

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-802

MICROBIOLOGY REVIEW

**DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
CONSULTATION FOR DIVISION OF DERMATOLOGIC AND DENTAL PRODUCTS (DDDP)
NDA 50-802 DATE REVIEW COMPLETED: 09/08/06**

Clinical Microbiology Reviewer: Harold V. Silver

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER/DDDP e-DATE</u>	<u>ASSIGNED DATE</u>
eResubmission / A-009	05/05/06	05/09/06	06/21/06
eNDA Amendment/A-0012	08/14/08	08/14/08	08/14/08
eNDA Amendment/A-0015	09/5/09	09/06/09	09/06/09

NAME & ADDRESS OF APPLICANT:

Dow Pharmaceutical Sciences, Inc. (DPSI)
1330 Redwood Way
Petaluma, CA 94954-1169
Tel: (707) 793-2600 / Fax: 707.793.0145

CONTACT PERSON(S):

Barry M. Calvarese, MS
Vice President, Regulatory & Clinical Affairs
Tel: (707) 793-2600 / Fax: 707.793.0145

SUBMISSIONS PROVIDE:

- **Document Date: 05/05/06:** The NDA application is submitted in response to the Agency's deficiency letter dated 12/07/04. The application is Dow's NDA 50-802 / A-009, formerly NDA 21-73, Dated: 05/21/06, ZIANA™, formerly named "Clin RA", Gel. The finished combination drug product consists of clindamycin (1.2%) and tretinoin (0.025%) as a topical gel for the treatment of acne vulgaris. No clinical microbiology was submitted in NDA 50-802.
- **E-mail Date: 08/14/08:** eNDA Amendment/A-0012. Word files for ZIANA (NDA 50802) Labeling Text and container artwork. An official eNDA Amendment (A0012) is being shipped to the Agency.
- **E-mails Dated: 09/05/06:** ZIANA (NDA 50802 / A-0015) Labeling. Attached were the MS Word files of the carton and container text, the package insert, the patient information sheet, PDF files of the redline package insert and the patient information sheet, along with the cover letter explaining the changes made.

STUDY DRUGs:

1. Clindamycin phosphate:

Proprietary: ZIANA™

Nonproprietary/USAN: clindamycin (as the phosphate)

CAS Registry ID: CAS-24729-96-2

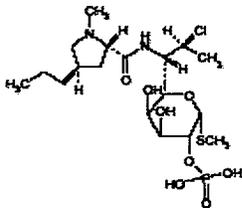
DRUG NAME, CHEMICAL NAME, STRUCTURE, MOL. FORMULA, and MOL. WT.:

Drug Name: clindamycin phosphate

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)

Structural Formula:



clindamycin phosphate

Molecular Formula: C₁₈H₃₄ClN₂O₈PS

Molecular Weight: 504.97

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CONCLUSIONS AND COMMENTS

The Clinical Microbiology Reviewer has the following microbiology labeling comments to be communicated to- and addressed by- the Sponsor:

In the Sponsor's **PACKAGE INSERT LABELING (SPL)**:

- HIGHLIGHTS OF PRESCRIBING INFORMATION

5.1. WARNINGS AND PRECAUTIONS section:

In the ~~_____~~ paragraph, "Studies indicate a toxin(s) produced by ~~_____~~ clostridia is one primary cause of antibiotic-associated colitis." The word "clostridia" is not italicized.

- FULL PRESCRIBING INFORMATION: CONTENTS*

3 DOSAGE FORMS AND STRENGTHS section:

~~_____~~

The aforementioned labeling statement is to be revised and read:

~~_____~~

11 DESCRIPTION section

~~_____~~

b(4)

The word ~~_____~~ is to be deleted from the aforementioned labeling statement.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

~~_____~~

~~_____~~

a. The 1st aforementioned microbiology labeling is to be removed and **appropriately** placed into **12.4 Microbiology** section.

b. The 2nd microbiology labeling is redundant and is to be deleted.

