CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-802

CHEMISTRY REVIEW(S)

NDA 50-802

Ziana (Clindamycin Phosphate and Tretinoin) Gel
1.2% and 0.025%

Dow Pharmaceutical Sciences

Jane L. Chang, Ph.D.

Review Chemist

Division of Dermatologic and Dental Drug Products
HFD-540

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Chemistry Review Data Sheet

1. NDA: 50-802

2. REVIEW #: 2

3. REVIEW DATE: 20-Sep-2006

4. REVIEWER: Jane L. Chang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission NDA 21-739 (changed to NDA 50-802 as of November 25, 2004)	06-Feb-2004
Amendment (SU)	20-Aug-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (C)	03-Feb-2006
Amendment (AZ)	05-May-2006
Amendment (BC)	08-Aug-2006
Amendment (BL)	11-Aug-2006
Amendment (BC)	28-Aug-2006
Amendment (BC)	31-Aug-2006
Amendment (BL)	31-Aug-2006
Amendment (BC)	06-Sep-2006
Amendment (BL)	07-Sep-2006
Amendment (BL)	14-Sep-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Dow Pharmaceutical Sciences
Address:	1330A Redwood Way Petaluma, CA 94954
Representative:	Barry M. Calvarese, MS Vice President, Regulatory and Clinical Affairs
Telephone:	707-793-2600

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ziana™
b) Non-Proprietary Name: Clindamycin Phosphate and Tretinoin (all-*trans* retinoic acid) (combination drug)
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antibiotic and Retinoid (combination drug)

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: Clindamycin Phosphate, 1.2%; Tretinoin, 0.025%

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:

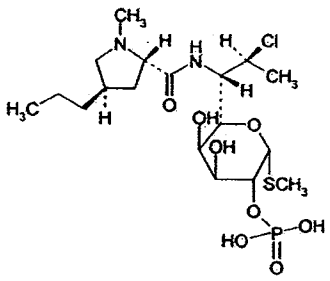
This is a combination drug product composed of two compendial drug substances, clindamycin phosphate and tretinoin (all-*trans* retinoic acid).

Clindamycin phosphate, USP

Chemical name: 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)
Molecular Formula: $C_{18}H_{34}ClN_2O_8PS$
Molecular Weight: 504.97
CAS Number: 24729-96-2

Chemistry Review Data Sheet

Chemical structure:



Tretinoin, USP

Chemical name: 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (all-*trans* form)

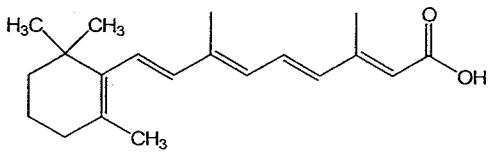
USAN name: all-*trans* retinoic acid

Molecular Formula: $C_{20}H_{28}O_2$

Molecular Weight: 300.44

CAS Number: 302-79-4

Chemical structure:



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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]					Adequate	July 26, 2006	By J. Chang.
					Adequate	July 26, 2006	By J. Chang. See below*
					Adequate	June 8, 2004	By L. Huang for [redacted] b(4)
					Adequate	July 10, 2000	By M. Shih for [redacted] See below**
					Adequate	August 23, 2006	By J. Chang

*After this DMF was reviewed, the applicant withdrew [redacted] as the [redacted] supplier in the 8/8/06 amendment.

**Two amendments (16-Jan-2001 and 05-Sep-2003) were submitted after the last review. The organization name change was the only change in the 05-Sep-2003 amendment, whereas the 16-Jan-2001 amendment included manufacturing sites and process changes. Review of these two amendments is not required as adequate information was provided in the NDA. [redacted] the supplier for the [redacted] stated that the materials complied with 21 CFR 175:300 for the [redacted] (See Attachment 4.3.9.1.2.1). [redacted] stated that the [redacted] meets the requirements of 21 CFR 177.1520(c)(2.2). These are considered sufficient to establish safety of the material of construction for liquid-based topical dosage forms (e.g., gels, creams, etc) according to the FDA "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics". Refer to section III.F.2 of the guidance.

[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	65,531	Clin-RA Gel (Clindamycin, 1%/Tretinoin, 0.025%)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	8/30/2006	J. D Ambrogio
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A, according to the current ONDQA policy*		
Office of Drug Safety	Review underway**		
EA	Categorical exclusion (see review #1)	12/7/2004	Saleh Turujman
Microbiology	N/A		

*The analytical procedures and their validations were reviewed in review #1 by Dr. Saleh Turujman and found to be adequate. Methods validation packages will not be sent to FDA laboratories because the methods do not meet the "method validation request criteria" according to the current ONDQA policy that was announced on 1/12/05.

