSOLUTION :

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _NO____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Mary Fanning, MD BRANCH : II

INITIAL : /S/ DATE : 12/10/01

TEAM LEADER : Rabindra Patnaik, Ph.D. BRANCH :

INITIAL : /S/ DATE : 12/10/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ _____ DATE : 12/10/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-090

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

ANDA: 76-090

DRUG PRODUCT: Permethrin Lotion, 1%

FIRM: Clay-Park Labs, Inc.

DOSAGE FORM: Lotion

POTENCY: 1%

cGMP STATEMENT/EIR UPDATE STATUS: EER acceptable on 11/16/01

BIO STUDY: Bioequivalence review was signed off on 12/10/01.

VALIDATION:
Method validation by Northeast Regional Laboratory was completed on 09/19/01. The methods are suitable for regulatory controls.

STABILITY:
Clay-Park manufactured (on 06/08/98) a lot of Permethrin Lotion, 1%, Lot # AH963 ——— batch), which was used in the bioequivalence study. Clay-Park provided satisfactory three months accelerated stability data and full term room temperature stability data of samples packaged in marketed container/closure system 2 fl oz —— bottles with ——————— snap caps).

The stability specifications are as follows:

Test	Specification
Color (visual)	Light peach
Odor (olfaction)	———
Appearance (visual)	Creamy emulsion
Identification (STP#D4300-8)	———
pH (1 in 10) (QC-143)	4.0-5.0 (see diagram on p. 2511 on pH measurement)
Assays (STP#D4301-7)	Permathrin: ——— w/w) ———
	Methylparaben: NLT — (w/w), NLT ———
	Propylparaben: NLT — (w/w), NLT ———
	Isopropyl alcohol: — (w/w)
Related substances (STP#D4301-7)	——— NMT —
	Other individual related substances: NMT —
	Total related substances: NMT —
Microscopic view (STP#4301-6)	———
Viscosity (STP#D4301-5)	———

LABELING: Labeling Approval Summary was signed off on 07/11/01

STERILIZATION VALIDATION: (IF APPLICABLE): N/A

SIZE OF BIO Batch: ——

SIZE OF STABILITY BATCHES: Same batch as above

PROPOSED PRODUCTION BATCHES: ——

STATUS OF DRUG SUBSTANCES: Type II DMF is adequate as of 12/13/01

Review Chemist: /S/ **DATE:** December 13, 2001
Shing H. Liu, Ph.D.

Team Leader: /S/ **DATE:** 12/15/01
James Fan

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-090

CORRESPONDENCE

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

September 6, 2001

NDA ORIG AMENDMENT
N/AA

Timothy Ames, Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

INFORMATIONAL AMENDMENT

Re: ANDA # 76-090 Permethrin Lotion, 1%

Dear Mr. Ames:

Pursuant 21 CFR 314.60 (a), Clay-Park Labs, Inc. hereby submits an Informational Amendment to ANDA # 76-090 for Permethrin Lotion, 1% to up date the ANDA file, regarding our retest policy for inactive ingredients.

As described on page 1683 (Attachment 1) in Section VIII (3) of the original ANDA, Clay-Park Labs, Inc., previously had a three (3) year retest policy for inactive ingredients. We received comments regarding the retest policy on pending ANDA applications from various review chemists, requesting a change in the retest policy for inactive ingredients.

We conferred with the District Office, and have revised the retest policy for inactive ingredients from three (3) years to one (1) year to meet the current Industry standards.

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director of Regulatory Affairs

Enclosure: Attachment 1
cc: Joseph Famulare
Director, Division of Manufacturing and Product Quality – HFD 320

Richard Trainor
Compliance Officer, FDA District Office

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

July 5, 2001

Timothy Ames
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

FAX AMENDMENT

RE: ANDA #76-090 Permethrin Lotion, 1%

Dear Mr. Ames:

In reference to the deficiency letter for the Chemistry, Manufacturing and Controls (CMC) section dated June 8, 2001 (**Attachment 1**) on our abbreviated new drug application for Permethrin Lotion, 1% ANDA #76-090, Clay-Park Labs, Inc. hereby submits the deficiency response for the CMC section designated as a Fax Amendment.

The deficiency response for the CMC section is being submitted by fax and a hard copy will follow.

Should you have any comments or require any further clarifications on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

Candis Edwards
Director of Regulatory Affairs

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

March 5, 2001

Elaine Hu
Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AA

ORIG AMENDMENT

RE: CORRESPONDENCE TO ANDA # 76-090 FOR PERMETHRIN LOTION, 1%

Dear Ms. Hu:

Clay-Park Labs, Inc. submitted an original Abbreviated New Drug Application (ANDA) for Permethrin Lotion, 1% in the hard copy format on December 28, 2000 and the electronic format on February 5, 2001. During the data entry in Entry Validation Application (EVA) for the electronic submission, discrepancies were noted in the hard copy of the ANDA. They have been corrected in the electronic submission document (ESD).

Clay-Park Labs, Inc. is hereby submitting the corrections to the following discrepancies to update the hard copy of ANDA for Permethrin Lotion, 1%:

OGD EVALUATION AND RESEARCH

/S/ 3-9-01

Certificate of Analysis is representative for all the five samples. The Certificate of Analysis has been revised to denote that the test was performed on individual samples and is included in **Attachment 4**.

Should you have any questions, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-090

Clay-Park Labs, Inc.
Attention: Candis Edwards
1700 Bathgate Avenue
Bronx, NY 10457

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Permethrin Lotion, 1%

DATE OF APPLICATION: December 28, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 29, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Elaine Hu
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

December 28, 2000

505(b)(2)(A) OK
/S/ 06-FEB-2001
/S/

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 29 2000
OGD

Mr. Gary Buehler, Acting Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA for Permethrin Lotion, 1%

Dear Mr. Buehler:

Clay-Park Labs, Inc. hereby submits an original abbreviated new drug application (ANDA) in hard copy format to be followed by electronic format, to seek approval to market Permethrin Lotion, 1% that is bioequivalent to the reference listed drug, Nix® Creme Rinse (1%), distributed by Warner-Lambert Consumer Healthcare pursuant to NDA # 019918.

This ANDA consists of eight (8) volumes. Clay-Park Labs, Inc. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) that contains all the information in the archival copy with the exception of the bioequivalence section (VI). A separate copy of the bioequivalence section is provided in orange folders.

Additionally, three copies of the safety data for [redacted], contained in **Section VIII (2)** is submitted along with this ANDA in red folders (See Executive Summary).

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is being sent to our local district office. This "field copy" is contained in burgundy folders.

For more detailed information on the organization of this ANDA, please refer to the "Executive Summary" attached after the Table of Contents.

Clay-Park Labs, Inc. will submit CMC ESD electronic submission (diskettes) for Permethrin Lotion, 1% as new correspondence within the 30 day grace period.

Should you have any comments or require any further clarification on this ANDA, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Thank you for your prompt handling of this submission.

Sincerely,

for Candis Edwards
Director of Regulatory Affairs