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12.4 Microbiology subsection:

a. Place the following microbiology labeling here, as follows:

[REDACTED]

The aforementioned microbiology is to be revised as follows:

[REDACTED]

The proprietary name is to be deleted: [REDACTED]. Proprietary names are not allowed in the **MICROBIOLOGY** section of the Package Insert labeling.

b(4)

c. The following microbiology labeling:

[REDACTED]

is to be revised to read:

[REDACTED]

Appears This Way
On Original

DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY PRODUCTS
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CONSULTATION FOR DIVISION OF DERMATOLOGIC AND DENTAL PRODUCTS (DDDP)
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INTRODUCTION

- The original NDA for this product was initially designated as NDA 21-739 and was submitted on Feb. 6, 2004. The NDA was later designated as NDA 50-802.
- A "not approvable" action letter was issued by the Agency on December 7, 2004, due to deficiencies in clinical data.
- The sponsor resubmitted the NDA on May 5, 2006, which addresses deficiencies in clinical data and CMC issues.
- There are no clinical microbiology data to review in this NDA.

BACKGROUND

Refer to "**BACKGROUND**" subsection in the **PACKAGE INSERT CLINICAL MICROBIOLOGY LABELING (SPL)** section in this review.

CLINICAL STUDY REPORTS (SYNOPSIS)

Dow submitted 2-clinical studies, containing no clinical microbiology, as follows:

- **MP-1501-01:** "A Multi-Center, Open-Label, Long-Term Safety Trial of Clin RA in the Treatment of Acne Vulgaris", and
- **MP-1501-02:** "A Multi-Center, Phase 3, Randomized, Double-Blind, Clinical Trial to Compare the Safety and Efficacy of Clin-RA Gel vs. Clindamycin Phosphate 1.2% Gel in the Treatment of Acne Vulgaris."

Clinical Study MP-1501-01

Title:

A Multi-Center, Open-Label, Long-Term Safety Trial of Clin RA Gel in the Treatment of Acne Vulgaris.

Protocol #: MP-1501-01

Date: Final 04/11/06

Developmental Phase: Phase 3

Study period: 01/23/04 through 01/21/05

Investigational Drug: Clin RA Gel (1.2% clindamycin phosphate and tretinoin 0.025%)

Regimen / Mode of Administration: Dose: Once-daily; Topically applied

Design:

This study was conducted as a multi-center, open-label study involving subjects with mild, moderate, or severe acne vulgaris meeting specific inclusion/exclusion criteria. Subjects were enrolled in thirteen (13 USA) independent study centers. The duration of treatment was one year for the first 200 subjects completing 6 months of the study and choosing to continue participation. The study duration for the remaining subjects was 6 months. Subjects were evaluated at Screen/Baseline and at monthly intervals.

Gender / Age:

Male or female subjects of any race, 12 years of age or older, with mild, moderate, or severe acne vulgaris.

Objectives:

- Primary Objective:

To assess the long-term safety of a new formulation of clindamycin and tretinoin as a monotherapy or with other concomitant acne medications for a six-month period or one-year period.

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- Secondary Objective:

To assess patterns of use of the new combination formulation by following the circumstances for treatment discontinuation and re-initiation of therapy.

Duration of Treatment: Either a six-month or one-year period

Criteria for Efficacy Evaluation:

Determinations included the "Evaluator's Global Severity Score", rationale for continuing therapy, as well as the rationale for re-initiating therapy

Clinical Study MP-1501-02**Title:**

A Multicenter, Phase 3, Randomized, Double-Blind, Clinical Trial to Compare the Safety and Efficacy of Clin RA Gel vs Clindamycin Phosphate 1.2% Gel in the Treatment of Acne Vulgaris

Protocol #: MP-1501-02

Date: 04/21/06

Developmental Phase: Phase 3

Study Period: 09/09/05 through 03/01/06

Investigational Drugs:

- Clin RA Gel (1.2% clindamycin phosphate and tretinoin 0.025%)
- Clindamycin phosphate 1.2% gel (in the same vehicle as the investigational product).

Regimen / Mode of Administration: Once-a-day application (at bedtime) / topically applied to the face.