**Recommendation from Office of Drug Safety is not yet available at the time this review is completed. From CMC perspective, labeling information is adequate.

The CMC Review for NDA 50-802

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls review perspective, this NDA may be approved.

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

None

II. Summary of Chemistry Assessments

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

(1) Drug Product

The proposed drug product, Ziana™ Gel, is a translucent yellow topical gel containing a combination of two active pharmaceutical ingredients (APIs), clindamycin phosphate, 1.2% (equivalent to 1% clindamycin) and tretinoin (all-*trans* retinoic acid) 0.025%. [redacted] Water comprises about [redacted] of the vehicle, with glycerin [redacted] the [redacted] agent is Carbopol 981 [redacted] Other than Polysorbate 80 [redacted], the remaining excipients are essentially [redacted] agents (methylparaben and propylparaben), [redacted] agents, and an [redacted]

b(4)

Each of these two APIs is also a component of several approved combination drug products. However this is the first combination of these two APIs. The current submission provides for the treatment of acne vulgaris.

Acceptable specification has been provided to ensure product quality at release. The specification includes appearance, pH, viscosity, particle size, package integrity, microbial limits, identification and assay of the active ingredients, preservatives, and antioxidant, HPLC analysis of related substances, as well as antimicrobial effectiveness test.

The drug product will be packaged in two commercial package size tubes, 30 g and 60 g, and a physician's sample container, 2 g tube.

Two years of real-time stability data have been provided for the [redacted] primary stability batches. The data showed a decrease trend for clindamycin phosphate assay and increase trends for clindamycin and lincomycin-2-phosphate assays. The data support the proposed expiration dating period of 24 months for storage at 25 °C. b(4)

(2) Drug Substance

Clindamycin phosphate and tretinoin are two well-established compendial chemicals whose structures have been fully elucidated. All CMC information for [redacted] and [redacted] has been referred to their respective DMFs: [redacted] for [redacted] and [redacted] for [redacted] b(4)

Both DMFs for clindamycin phosphate suppliers have been reviewed by this reviewer and found to be adequate. The applicant withdrew [redacted] (DMF [redacted]), as the [redacted] supplier in the 8/806 amendment. The DMF of the [redacted] supplier was last reviewed by Liang Lii Huang and found to be adequate. These DMFs are currently adequate to support this NDA. b(4)

Both clindamycin phosphate and tretinoin are individually marketed in various formulations for the treatment of acne vulgaris, as indicated below.

Clindamycin phosphate, a lincosamide, which is a synthetic derivative of lincomycin, is a compendial antibiotic API used in several approved formulations, such as an injectable solution (NDA 50-441), a topical solution (NDA 50-537), a topical lotion (NDA 50-600), several topical gels (e.g., NDAs 50-615 and 50-782) and a topical foam (NDA 50-801). Except for NDA 50-441, which is formulated equivalent to 150 mg clindamycin/mL, all the afore-mentioned dosage forms use the same strength of clindamycin phosphate (equivalent to 1.0% clindamycin) proposed by the applicant.

Tretinoin is also a compendial drug substance which is used in several approved drug formulations. Examples include several topical creams (NDAs 19-963, 21-108, 19-049, 17-522, 17-340, 20-404 at concentrations of 0.05%, 0.02%, 0.025%, 0.05%, 0.1%, and 0.025%, respectively), several topical gels (NDAs 17-955, 17-579, 20-475, and 20-400 at concentrations of 0.01%, 0.025%, 0.04%, 0.025%, respectively), a topical solution (NDA 16-921, 0.05%), and an oral capsule (NDA 20-438, 10 mg). Tretinoin, all-*trans* retinoic acid, isomerizes easily under the influence of oxygen (air), heat, and light. Some of the *cis*-isomers are biologically active, e.g. 13-*cis* retinoic acid (USAN: isotretinoin, the API in Accutane). The manufacture of tretinoin drug products requires protection of the API from air and

light during processing. Antioxidants are also generally required in the formulation of tretinoin containing products.

B. Description of How the Drug Product Is Intended to Be Used

This combination drug product is intended to be applied to the face once daily at bedtime for the treatment of acne vulgaris in patients 12 years and older. Exposure to sunlight, including sunlamps, should be minimized during the use of ZIANA™, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided.

