CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-741

CHEMISTRY REVIEW(S)

AUG 23 2000

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-741 **CHEM.REVIEW #**: 2 **REVIEW DATE**: 23-Aug-00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	03-May-96	14-May-96	Chemist Rev #1
Amendment BC	19-Jun-96	20-Jun-96	Chemist Rev #1
Amendment BZ	27-Aug-96	30-Aug-96	Chemist Rev #1
Resubmission	03-Mar-00	06-Mar-00	28-Mar-00
Amendment/BC	13-Apr-00	14-Apr-00	28-Apr-00
Amendment/BC	02-May-00	04-May-00	09-May-00
Amendment/BC	14-Jul-00	17-Jul-00	24-Jul-00
Amendment/BC	08-Aug-00	10-Aug-00	16-Aug-00

NAME & ADDRESS OF APPLICANT:

Stiefel Laboratories, Inc.
255 Alhambra Circle, Suite 1000
Coral Gables, Florida 33134
ATTN: Mary Jane Carr
Senior Manager, Regulatory Affairs
Telephone No. (518) 239-6901
Fax No. (518) 239-6341

DRUG PRODUCT NAME

Proprietary: Clindoxyl™ Gel
Nonproprietary/USAN: Clindamycin phosphate
Benzoyl peroxide

Code Names/#'s:
Chemical Type/ Clindamycin phosphate: antibiotic
Benzoyl peroxide: keratolytic agent

Therapeutic Classes: 4s

ANDA Suitability Petition/DESI/Patent Status: Not Applicable

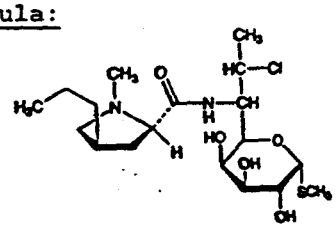
PHARMACOLOGICAL CATEGORY/INDICATION: Acne vulgaris
DOSAGE FORM: Gel
STRENGTHS: 1% clindamycin phosphate
5% benzoyl peroxide
ROUTE OF ADMINISTRATION: Topical
DISPENSED: X Rx ____ OTC

CHEMICAL NAME:
Clindamycin phosphate: (2S-trans)-Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-dihydrogen phosphate
Benzoyl Peroxide: Dibenzoyl peroxide

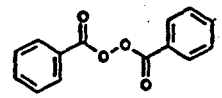
Molecular Weight: 504.97, clindamycin phosphate
242.23, benzoyl peroxide

Molecular Formula: $C_{18}H_{34}ClN_2O_8PS$, clindamycin phosphate
$C_{14}H_{10}O_4$, anhydrous benzoyl peroxide

Structural Formula:



Clindamycin phosphate



benzoyl peroxide

SUPPORTING DOCUMENTS:

- — / — , — Manufacture of the drug substance, clindamycin phosphate .
- — / — — manufacture of clindamycin phosphate.
- —
- 5/14/97 Deficiency letter from Agency to Stiefel Laboratories.
- 3/9/98 Information Amendment Letter from Steifel Laboratories to Agency.
- NDA 50-741/000, the original NDA with associated data/information on Clindoxyl Gel.
- 4/27/00 Agency Informational Request Letter.

REMARKS/COMMENTS:

Clindoxyl Gel is a combination drug product containing 1% clindamycin phosphate, USP, and 5% benzoyl peroxide, USP, for the treatment of Acne vulgaris. The original NDA 50-741 was submitted on 5/14/96. However, the initial CMC review conducted on 4/17/97 was recommended as Not Approvable from a CMC perspective. The formal Agency Not Approvable Letter issued on 5/14/97. The major concern in that CMC review was an Application Integrity Policy (AIP) problem with —— , the manufacturer of clindamycin phosphate, USP, who was found not to be in compliance with GMPs. The applicant, Stiefel Laboratories, approached the FDA claiming no knowledge of —— regulatory status. Stiefel added they were beginning Phase III pivotal trial clinicals and requested the use of clindamycin phosphate from a new supplier, e.g. —— and later, —— The Agency agreed to Stiefel's use of a new source of drug substance but only if the applicant acknowledged their Clindoxyl Gel might not have sufficient stability data and their clinicals could be at risk. Both parties agreed to the arrangement.