Design: Multicenter (47 USA), randomized, double-blind, parallel comparison.

Enrollment:

The planned sample was 1930 subjects, with 965 subjects randomized to receive Clin RA Gel and 965 subjects to receive clindamycin phosphate 1.2% gel. The actual enrollment was 2010 subjects, 1008 subjects randomized to Clin RA Gel and 1002 subjects to clindamycin phosphate 1.2% gel. All of the enrolled subjects were included in the Intent-to-Treat (ITT) efficacy analysis and in the analysis of safety.

Gender / Age:

Male or female subjects of any race, 12 years of age or older, with acne vulgaris.

Objective:

To compare the efficacy and safety of Clin RA Gel to clindamycin phosphate 1.2% gel alone in the

Duration of Treatment: 12 weeks

Criteria for Efficacy Evaluation:

Determinations include the "Evaluator's Global Severity Score" (EGSS), rationale for continuing therapy, as well as the rationale for re-initiating therapy.

Primary Efficacy Variables:

- Percent change from Baseline to Week 12 in inflammatory lesion counts;
- Percent change from Baseline to Week 12 in noninflammatory lesion counts;
- Percent change from Baseline to Week 12 in total lesion counts;
- Percentage of subjects who were clear or almost clear at Week 12 or achieved at least 2 grades of improvement in the EGSS (treatment success) from Baseline to Week 12.

Secondary Efficacy Variables:

- Percentage of subjects with a Baseline EGSS of severe (=4) or worse who were clear or almost clear at Week 12 or achieved at least a 2-grade improvement in the EGSS from Baseline to Week 12.
- Percentage of subjects who achieved at least a 2-grade improvement from Baseline to Week 12 in the EGSS.

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PACKAGE INSERT LABELING (SPL)

BACKGROUND

The original NDA 21-739 Clinical Microbiology Reviewer, Fred Marsik, Ph.D. and the Clinical Microbiology Team Leader had concerns on allowing any microbiology claims into the labeling of the finished drug product.

The following are excerpted from Dr. Marsik's Clinical Microbiology Review on IND 21-739 and Date Completed 02/25/04:

"Clin-RA-Gel is the subject of a 505(b)(2) New Drug Application of the Food, Drug and Cosmetic Act in accordance with Title 21 of the Code of Federal Regulations, §314.50. The applicant did not provide clinical microbiology information in the microbiology section of this submission because they are **not** pursuing an antibacterial claim for the product (section 3.8.1)."

"The applicant is not seeking antibacterial claims for Clin-RA-Gel (summary pg. 54). In this submission the applicant has not provided any clinical microbiology data from clinical trials conducted with their product. The Agency (HFD-540) at a Pre-NDA meeting with the applicant on 1 October 2003 proposed the following wording for the "Microbiology Section" of the package insert if the applicant elected not to include clinical microbiology data in their NDA. There was no clinical microbiology representation at the October 1, 2003 meeting. No clinical microbiologist from HFD-520 was consulted about the wording prior to the October 1, 2003 meeting or prior to this HFD-540 clinical microbiology consults for HFD-520."

"Microbiology" _____

b(4)

"It is the opinion of this reviewer that the microbiology section wording proposed by the Agency (HFD-540) at the October 1, 2003 meeting with the applicant implies antibacterial activity of a component of the applicant's product. Because the applicant has stated that they are **not** seeking antibacterial claims the wording proposed for the microbiology section of the package insert by the Agency at the October 2003 meeting is inappropriate. Also the package insert wording proposed by the applicant makes no mention of an association between acne vulgaris and *Propionibacterium acnes* except in the proposed microbiology section. It is proposed that the microbiology section not be included in the package insert so there is no implied antibacterial activity of the applicant's product."

Clinical Microbiology Comment:

The Agency's (HFD-540) suggested wording (and probably "policy" at that time): "Microbiology:

b(4)

_____ is permitted in the microbiology labeling in this NDA.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
(e-Mail / Revised: September 5, 2006)

ZIANA™

b(4)

Clinical Microbiology Comment:

The word "clostridia" is not italicized. The other various aforementioned microbiology labeling are acceptable.