Ziana™ Gel is to be stored at 25°C (77°F). When stored under the specified conditions, the drug product has an expiration dating period of two years. The drug product should be protected from light and freezing.

C. Basis for Approvability or Not-Approval Recommendation

The complete responses to the NA letter addressed all the CMC issues adequately to ensure the drug product's identity, strength, quality, purity, potency, and stability. All manufacturing and testing facilities were found to be acceptable by the Office of Compliance. Therefore, from a CMC standpoint, this new drug application may be approved.

III. Administrative

A. Reviewer's Signature: electronically signed in DFS

B. Endorsement Block: electronically signed in DFS

C. CC Block: entered electronically in DFS

25 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Jane Chang
9/20/2006 05:48:56 PM
CHEMIST

Moo-Jhong Rhee
9/22/2006 01:18:17 PM
CHEMIST
Chief, Branch III

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Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Dermatology and Dental Products
NDA:	50-802
Applicant:	Dow Pharmaceutical Sciences, Inc.
Stamp Date:	May 8, 2006
PDUFA Date:	November 8, 2006
Trademark:	Clin RA Gel
Established Name:	Clindamycin and Tretinoin
Dosage Form:	Gel
Route of Administration:	Topical
Indication:	Acne vulgaris
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

This NDA was resubmitted in response to the deficiencies identified in the CMC review #1. It is considered to be a complete response. However, some of the responses are inadequate and are listed in Section C.

B. Critical issues for review

See Section C.

C. Comments for 74-Day Letter

1.

b(4)

2.

3.

4.

b(4)

D. Recommendation:

This NDA is fileable from a CMC perspective. The comments for 74-day letter should be sent to the applicant.

(See attached electronic signature page)

Jane L. Chang, Ph.D.
Review Chemist

Date

(See attached electronic signature page)

Moo-Jhong Rhee, Ph.D.
Branch Chief

Date

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

/s/

Jane Chang
6/6/2006 04:02:20 PM
CHEMIST

Moo-Jhong Rhee
6/6/2006 05:19:43 PM
CHEMIST
Chief, Branch III

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On Original

NDA 50-802

Tradename (Clindamycin, 1%; Tretinoin, 0.025%) Gel

Dow Pharmaceutical Sciences

Saleh A. Turujman, Ph.D.
Division of Dermatologic and Dental Drug Products
HFD-540

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Chemistry Review Data Sheet

1. NDA: 50-802 (Original submission given NDA Number 21-739)

2. REVIEW #: 1

3. REVIEW DATE: 12/6/04

4. REVIEWER: Saleh A. Turujman, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission NDA 21-739 (Changed to NDA 50-802 as of November 25, 2004)	6 February 2004
NDA 21-739/N-001 (Changed to NDA 50-802 as of November 25, 2004)	20 August 2004

6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission NDA 21-739 (Changed to 50-802 as of November 25, 2004)	6 February, 2004
NDA 21-739/N-001 (Changed to NDA 50-802 as of November 25, 2004)	20 August 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Dow Pharmaceutical Sciences
Address:	1330A Redwood Way Petaluma, CA 94954
Representative:	Clawson C. Bowman, JD., RAC Vice President, Regulatory Affairs
Telephone:	(707) 793-2600

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Trade name to be determined (Clin-RA, the proposed trade name, not acceptable to DMETS)
   b) Non-Proprietary Name (USAN): Clindamycin Phosphate and Tretinoin (all-*trans* Retinoic Acid) (combination drug)

c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antibiotic and Retinoid (combination drug)

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: Clindamycin, 1%; Tretinoin, 0.025%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

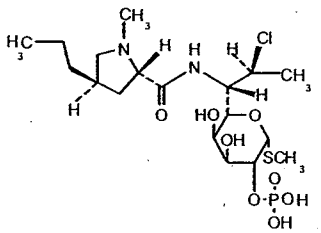
___X___Not a SPOTS product

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

This is a combination drug product composed of two compendial drug substances, clindamycin phosphate and tretinoin (all-*trans* retinoic acid).

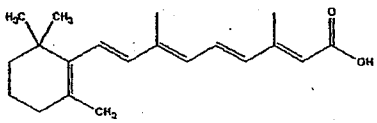
Clindamycin phosphate, USP

The chemical name is methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-4-*trans*-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate)
Molecular Formula: $C_{18}H_{34}ClN_2O_8P_8S$
Molecular Weight: 504.97
CAS Number: 24729-96-2.
The chemical structure is shown below.



