CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-049

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. **3** 2. ANDA # **65049**

3. NAME AND ADDRESS OF APPLICANT
Clay-Park Labs, Inc.
1700 Bathgate Ave
Bronx, NY 10457

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Cleocin® (Swab; Topical)
Innovator Company: Pharmacia & Upjohn (NDA #50537)
Firm states (page 0016) that there is no unexpired marketing exclusivity for Cleocin T® (Solution; Topical) or Cleocin® (Swab; Topical) under section 505 (j)(4)(D) of the Act.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Clindamycin Phosphate Topical Solution USP, 1%

7. NONPROPRIETARY NAME
Clindamycin Phosphate Pledgets, 1%

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
06/24/99	**Original**
02/04/00	**Amendment**
03/24/00	**Amendment**
5/23/00	**Amendment**

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

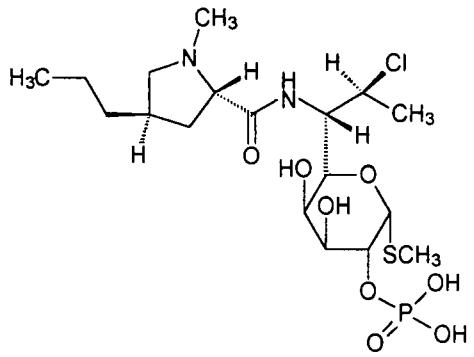
DMF number	DMF type	DMF holder	LOA(s)

13. DOSAGE FORM
Solution

14. POTENCY
1% (base); 0.01 mg/g

15. CHEMICAL NAME AND STRUCTURE

Clindamycin Phosphate. L-*threo*-α-*galacto*-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]-amino]-1-thio-, 2-(dihydrogen phosphate), (2*S*-*trans*)-. $C_{18}H_{34}ClN_2O_8PS$. 504.97. 24729-96-2. Antibacterial.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
This is the second generic product. Stiefel's Clindamycin Phosphate Swab #64-136 was approved 9/30/96.

In Amendment 3/24/00, Firm answers in order: (All Acceptable)

Q1. It is recommended that you include "Residual solvents" and "Impurities" for routine QC release testing for the active ingredient, Clindamycin Phosphate, USP.

A1. Firm commits to perform the test for "Residual solvents" and "Impurities" on one lot annually.

Q2. It is noted that in the revised Tables 1 and 3 enclosed in Attachment 3, the total in Pharmacia & Upjohn's formulation still slightly exceeds 100% [redacted]. The water content should be listed as [redacted] in both Tables.

A2. Firm includes the revised Tables 1 and 3 in Attachment 3.

Q3. The meaning of the statements on page 25 for "Retest Schedule" is not clear:

Q3a. "The next test station for active raw materials is one year from release". What is your policy regarding expiration date/retesting date? Do you use the active ingredient after expiration date as long as you perform retesting?

A3a. Firm states that their policy regarding retesting is that

date.

Q3b. You state that "Inactive raw materials are assigned a

For how long? Please clarify.

A3b. Firm states that their policy regarding retesting is that the

if available. If not available, then the data accumulated by will be used to determine the appropriate expiry period, not to exceed

Q4. Please provide stability data to justify the proposed four months holding period for the bulk solution prior to filling.

A4. (In Attachment 4) Firm provides the bulk product stability data (Lot #AJ523) tested at 5 months of storage in the bulk container. The bulk product met all specifications after 5 months of storage.

Q5. Please explain the computation of the expiration dating period for the drug product. Do you start the "zero time" at the time of introduction of the active drug substance, or at the release of the product?

A5. Firm states that the "zero time" is at the time of introduction of active drug substance, which occurs on the date of manufacture of the batch. The product is manufactured within a 24 hour period.

Q6. It is recommended that a specification for Total Related Substances/Impurities be established for the finished product.

A6. The revised specification (Attachment 6) includes the specification for Total Related Substances, which is NMT This specification was established based on the active drug substance manufacturer's specification for Total Related Substances.

Regarding the stability studies, we have the following comments:

Q7a. Specification for "Total Related Substances" is needed.

A7a. Firm includes the revised specification in Attachment 7.

Free Clindamycin: _____
Total: _____

Q7b. In the original electronic submission, we note the limit for "Free Clindamycin" is listed as _____ Data at various test stations from three month accelerated are all well below the limit (with highest reading of _____ reported at 3-month station). In the hard copy, "_____ and _____" are reported respectively at the one, two, and three months stations. Please explain the discrepancies.

A7b. Firm corrects the mistakes in the electronic submission which will be submitted separately.

Q7c. The submitted results from the accelerated and RT stability data do not justify the proposed _____' for "Free Clindamycin". Please reevaluate and propose an appropriate limit based on the analytical findings.

A7c. See answer under A7a.

Status Summary for #65-049:

DMF:	**DMF _____ acceptable**
Labeling:	**Acceptable 3/29/00**
EER:	**Acceptable 10/27/99**
Sample:	**Not requested (USP drug)**
Bio:	**Acceptable 8/12/99**

(see additional comments at #26 and in memo to file regarding physicochemical testing of pads, results of which were received with 5/23/00m amendment)(RCA)

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended

19. REVIEWER: Maria C. Shih

DATE COMPLETED: 4/17/00
5/23/00

Page(s) 10

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chem Rev 3
4/17/00

JAN 18 2000

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-049 APPLICANT: Clay-Park Labs, Inc.
DRUG PRODUCT: Clindamycin Phosphate Pledgets, 1%

The deficiencies presented below represent MAJOR deficiencies

Chemistry Deficiencies:

1. In your correspondence dated 7/26/99, you state that the revised scale-up Batch Weighing Record and Manufacturing Instructions will be submitted to the ANDA file within ten working days. We have not received such information.

2. In Table 3 (page 52), the total for Pharmacia & Upjohn's formulation exceeds 100% (before adding of clindamycin). Explain. Please also address the same concern on page 21.

3. Regarding your composition statements, we find them confusing and misleading:

   On page 0059 of the hard copy:

   a. The quantities under "mg/g" and "% w/w" should be expressed as Clindamycin Phosphate in order to be consistent with the quantities listed for the exhibit batch and proposed production batch.

   d. Under "Scale-up Batch", a footnote should be added that the listed quantity for Clindamycin Phosphate represents the corrected version using the same potency as the ANDA batch.

   e. Clindamycin Phosphate should be described as "Active Ingredient" instead of "Inactive".

   For the electronic submission:

   The quantities for Clindamycin Phosphate, USP and Purified Water, USP listed under the two batches were in disagreement. Please refer to the above comments.

4. The supplier's COA for the bulk substance (page 68) does not include an expiration date.

5. Please clarify the retesting date for all inactive ingredients.

6. Please explain the calculations on page 233. It is not clear how you obtained the potency value of _____ for clindamycin phosphate. The COA provided on page 0080 for Lot #113081 cited _____ as the value for _____ base.

7. It appears from the submitted batch records for Lot AJ523, that there is considerable time lag between manufacturing date and packaging date. When the topical solution is manufactured, how long is the holding period before it is filled and packaged? Please provide a time frame limitation and the procedure for handling and storage of the solution.

8. Please submit the revised copy of The Certificate of Analysis for AJ523 (page 0397).

9. In regard to the post-approval stability protocol, please revise to include the following:

   The first three marketable production lots of the product should be placed on stability. Yearly thereafter, one production batch should be added to the stability program.

10. We note from the submitted thermal cycling study that testing for Appearance, Color, and Microscopic Evaluation were performed, in order to determine the effects of temperature variation during the shipping and storage of this product. Please comment on the adequacy of these selected tests.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research