FULL PRESCRIBING INFORMATION: CONTENTS*

3 **DOSAGE FORMS AND STRENGTHS**

Clinical Microbiology Comment:

The aforementioned labeling statement is to be revised and read: _____

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5 WARNINGS AND PRECAUTIONS

b(4)

Clinical Microbiology Comment:

The aforementioned microbiology labeling is acceptable.

5.2 General

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi.

Clinical Microbiology Comment:

The aforementioned microbiology labeling is acceptable.

7 DRUG INTERACTIONS

7.2 Clindamycin and Erythromycin

b(4)

~~_____~~ *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Clinical Microbiology Comment:

The aforementioned microbiology labeling is acceptable.

11 DESCRIPTION

b(4)

Clinical Microbiology Comment:

The word "_____" is to be deleted from the first labeling statement. The 2nd microbiology labeling is acceptable.

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12 CLINICAL PHARMACOLOGY

12.2 Mechanism of Action

[Redacted]

b(4)

Clinical Microbiology Comments:

- a. The 1st aforementioned microbiology labeling is to be removed, revised, and appropriately placed into 12.4 MICROBIOLOGY section.
- b. The 2nd microbiology labeling is redundant and is to be deleted.

12.4 Microbiology

Clinical Microbiology Comments

- a. Place the aforementioned microbiology labeling here, as follows:

[Redacted]

The aforementioned microbiology is to be revised as follows:

[Redacted]

b(4)

- b. [Redacted]

[Redacted]

The proprietary name is to be deleted: _____ Proprietary names are not allowed in the MICROBIOLOGY section of the Package Insert labeling.

- c. The following microbiology labeling:

[Redacted]

is to be revised to read:

[Redacted]

b(4)

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CONSULTATION FOR DIVISION OF DERMATOLOGIC AND DENTAL PRODUCTS (DDDP)
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b(4)

CONCLUSIONS AND COMMENTS

The Clinical Microbiology Reviewer has the following microbiology labeling comments to be communicated to- and addressed by- the Sponsor as stated on pages 3 and 4 of this review.

Harold V. Silver
Clinical Microbiology Reviewer
DAIOP/HFD-520

cc: NDA 50-802
DAIOP/Division File
DAIOP/Micro/H.V.Silver

Concurrence Only:
DAIOP/MicroTL/F. Marsik
11 Sep 06 FIN FJM

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

/s/

Harold Silver
9/12/2006 03:02:18 PM
MICROBIOLOGIST

Please sign off on DDDP Consultation: Clinical Microbiology Review
on Dow's NDA 50-802/A-009, ZIANA₂ Gel, for acne
vulgaris.

Frederic Marsik
9/13/2006 02:46:14 PM
MICROBIOLOGIST

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DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW
DERMATOLOGY (HFD-540) CONSULT
NDA 21-739 Date review completed: 25 Feb 04

Date company submitted: 6 Feb 04

Date received by CDER: 7 Feb 04

Reviewer: Fred Marsik, Ph.D.

Date assigned: 12 Feb 04

NAME AND ADDRESS OF APPLICANT

Dow Pharmaceutical Sciences
1330A Redwood Way
Petaluma, CA 94954-1169

CONTACT PERSON

Barry M Calvarese, MS
Vice President, Regulatory and Clinical
Phone #: 707-793-2600

DRUG PRODUCT NAME

Proprietary: Clin-RA-Gel

Established Name: Clindamycin and Tretinoin

Code name/Number: None

Chemical name: Clindamycin phosphate - Methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thi-L-threo-D-galactopyranoside 2-(dihydrogen phosphate)

Tretinoin - (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic

Chemical formula: Clindamycin phosphate - $C_{18}H_{34}ClN_2O_8PS$

Tretinoin - $C_{20}H_{28}O_2$

PROPOSED INDICATION

Treatment of acne vulgaris

PROPOSED DOSAGE FORM, DOSAGE, STRENGTH, ROUTE OF ADMINISTRATION, AND DURATION OF TREATMENT

Proposed dosage form: Gel

Strength and dosage: Clindamycin phosphate, 1%; Tretinoin, 0.025% applied topically once daily at bedtime; each gram of Clin-RA-Gel topical gel contains 10 mg (1%) clindamycin phosphate, and 0.25 mg (0.025%) tretinoin in a base of butylated hydroxytoluene citric acid edetate disodium, methylparaben, propylparaben, polysorbate 80, glycerin, carbomer , tromethamine and purified water.