In addition to the major AIP concern, three other major deficiencies were noted and are listed below. Both the AIP concern and three other deficiencies were addressed in the 3/3/00 resubmission. Therefore Chemistry Review #2 is a review of the applicant's replies to the following four deficiencies:

Reply to Deficiency #1: — and later — were selected by the applicant to replace — as the new suppliers for clindamycin phosphate. Inspection of both — and — manufacturing sites were found acceptable. All pivotal trial clinicals were conducted with formulations manufactured with the — material. However, no comparative studies such as physical/chemical, specifications, impurity profiles or stability studies were conducted with the — and — clindamycin phosphates to indicate comparability. The sponsor's response to Deficiency #1 remains unacceptable.

Reply to Deficiency #2: A review of all submitted stability data indicated an acceptable 18 month expiration date could be granted the Clindoxyl Gel Batches manufactured with only — clindamycin phosphate. However. insufficient stability data in the proper packaging indicated the — clindamycin phosphate formulations continued to remain unacceptable.

Reply to Deficiency #3: No specification limits were originally submitted for — identified when clindamycin phosphate and benzoyl peroxide was mixed. However, the — were identified as two clindamycin — — Deficiency #3 was corrected in this resubmission and found acceptable.

Reply to Deficiency #4: The chemical degradative pathway was requested when clindamycin phosphate and benzoyl peroxide are combined. The degradative pathway and synthetic impurity pathway were both submitted and found acceptable.

Labeling Comments:
Two labeling recommendations are provided. The first is to highlight the storage phrase "To the pharmacist:" in order to avoid confusion in storage conditions for patients. Secondly, to provide for comparable prominences for both the established name as with the proprietary name. As stated in 21 CFR 201.10(f)(2), "The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, . . ."

CONCLUSIONS & RECOMMENDATIONS:

The resubmitted NDA 50-741/000 is Not Recommended for Approval for Clindoxyl Gel from a CMC perspective. Although —— clindamycin phosphate was acceptable, review of the —— clindamycin phosphate was not acceptable.

Two labeling changes are recommended.

/S/ 8/23/00

James D. Vidra, Ph.D.
Review Chemist

Attachment

cc: Original NDA 50-741
HFD-540/Division File
HFD-540/DivDir/Wilkin
HFD-540/ProjMan/Cintron
HFD-540/MedOff/Freidlin
HFD-540/PharmTox/Mainigi
HFD-540/BioPharm/Bashaw
HFD-540/Chem/Vidra
HFD-540/ChemTL/DeCamp JD 8/23/00
HFD-830/DivDir/Chen

filename: N50741.RS

9/5/00

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

7 pages

MAY 9 1997

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-741 CHEM.REVIEW #: 1 REVIEW DATE: 04-17-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	5-14-96	5-15-97	9-29-96
AMENDMENT/BC	6-19-96	6-20-96	
AMENDMENT/BZ	6-24-96	6-24-96	
AMENDMENT/BZ	8-27-96	8-30-96	
AMENDMENT/BZ	2-25-97	2-25-97	

NAME & ADDRESS OF APPLICANT: Stiefel Laboratories, Inc.
255 Alhambra Circle, Site 1000
Coral Gables, FL 33134
Tel: (518)239-6901

DRUG PRODUCT NAME
Proprietary: Clindoxyl Gel

Nonproprietary/USAN: Clindamycin Phosphate & Benzoyl Peroxide

Code Names/#'s:
Chemical Type/
Therapeutic Class: 4 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Antibacterial/Topical
treatment of acne vulgaris

DOSAGE FORM: Gel
STRENGTHS: 1% & 5%
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
USP
Clindamycin Phosphate, methyl 7-chloro-6,7,8-trideoxy-6-[(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-*alpha*-*D*-*galacto*-octo-pyranoside 2-(dihydrogen phosphate)

$C_{18}H_{34}ClN\,O_8PS$ Mol.weight:504.97
CAS# [24729-96-2]

Benzoyl Peroxide, Dibenzyl Peroxide

$C_{14}H_{10}O_4$ Mol.weight: 242.23
CAS# [94-36-0]

PATENT STATUS:

5,466,446 November 14, 1995; with expiration date of February 16, 2014. The subject patent is a composition and a method of use patent.

SUPPORTING DOCUMENTS:

DMF

[redacted]

[redacted] letter of authorization is signed by [redacted] on August 31, 1993. The referenced AADA was withdrawn by [redacted] due to the Application Integrity Policy (API) on November 15, 1996. The following AADAs have also been impacted by API action:

IND [redacted]

IND [redacted]

IND [redacted]

NDA 50-681 Targocid (Teicoplanin) Injection, Hoechst Marion-NA
NDA 50-669 Clindamycin Phosphate Topical Powder, Paddock Labs Inc.
This NDA has been officially changed to NDA 50-741.

