# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**50-819**

# CHEMISTRY REVIEW(S)

# NDA 50-819

## Acanya

(Clindamycin Phosphate and Benzoyl Peroxide) Gel
1.2% and 2.5%

## Dow Pharmaceutical Sciences, Inc.

**Rajiv Agarwal**

**Review Chemist**

**Office of New Drug Quality Assessment**
**Division of Pre-Marketing Assessment II**
**Branch III**

**CMC REVIEW OF NDA 50-819**
**For the Division of Dermatology and Dental Products (HFD-540)**

# Table of Contents

**Table of Contents** ..... 2

**CMC Review Data Sheet** ..... 4

**The Executive Summary** ..... 9

I. Recommendations ..... 9

A. Recommendation and Conclusion on Approvability ..... 9

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable ..... 9

II. Summary of CMC Assessments ..... 9

A. Description of the Drug Product(s) and Drug Substance(s) ..... 9

B. Description of How the Drug Product is Intended to be Used ..... 10

C. Basis for Approvability or Not-Approval Recommendation ..... 11

III. Administrative ..... 11

**CMC Assessment** ..... 12

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data ..... 12

S DRUG SUBSTANCE ..... 12
- S.1 General Information ..... 12
- S.2 Manufacture ..... 13
- S.3 Characterization ..... 15
- S.4 Control of Drug Substance ..... 16
- S.5 Reference Standards or Materials ..... 18
- S.6 Container Closure System ..... 18
- S.7 Stability ..... 18

P DRUG PRODUCT ..... 19
- P.1 Description and Composition of the Drug Product ..... 19
- P.2 Pharmaceutical Development ..... 21
- P.3 Manufacture ..... 27
- P.4 Control of Excipients ..... 36
- P.5 Control of Drug Product ..... 37
- P.6 Reference Standards or Materials ..... 53
- P.7 Container Closure System ..... 53
- P.8 Stability ..... 54

A APPENDICES ..... 61
- A.1 Facilities and Equipment (biotech only) ..... 61
- A.2 Adventitious Agents Safety Evaluation ..... 61
- A.3 Novel Excipients ..... 61

R REGIONAL INFORMATION ..... 61

R1 Executed Batch Records ....61
R2 Comparability Protocols ....61
R3 Methods Validation Package ....62

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 ....62

A. Labeling & Package Insert ....62

B. Environmental Assessment Or Claim Of Categorical Exclusion ....67

III. List Of Deficiencies to be Communicated ....68

# CMC Review Data Sheet

1. NDA 50-819

2. REVIEW #: 1

3. REVIEW DATE: 01-OCT-2008

4. REVIEWER: Rajiv Agarwal

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 21-DEC-2007 |
| Amendment | 09-APR-2008 |
| Amendment | 07-MAY-2008 |
| Amendment | 19-JUN-2008 |
| Amendment | 23-JUL-2008 |
| Amendment | 18-AUG-2008 |
| Amendment | 03-SEP-2008 |
| Amendment | 15-SEP-2008 |
| Amendment | 29-SEP-2008 |

7. NAME & ADDRESS OF APPLICANT:

Name: Dow Pharmaceutical Sciences, Inc.
Address: 1330 Redwood Way, Petaluma, CA 94954-7121
Representative: Barry M. Calvarese
Telephone: 707-793-2600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Acanya
Non-Proprietary Name: 1.2% clindamycin Phosphate, 2.5% benzoyl peroxide
b) Code Name/# (ONDQA only): IDP-110 Gel
c) Chem. Type/Submission Priority (ONDQA only):

CMC Review Data Sheet

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Acne vulgaris

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 1.2% Clindamycin Phosphate*, 2.5% Benzoyl Peroxide (* 1.0% clindamycin)

13. ROUTE OF ADMINISTRATION: Topical

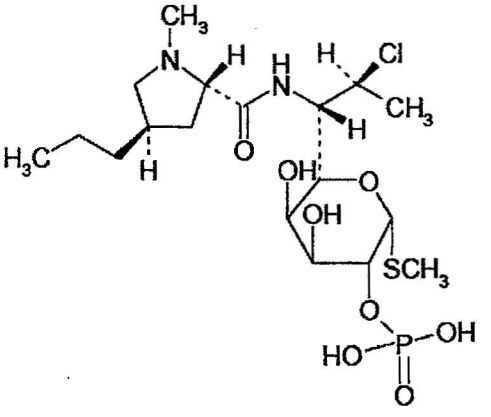
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

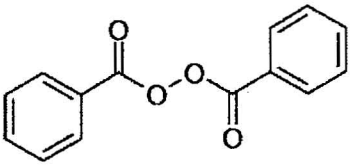
1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Clindamycin Phosphate, USP:** Methyl-7-chloro-6, 7, 8-triddeoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside-2-(dihydrogen phosphate)



**Molecular Formula:** $C_{18}H_{34}ClN_2O_8PS$
**Molecular weight:** 504.97

**Benzoyl Peroxide:** Dibenzoyl peroxide



**Molecular Formula:** $C_{14}H_{10}O_4$
**Molecular weight:** 242.23

## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 3 | Adequate | 02-NOV-2007 | |
| | II | | | 1 | Adequate | 18-JUN-2008 | Rajiv Agarwal NDA 50-819 |
| | II | | | 3 | Adequate | 13-MAR-2008 | by Benjamin Lim |
| | III | | | 3 | Adequate | 16-JUL-2004 | |
| | | | | 1 | Adequate | 24-JUN-2008 | |

b(4)