Chemistry Review Data Sheet
NDA 50-802 (originally 21-739)

Tretinoin, USP
The chemical name is 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (all-trans form). The USAN name is all-*trans* retinoic acid.
Molecular Formula: $C_{20}H_{28}O_2$; Molecular Weight: 300.44
CAS Number: 302-79-4.
The chemical structure is shown below.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	DMF HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Adequate	September 8, 2003	
					Adequate	November 23, 2004	See below*
					Inadequate	March 12, 2004	
					Inadequate	August 15, 2003	
					Adequate	October 7, 2003	
					Adequate	July 10, 2000	
					Adequate	June 5, 2002	

b(4)

*** In the initial review of March 24, 2004 the OGD reviewer determined that DMF Type [redacted] number [redacted] for [redacted] the [redacted] material for the [redacted] in DMF [redacted] was inadequate. More recently, however, the ONDC reviewer found DMF [redacted] be adequate. Hence [redacted] used in DMF [redacted] was acceptable, and DMF [redacted] therefore also adequate (acceptable).**

[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)

Chemistry Review Data Sheet
NDA 50-802 (originally 21-739)

B. Other Documents:

DOCUMENT TYPE	APPLICATION NUMBER	HOLDER	DESCRIPTION
IND	65,531	Dow Pharmaceutical Sciences	Clin-RA Gel (Clindamycin, 1%/Tretinoin, 0.025%

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES* (Drug substance: [redacted] Manufacturer/Packager/Tester: [redacted]	Acceptable	3 March 2004	Janine D'Ambrogio
EES* (Drug substance: [redacted] Manufacturer/Packager/Tester: [redacted]	Acceptable	2 March 2004	Janine D'Ambrogio
EES* (Drug substance: [redacted] Manufacturer/Packager/Tester: [redacted]	Acceptable	15 April 2004	Shawnte L. Adams (Applicant initially provided the incorrect address, hence initial decision on March 4, 2004 of "withhold" and comment "facility not doing function"
EES* (Drug product: Manufacturer/Packager/Tester: [redacted]	Acceptable	5 March 2004	Janine D'Ambrogio
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Deferred	N/A	
DMETS	"Clin-RA" Gel Not acceptable	5 October 2004	Linda M. Wisniewski, R.N.
EA	Categorical Exclusion	N/A	
Microbiology	N/A	N/A	

b(4)

* See Appendix 1 for EES report

The Chemistry Review for NDA 50-802

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation for this NDA, after discussion with the Team Leader, is Approvable from a chemistry, manufacturing and controls standpoint.

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

None recommended.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

The proposed drug product is a translucent yellow topical gel containing a combination of two active pharmaceutical ingredients (APIs), clindamycin phosphate, 1.2% (equivalent to 1% clindamycin) and tretinoin (all-*trans* retinoic acid) 0.025%. [redacted] Water comprises about [redacted] of the vehicle, with glycerin [redacted] The [redacted] agent is Carbopol 981 [redacted]. Other than Polysorbate 80, a [redacted] the remaining excipients are essentially [redacted] agents (Methylparaben and Propylparaben), and [redacted] agents and an [redacted]. The drug product will be packaged in two commercial package size tubes, 30 g and 60 g, and a physician's sample container, 2 g tube. b(4)

Clindamycin phosphate and tretinoin are two well-established compendial chemicals whose structures have been fully elucidated. They are listed in USAN and in the Merck Index. The DMF of both drug substance suppliers have been previously reviewed and found to be adequate. Both clindamycin phosphate and tretinoin are individually marketed in various formulations for the treatment of acne vulgaris, as indicated below. b(4)

Clindamycin phosphate, a lincosamide, which is synthetically a derivative of lincomycin, is a compendial antibiotic API used in several approved formulations, such as a sterile solution (NDA 50-441), a topical solution (NDA 50-537), a topical lotion (NDA 50-600), several topical gels (e.g., NDA 50-615, NDA 50-782) and a [redacted] (NDA [redacted]. All the afore-mentioned dosage forms use the same strength of clindamycin phosphate (equivalent to 1.0% clindamycin) proposed by the applicant.