AMENDMENTS:
Dated: June 19, 1996, Antimicrobial Preservative Effectiveness
Received: June 20, 1996.

Dated: June 24, 1996, Readiness for inspection
Received: June 24, 1996.

Dated: August 27, 1996, Response to incomplete EA
Received: August 30, 1996.

Dated: February 25, 1997, Applicant's response to 483
Received: February 25, 1997.

CONSULTS:

Environmental Assessment consult for Clindoxyl Gel is deferred based on AIP action and identification of new supplier for clindamycin phosphate which will impact on the review of EA. Trade name consult was sent to Nomniclature and Labeling Committee on April 10, 1997 (Appendix A).

REMARKS/COMMENTS:

The subject of this application is Clindoxyl which was first submitted as ——— . However, the NDA number was officially changed to NDA 50-741. The application was filed on July 13, 1996. The response to CMC deficiencies found at the time of fileability of the NDA was received on June 24, 1996.

Clindoxyl Gel gel is a combination product which contains 1% clindamycin phosphate, USP, and 5% benzoyl peroxide, USP, (BPO). The synthesis of the two active ingredients are not a major concern because both ingredients are compendial items, and have been approved and used as individual drugs for treatment of acne vulgaris for several years. However, the major issue is the Application Integrity Policy (AIP) problem with ——— (cross-referenced ———), the supplier of Clindamycin Phosphate USP. The Reference AADA was withdrawn by ——— on November 15, 1996.

On December 12, 1996, a letter signed by Dr. Woodcock, Center Director, was sent to ——— ——— notifying them of the suspension/audit action. The applicant was informed about the ——— situation that the agency cannot accept their reliance on the ——— AADA ——— see letter of February 28, 1997. Stiefel was also advised to provide a new supplier for clindamycin phosphate.

It should be noted that all manufacturing, testing, stability and packaging for this product as well as raw materials testing and release is performed by Stiefel Laboratories Inc. A recent audit for quality review of clindamycin phosphate supplied by ——— facility (used in the clinical batches) was completed by Nancy Saxenian, BUF-DO Inspector, on February 7-19, 1997. At the conclusion of this inspection at Stiefel, a 483 was issued with one only observation specific to an incorrect moisture calculation which does not impact the quality of clindamycin (Appendix B). The inspector has also indicated that "Batch records reviewed cover raw material lots #B0048R, B0056R, B0294R, &B0147R." However, the review of the NDA indicates that the clindamycin phosphate raw materials batches #94192 & 91779

used in the formulation of clinical batches #210404 & 280308 have not been evaluated in this inspection. This observation was confirmed during a telephone conversation with Randy Hayward and Mary Jean Praver, Regulatory Affairs at Stiefel (see MEMORANDUM OF TELEPHONE CONVERSATION dated April 8, 1997).

The applicant responded to the 483 observation on February 25, 1997 (Appendix C). The firm's response, copies of corrected Certificate of Analysis, was supplied to the inspector prior to the conclusion of the audit. Per amendment of February 25, 1997, Stiefel has noted "significant data (tox, clinical, stability) submitted to FDA was developed with Clindamycin produced at - a facility that was apparently satisfactory." This statement was very confusing because the facility was not identified in the original NDA. Per MEMORANDUM OF TELEPHONE CONVERSATION dated April 8, 1997, it appears that the BUF-DO inspection of Februry 97, only focused on the quality of recent (1995) lots of clindamycin manufactured at the switched facility of facility with GMP problems. The clindamycin phosphate (lots 94192 & 91779) used in the clinical batches was produced at facility on 1991 & 1994, respectively. Appraently, facility has been found satisfactory from GMP standpoint during the last inspection. The status of facility and the quality of clinical trials needs to be reconfirmed.

In conclusion, the testing results of clindamycin phosphate made by does not confirm the quality of the product used in the clinical batches. The reliability of data submitted for clindamycin phosphate is in question. The applicant is now seeking for a new supplier. A pilot batch of Clindoxyl Gel using clindamycin phosphate produced by an is undertaken to conducts confirmatory QC lot release, stability and bioequvalency testing. The applicant should provide a comparison of stability data and bioequivalency data for the new and old manufacturing batches used in the production of Clindoxyl Gel.