CMC Review Data Sheet

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | reviewer on 24-JUN-2008. |
| | III | | | 3 | Adequate | 7-JAN-2004 | |
| | III | | | 3 | Adequate | 11-JUL-2003 | |
| | III | | | 3 | Adequate | 17-MAR-1992 | |
| | III | | | 1 | Adequate | 18-JUN-2008 | Rajiv Agarwal for NDA 50-819 |

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

## B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| IND | 41,733 | Original IND |
| Guidance Meeting | 41,733 | 07-MAR-2005 |
| EOF-2 | 41,733 | 18-SEP-2006 |
| EOF-2 | 41,733 | 27-OCT-2007 |

CMC Review Data Sheet

| | | |
|---|---|---|
| Pre-NDA | 41,733 | 27-NOV-2007 |
| 74-Day letter | 50-819 | 05-MAR-2008 |

## 18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | Acceptable | 15-APR-2008 | Office of Compliance |
| Methods Validation | N/A, according to the current ONDQA policy | | |
| DMEPA | Adequate | 26-SEP-2008 | Andrew Haffer |
| Pharm/Tox | Adequate | 25-SEP-2008 | Jiaqin Yao |
| EA | Categorical exclusion granted | 28-JUL-2008 | Rajiv Agarwal |

# The CMC Review for NDA 50-819

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for "Approval".

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

## II. Summary of CMC Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

b(4)

**(1) Drug Substance:** One of the two active drug substance is Clindamycin Phosphate, USP, which is available as a white to off-white crystalline powder. [redacted] manufacturers this drug substance. The Chemistry, Manufacturing, and Controls information pertinent to this drug substance, sourced from the two suppliers is provided in DMFs [redacted], respectively, and deemed adequate.

The other drug substance is Benzoyl Peroxide, which is available in a white crystalline form. This [redacted] drug substance melts at [redacted] benzoyl peroxide [redacted]. The [redacted] form of benzoyl peroxide ([redacted] benzoyl peroxide, USP) is used in the formulation. The Chemistry, Manufacturing, and Controls information pertinent to this drug substance, sourced from the [redacted], is provided in DMF [redacted] and deemed adequate.

b(4)

The manufacturing sites for both drug substances have been recommended as ACCEPTABLE based on profile (15-APR-2008).

**(2) Drug Product**: The drug product, a topical gel, is packaged in two different configurations, depending on whether it is the presentation for commercial distribution or the physician samples.

Executive Summary Section

b(4)

**Commercial Drug Product:** For commercial use, IDP-11- Gel comes as a kit consisting of two separate component products, clindamycin phosphate and benzoyl peroxide . The clindamycin phosphate % is provided as a 10 gram . The benzoyl peroxide is provided as a forty gram . At the time of dispensing the clindamycin phosphate is added to the jar containing benzoyl peroxide and is admixed by a pharmacist using a spatula that is provided as a part of the kit. Both drug product components contain propylene glycol used for different purposes. In clinamycin phosphate solution, , in benzyl peroxide gel, of benzoyl peroxide.

b(4)

An 18-month of expiration dating period is granted for trade components (clindamycin phosphate solution. % and benzoyl peroxide gel, ). For trade admixed drug product, **2 month** of expiration dating -25$^0$C ( -77$^0$F) (post mixing and post dispensed) is granted.

b(4)

The admixed gel was used at each clinical trial site. To show the equivalency of the physically *vs* mechanically mixed gel, the applicant was asked to conduct an in vitro release study of clindamycin and benzoyl peroxide from the admixed and premixed topical gel. It is demonstrated that clindamycin phosphate and benzoyl peroxide release rates from both admixed and pre-mixed gels were statistically equivalent.

## B. Description of How the Drug Product is Intended to be Used

The drug product is to be used as directed by the physician. When applying the drug product, use a size amount of the drug product and apply onto 6 areas (chin, left cheek, right cheek, nose, left forehead, right forehead) on the face.

- An 18-month of expiration dating period is granted for components (clindamycin phosphate and benzoyl peroxide ).
- For admixed sample, 2 month of expiration dating period -25$^0$C ( – 77$^0$F) (post mixing and post dispensed) is granted.

b(4)

b(4)

- The storage condition for the drug product components is "Store at 25$^0$C ( - 77$^0$F)".
- The storage condition for the admixed and premixed drug products is "Store at -25$^0$C ( - 77$^0$F)" for 2 months and 3 months, respectively.

b(4)

### C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the shelf life. On 15-APR-2008, the Office of Compliance has issued an "Acceptable" overall recommendation for all the facilities involved (**Attachment-1**). Labels have required information.

- Satisfactory responses to the CMC requests from 74 day letter/Information requests dated 24-APR-2008 and 9-JUN-2008 were received on 7-MAY-2008, 19-JUN-2008, 23-JUL-2008, 18-AUG-2008, 3-SEP-2008 and 15-SEP-2008.

- The DMEPA found the proposed trade name "ACNAYA" Acceptable on 26-SEP-2008.

## III. Administrative

### A. Reviewer's Signature:

*(See appended electronic signature page)*

Rajiv Agarwal

### B. Endorsement Block:

*(See appended electronic signature page)*

Moo-Jhong Rhee, Branch Chief, Branch III, ONDQA

### C. CC Block: entered electronically in DFS

68 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry-* 1

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Rajiv Agarwal
10/3/2008 11:52:40 AM
CHEMIST

Moo-Jhong Rhee
10/3/2008 11:53:48 AM
CHEMIST
Chief, Branch III