Tretinoin is also a compendial drug substance which is used in several approved drug formulations. Examples include several topical creams (NDA 19-963, NDA 21-108, NDA 19-049, 17-522, NDA 17-340, NDA 20-404 at concentrations of [redacted] respectively), several topical gels (NDA 17-955, NDA 17579, NDA 20-475, NDA 20-400 at concentrations of 0.01%, 0.025%, 0.04%, 0.025%), a topical solution (NDA 16-921, 0.05%), and an oral capsule (NDA 20-438, 10 mg). Tretinoin, all-*trans* retinoic acid, is the most stable of several isomers of retinoic acid, all of which isomerize easily under the influence of oxygen (air), heat, light, acid, or sonication. Some of these isomers are biologically active, e.g. 13-*cis* retinoic acid (USAN: isotretinoin, the API in Accutane). The manufacture of tretinoin drug products requires the shielding of the API from air and light during processing. Antioxidants are also generally required in the formulation of tretinoin containing products, which have to be protected from exposure to air, heat and light.

b(4)

Each of these two APIs is also a component of several approved combination drug products. However this is the first combination of these two APIs. The current submission provides for the treatment of acne vulgaris. In addition to clindamycin (gel, solution, lotion, swab), prescription topical treatments indicated for acne vulgaris include erythromycin (gel, ointment, solution, swab), azelaic acid cream, benzoyl peroxide gel, benzoyl peroxide and erythromycin gel, benzoyl peroxide and clindamycin gel, tretinoin (gel, cream, solution), adapalene (gel and cream) and tazarotene (gel and cream).

Clin-RA Gel, the proprietary name initially proposed for this drug product was found to be unacceptable by DMETS.

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

This combination drug product is proposed for the treatment of acne vulgaris in patients 12 years and older. It is intended for a once daily application. The two APIs in this drug product target a different aspect of the acne pathogenic pathway. In general, physicians recommend a twofold approach for acne treatment: application of a topical antimicrobial, such as clindamycin phosphate, in the morning, and a topical tretinoin formulation in the evening. The proposed drug product would provide for a dual-action product with once daily application. However, the recommendation for this combination drug product is "Not Approvable" because of efficacy concerns (the contribution of each component to efficacy was not adequately demonstrated; refer to the clinical review for details). The clinical reviewer expressed no safety concerns.

The applicant proposes an expiration dating period of 24 months, which is supported by 12 months of long-term stability data (25°C/60% RH) for [redacted] primary stability batches, 18 months of long-term-stability data for [redacted] primary stability batch, 12 months of stability data under intermediate conditions (30°C/60% RH), and 6 months of stability data at 40°C/75% RH. Regression analysis is also provided. Since the

recommendation for this NDA is "Not Approvable" from a clinical standpoint, the applicant should be requested to provide the available stability data for the [entire] proposed shelf life of the drug product, when this NDA is resubmitted, as indicated in Section III. "List Of Deficiencies To Be Communicated" of this review.

Review of the labeling is deferred since this application is not approved from a clinical standpoint.

C. Basis for Approvability or Not-Approval Recommendation

After evaluation for GMP compliance, all manufacturing and testing facilities were found to be acceptable. However, [redacted] an [redacted] was not submitted for inspection. Instead, a letter of cGMP compliance for the [redacted] is provided, presumably in lieu of an FDA inspection. However, self-certification is not an acceptable alternative to an inspection by FDA. It is not an obstacle to approval, since the [redacted] site could be withdrawn until it is inspected by the Agency. b(4)

The applicant does not identify critical points or critical steps in the manufacturing process. The applicant was reminded at the pre-NDA meeting on October 1, 2003, of such a requirement. The applicant should be requested to provide the results of the adequacy of the [redacted] test. This is also not an approvability issue, because we have not insisted on such information from previous gel manufacturers. The information is now being explored as a way of guiding the applicant through process quality control (quality by design). b(4)

The following issues should be addressed in the resubmission:

- [redacted]

b(4)

- [redacted]

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Saleh A. Turujman, Ph.D./4 December 2004
Chemistry Team Leader Name/Date: Ramesh Sood, Ph.D./
Project Manager Name/Date: Jacqueline Smith

C. CC Block

Cc: NDA 21-739
HFD-540/Division File
HFD-540/830/Chem/SATurujman
HFD-830/ChemTL/RSood
HFD-540/ProjMgr/JSmith
HFD-540/MedOff/BCarr
HFD-540/Pharm/JMerrill
HFD-540/BioPharm/EBashaw
HFD-540/Biometrics/SLee

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/s/

Saleh Turujman
12/7/04 02:52:33 PM
CHEMIST

For your concurrence

Ramesh Sood
12/7/04 02:55:28 PM
CHEMIST

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