A copy of recommendation to withhold approval from Office of Compliance, EIR FD-483, based on (OAI Alert) was issued by M. Egas, on December 18, 1996, and was received on March 26, 1997 (Appendix B). Stiefel's response to the FD 483 is attached (Appendix C). In addition, a copy of all correspondence regarding resolving the AIP issues is also included (Appendix B).

In addition, due to the potential instability of clindamycin in the presence of benzoyl peroxide, the regulatory specifications should include limits for all known degradation

products for the finished product. This should be both a release and a stability specification. The applicant should be advised to submit the chemical degradation pathway for degradation products of Clindoxyl Gel.

Method validation packages were sent to BUF-DO on April 17, 1997 (Appendix D). The report will be reviewed when is found acceptable by our laboratory.

CONCLUSIONS:

This application is NOT APPROVABLE from a manufacturing and control standpoint and GMP compliance. The major manufacturing and control concerns are the Application Integrity Policy (AIP) problem with ——— , the supplier of Clindamycin Phosphate USP, stability data from the new supplier ——— , as well as ——— , for the Clindoxyl Gel.

Deficiencies are outlined in the Review Notes and the Draft Letter to the applicant. The CSO is to convey these deficiencies to the applicant.

/S/

Nahid Mokhtari-Rejali, Ph.D.
Review Chemist

cc: Orig. NDA 50-741
HFD-540/
HFD-540/Division File
HFD-540/Mokhtari-Rejali/5/5/97
HFD-540/Fornaro
HFD-540/Wilkin
HFD-540/White
HFD-540/WHDeCamp
R/D Init by: SUPERVISOR WD 5/9/97
filename:
NDA50741.rv1

GJO 5/12/97

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

22 pages

NDA 50-741

Duac (clindamycin phosphate, 1% and benzoyl peroxide, 5%) Gel,

Stiefel Laboratories, Inc.

James D. Vidra, Ph.D.
Division of Dermatological and Dental Drug Products
HFD-540

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 50-741

2. REVIEW #: 3

3. REVIEW DATE: 20-Aug-2002

4. REVIEWER: James D. Vidra, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA 50-741.000	03-May-1996
Amendment BC	19-Jun-1996
Amendment BZ	27-Jun-1996
Amendment AZ	03-Mar-2000
Amendment BC	13-Apr-2000
Amendment BC	02-May-2000
Amendment BC	14 Jul-2000
Amendment BC	08-Aug-2000
Amendment BZ	11-May-2001
Amendment BZ	29-May-2001
Amendment BZ	06-Nov-2001

7. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment AZ	22-Feb-2002
Telephone Amendment BZ	15-Mar-02
Amedment BL	10-Jul-02

7. NAME & ADDRESS OF APPLICANT:

Name: Stiefel Laboratories, Inc.

Address: Oak Hill, New York 12460

Representative: William A. Carr, Jr.
Vice President

Telephone: (518) 239-6901

Fax:: (518) 239-6341

8. DRUG PRODUCT NAME/CODE/TYPE:

a) **Proprietary Name:** Duac Gel

b) **Non-Proprietary Name (USAN):** Clindamycin Phosphate
Benzoyl Peroxide

c) **Code Name/# (ONDC only):** N/A

d) **Chem. Type/Submission Priority (ONDC only):**

- **Chem. Type:** Clindamycin Phosphate, antibiotic
  Benzoyl Peroxide, keratolytic agent
- **Submission Priority:** 4S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Acne vulgaris

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 1% Clindamycin phosphate
5% Benzoyl peroxide

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

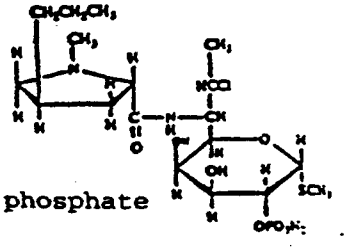
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Clindamycin Phosphate: (2S-trans)-methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-dihydrogen phosphate.
Benzoyl Peroxide: Dibenzoyl peroxide.

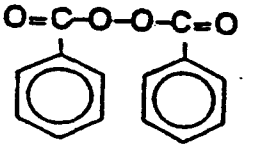
Molecular Weight: 504.97, Clindamycin Phosphate
242.23, Benzoyl Peroxide

Molecular Formula: $C_{18}H_{34}ClN_2O_8PS$, Clindamycin Phosphate
$C_{14}H_{10}O_4$, Benzoyl Peroxide

Molecular Structure:



Clindamycin phosphate



benzoyl peroxide

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	Adequate	7/17/00	DMF decommissioned on May 1998.
[redacted]	II	[redacted]	[redacted]	3	Adequate	8/16/01	Continued to be Adequate.