Route of administration: Topical

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Duration of treatment: 12 weeks

DISPENSED

Rx

RELATED DOCUMENTS

IND 65,531

REMARKS

Clin-RA-Gel is the subject of a 505(b)(2) New Drug Application of the Food, Drug and Cosmetic Act in accordance with Title 21 of the Code of Federal Regulations, §314.50. The applicant did not provide clinical microbiology information in the microbiology section of this submission because they are not pursuing an antibacterial claim for the product (section 3.8.1).

CONCLUSION

The applicant is not seeking antibacterial claims for Clin-RA-Gel (summary pg. 54). In this submission the applicant has not provided any clinical microbiology data from clinical trials conducted with their product. The Agency (HFD-540) at a Pre-NDA meeting with the applicant on 1 October 2003 proposed the following wording for the "Microbiology Section" of the package insert if the applicant elected not to include clinical microbiology data in their NDA. There was no clinical microbiology representation at the October 1, 2003 meeting. No clinical microbiologist from HFD-520 was consulted about the wording prior to the October 1, 2003 meeting or prior to this HFD-540 clinical microbiology consults for HFD-520.

"Microbiology" ~~_____~~

b(4)

It is the opinion of this reviewer that the microbiology section wording proposed by the Agency (HFD-540) at the October 1, 2003 meeting with the applicant implies antibacterial activity of a component of the applicant's product. Because the applicant has stated that they are not seeking antibacterial claims the wording proposed for the microbiology section of the package insert by the Agency at the October 2003 meeting is inappropriate. Also the package insert wording proposed by the applicant makes no mention of an association between acne vulgaris and *P. acnes* except in the proposed microbiology section. It is proposed that the ~~_____~~ so there is no implied antibacterial activity of the applicant's product.

b(4)

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DERMATOLOGY (HFD-540) CONSULT
NDA 21-739 Date review completed: 25 Feb 04

INTRODUCTION

Back Ground and Summary

Dow Pharmaceutical Sciences is submitting this New Drug Application (NDA), for ClinRA-Gel under section 505(b)(2) of the Food, Drug and Cosmetic Act in accordance with Title 21 of the Code of Federal Regulations, §314.50. No microbiology information has been submitted because the applicant is making no antibacterial claims for their product.

Acne vulgaris

Acne vulgaris is a skin disorder of the sebaceous follicles that commonly occurs in adolescence and in young adulthood. While the exact cause of acne vulgaris is not understood some factors that may contribute to the condition have been identified. Acne vulgaris lesions may occur because local metabolism of sex hormones stimulates an increase in the size of the sebaceous glands resulting in the production of excess sebum, the lipid rich secretion of the sebaceous gland. Sebum is believed to be a pivotal player in acne pathogenesis and provides a growth medium for *Propionibacterium acnes*. The major factors contributing to the pathogenesis are hyperkeratinization, obstruction of sebaceous follicles resulting from abnormal keratinization of the infundibular epithelium, stimulation of sebaceous gland secretion by androgens, and microbial colonization of pilosebaceous units by the anaerobic bacterium *P. acnes*, which promotes perifollicular inflammation (1,2,3). The increased activity of sebaceous glands, elicited by androgen, causes proliferation of *P. acnes* in the pilosebaceous ducts. The organism possesses a ribosome-rich cytoplasm and a relatively thick cell wall and produces several biologically active mediators that may contribute to inflammation, for instance, by promoting leukocyte migration and follicular rupture. In inflamed lesions, neutrophils and macrophages infiltrate around hair follicles and sometimes phagocytosis *P. acnes* (4). The immunologic response to *P. acnes* involves the humoral, cell-mediated, and complement pathways (3). The suppression of *P. acnes* is associated with clinical improvement although absolute numbers of *P. acnes* do not correlate with the severity of acne (5).