[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
Approved New Drug Application	NDA 50-774.000, AP on 11/8/00	BenzaClin Pak
Type II, Drug Master File	[redacted]	[redacted]; Clindamycin Phosphate

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	19-Aug-2002	J.D. Ambrogio
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	N//A		
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-415

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
NDA 50-741 is Recommended for Approval from a chemistry review perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
No Phase 4 commitments.

II. Summary of Chemistry Assessments

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

The USAN names for the two drug substances formulated in Duac Gel are clindamycin phosphate (CAS #24729-96-2) and benzoyl peroxide (CAS #94-36-0). Both are USP grade with the Duac Gel having concentrations of 1% clindamycin and 5% benzoyl peroxide. Clindamycin is a white to off-white crystalline powder whereas the hydrous benzoyl peroxide generally contains about 26% water for the purpose of reducing flammability and shock sensitivity. *Hydrous Benzoyl Peroxide may explode at temperatures higher than 60°C or cause fires in the presence of reducing agents.* Numerous process impurities exist for either drug substance; for example benzoyl peroxide contains — Benzoyl peroxide is manufactured by the —

Clindamycin phosphate's process impurities consist of — etc. The manufacturing process and details of the — clindamycin phosphate are further described in —. All related substances are controlled in both sets of specifications.

This applicant has identified and solicited numerous drug substance suppliers during the review of this application. The clindamycin phosphate manufacturer is now —. The current supplier of benzoyl peroxide is — currently under consideration as an alternate benzoyl peroxide supplier. In addition, there have been two chemistry reviewers conducting these three reviews. In summary, the drug substance manufacturers for this applicant have had numerous deficiencies resulting in two Non-Approvals.

(2) Drug Product:

Duac Gel is a combination drug product containing 1% clindamycin phosphate, USP, and 5% benzoyl peroxide, USP, for the treatment of acne vulgaris. The excipients in Duac Gel conform to USP, NF or INCI (International Nomenclature cosmetic Ingredient). Certificates of Analysis for all compendial and non-compendial excipients were provided with specifications and test methods added for the non-compendial excipients.

The manufacturing process is a two-step process utilizing an intermediate AIO (All-In-One) gel. This AIO gel consists of benzoyl peroxide at a low concentration. The clindamycin phosphate aqueous solution is added to the AIO and mixed to yield finished drug product. An Method that complied with the USP assay was used to differentiate between clindamycin phosphate and its related substances.

Duac Gel was packaged in a [redacted] The tube is [redacted] The dispensing tip is white [redacted]

When the new [redacted] clindamycin phosphate was formulated into Duac Gel, the gel was stable for 24 months at 6°C in [redacted] batches ([redacted]). A successful comparison study of the [redacted] clindamycin phosphate compared impurity profiles, physical properties and compendial chemistry specifications indicated equivalence to the original [redacted] clindamycin phosphate. Successful three month accelerated stability studies were conducted at 25°C/60%RH.

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

Clindamycin and benzoyl peroxide components have been shown to have *in vitro* activity against *Propionibacterium acnes,* an organism associated with acne vulgaris, however, the clinical significance of these results is not known. The mechanism of action of clindamycin indicates that it binds to the 50S ribosomal subunits of susceptible bacteria to prevent the elongation of peptide chains by interfering with peptidyl transfer, thus suppressing protein synthesis. Benzoyl peroxide is a potent oxidizing agent. Duac Gel is applied once daily to the affected area.

C. Basis for Approvability or Not-Approval Recommendation

The basis for the Approval recommendation is for the acceptable comparative studies submitted indicate that the [redacted] and [redacted] clindamycin phosphates are equivalent. In addition, that Duac Gel manufactured with [redacted] clindamycin phosphate is stable at 6°C for 24 months. In addition, Establishment Evaluation Request (EER) inspections were conducted on four domestic facilities with an overall recommendation of Acceptance received from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

10 pages

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

/s/

Jim Vidra
8/21/02 05:05:09 PM
CHEMIST

PDUFA Date: 8/26/02.

Wilson H. DeCamp
8/21/02 05:25:56 PM
CHEMIST
concur