Topical clindamycin phosphate is prescribed for the treatment of mild to moderate acne vulgaris (6). Clindamycin phosphate is a lincosamide antibiotic with activity against a variety of gram-positive bacteria as well as gram-positive and gram-negative anaerobes. Clindamycin binds to the 50S subunit of the bacterial ribosome and inhibits early stages of protein synthesis. It is primarily a bacteriostatic agent. Clindamycin phosphate is biologically inactive being hydrolyzed to the active form of free clindamycin. This hydrolyzation occurs following oral, parenteral and topical administration (7). The literature indicates that the MIC₉₀ range for clindamycin against *P. acnes* is in the range of ≤ 0.06 to 0.125 $\mu\text{g/mL}$ (8,9). Studies of the use of clindamycin and erythromycin for the treatment of acne vulgaris have documented the development of resistance to both

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antimicrobials between 6 to 18 weeks (4,10,11). Resistance to clindamycin is associated with cross-resistance to erythromycin (10).

Tretinoin, also a component of this product, is a natural metabolite of vitamin A (retinol). Topical tretinoin was first used for the treatment of acne in 1969, and currently is used in a range of concentrations (0.01 to 0.1%) in the treatment of acne vulgaris, under the brand names of Retin A[®], Retin A[®] Micro, Avita[®] (gel or cream) (12). The applicant did not indicate in this submission whether tretinoin has any microbiological activity. A review of the literature did not find any evidence that tretinoin (all-trans-retinoic acid) has antibacterial activity (13).

MICROBIOLOGY DATA

No microbiology data has been submitted with this application because the applicant is not seeking antibacterial claims for their product. The following wording for the "Microbiology" section of the package insert was suggested to the applicant by the Agency (HFD-540) at a Pre-NDA meeting on October 1, 2003 (see meeting minutes "Additional Comments") in the event the NDA did not contain a clinical microbiology section. No clinical microbiologist was present at the October 1, 2003 meeting and no clinical microbiologist from HFD-520 was consulted about the wording prior to this clinical microbiology consult requested by HFD-540.

b(4)

SUMMARY OF CONTROLLED CLINICAL STUDY RESULTS

Two phase 3 studies (7001.G2HP-06-02 and 7001.G2HP-07-02) were performed using Clin-RA-Gel formula #781-62. These studies were conducted as multi-center, randomized, double-blinded, active-controlled and vehicle-controlled, parallel comparison studies involving subjects with acne vulgaris. Topical application of the study materials was made to the entire face (excluding the mouth, eyes, and lips) once daily prior to bedtime for a period of 12 weeks. Study material was applied as a thin coat. The description of the application of the study materials does not specify that a specific amount of material was to be applied. Subjects were evaluated at screening/baseline and at weeks 2, 4, 8, and 12. The age of the subjects in both studies ranged from 11 to 59 years with an average age of 19 years. One thousand seven hundred seventy nine subjects (70%) were White, 356 (14%) were black, 49 (2%) were Asian/Pacific Islander, 314 (12%) were Hispanic/Latino, 17 (1%) were American/Alaskan Native and 25 (1%) were other.

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Table 1 is a summary of the clinical study results prepared by the applicant. The results in Table 1 suggests that Clin-RA gel reduces both inflammatory and non-inflammatory lesions associated with acne vulgaris. The reader is referred to reviews prepared by Agency statisticians and medical officers for a comprehensive analysis of the data.

Table 1. Percent reductions in lesion counts after treatment for 12 weeks with study materials

Study 1

<u>Clin-RA Gel</u> 420 subjects	<u>Tretinoin</u> 417 subjects	<u>Clindamycin</u> 208 subjects	<u>Vehicle</u> 207 subjects
	Mean percent reduction in inflammatory lesion counts		
46.0	37.5	39.7	19.6
	Mean percent reduction in non-inflammatory lesion counts		
37.6	31.9	24.1	13.5
	Mean percent reduction in total lesion counts		
41.4	34.7	31.3	16.5

Study 2

<u>Clin-RA Gel</u> 425 subjects	<u>Tretinoin</u> 429 subjects	<u>Clindamycin</u> 218 subjects	<u>Vehicle</u> 216 subjects
	Mean percent reduction in inflammatory lesion counts		
50.6	40.1	43.6	31.7
	Mean percent reduction in non-inflammatory lesion counts		
41.3	36.6	33.3	21.4
	Mean percent reduction in total lesion counts		
41.8	34.2	35.9	23.2

CONCLUSION

The applicant is not seeking antibacterial claims for Clin-RA-Gel (summary pg. 54). In this submission the applicant has not provided any clinical microbiology data from clinical trials conducted with their product. The Agency (HFD-540) at a Pre-NDA meeting with the applicant on 1 October 2003 proposed the following wording for the "Microbiology Section" of the package insert if the applicant elected not to include clinical microbiology data in their NDA. There was no clinical microbiology representation at the October 1, 2003 meeting. No clinical microbiologist from HFD-520 was consulted about the wording prior to the October 1, 2003 meeting or prior to this HFD-540 clinical microbiology consults for HFD-520.

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DERMATOLOGY (HFD-540) CONSULT
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“Microbiology: _____”

b(4)

It is the opinion of this reviewer that the microbiology section wording proposed by the Agency (HFD-540) at the October 1, 2003 meeting with the applicant implies antibacterial activity of a component of the applicant's product. Because the applicant has stated that they are not seeking antibacterial claims the wording proposed for the microbiology section of the package insert by the Agency at the October 2003 meeting is inappropriate. Also the package insert wording proposed by the applicant makes no mention of an association between acne vulgaris and *P. acnes* except in the proposed microbiology section. It is proposed that _____

b(4)

_____ so there is no implied antibacterial activity of the applicant's product.

REFERENCES

1. Toyoda M, M Morohashi. 2001. Pathogenesis of acne. *Med Electron Microscopy* 34:29-40.
2. Thiboutot D. Acne. Introduction. *Semin Cutan Med Surg* 20:137-138.
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NDA 21-739 Date review completed: 25 Feb 04

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Frederic J. Marsik, Ph.D. Date: _____

CONCURRENCE ONLY

RD#1 and Final Initialed 03/02/04ATS
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NDA 21-739 FILEABILITY REVIEW
Reviewer: Fred Marsik, Ph.D. Date Review Completed: 12 Feb 04

1. Is the microbiology section organized in a manner to allow substantive review to begin? Not applicable*
2. Is the microbiology section indexed and paginated in a manner to allow substantive review to begin? Not applicable
3. Is the microbiology section and other microbiologically pertinent Sections of the NDA legible so that substantive review can begin? Not applicable

HAS THE APPLICANT SUBMITTED:

1. in vitro data in sufficient quantity, using necessary clinical and non-clinical strains and using necessary numbers of approved laboratories to meet current Divisional standards for approvability of the product based on submitted draft labeling? Not applicable
2. any required animal studies necessary for approvability of the product based on the submitted draft labeling? Not applicable
3. draft breakpoints and interpretive criteria in a manner consistent with contemporary standards, in a manner that attempts to correlate criteria with clinical results on NDA studies, and in a manner to allow substantive review to begin? Not applicable
4. all special studies/data requested by the Division during pre-submission discussions? Not applicable
5. draft labeling consistent with 201.56 and 201.57, current Divisional policy and the design of the development package. Yes

From a Microbiology perspective, is this NDA fileable? If NO give reasons below. Yes

*This application is being filed under 505(b)(2) no new microbiology data is required.

_____ Date: 12 Feb 04
Fred Marsik, Ph.D., Review Microbiologist
Concurrence Only:
Final Initialed 02/19/04 ATS
HFD-520/TLMicro/A T Sheldon, Jr., Ph.D.

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