

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-443

Name: Clindamycin Phosphate and Benzoyl Peroxide Gel, 1% (base)/5%

Sponsor: Dow Pharmaceutical Sciences, Inc.

Approval Date: August 11, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-443

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-443

APPROVAL LETTER



ANDA 65-443

Dow Pharmaceutical Sciences, Inc.
Attention: Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 7, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Clindamycin Phosphate and Benzoyl Peroxide Gel, 1% (base)/5%. We note that this product is subject to the exception provisions of section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated December 18, 2007, December 20, 2007, February 27, 2008, June 20, 2008, July 8, 2008, August 19, 2008, November 6, 2008, December 11, 2008, January 12, January 29, February 11, February 18, July 1, July 22, July 24, and July 30, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Clindamycin-Benzoyl Peroxide Gel, 1% (base)/5% to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Benzaclin Topical Gel, of Sanofi Aventis US.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory

requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as “*Miscellaneous Correspondence – SPL for Approved ANDA*”.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

GARY J BUEHLER
08/11/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-443

LABELING



One 50 gram Jar
(after admixing)

Rx only

CLINDAMYCIN PHOSPHATE and BENZOYL PEROXIDE GEL, 1% /5% FOR TOPICAL USE ONLY



NDC 0378-8688-54

See Back
Panel For
Mixing
Instructions

See Back
Panel For
Mixing
Instructions

TO THE PHARMACIST:

Important: Prior to dispensing, add the solution in the bottle to the gel and stir until homogenous in appearance (1 to 1 1/2 minutes). Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% can be stored at room temperature up to 25°C (77°F) for 3 months. Place a 3 month expiration date on the labeling immediately following mixing.

Distributed by:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
Manufactured by:
Contract Pharmaceuticals Ltd.
Buffalo, NY 14213

LOT & EXP DATE
NO COATING

DW-M-8688-2C:R3



NDC 0378-8688-54

CLINDAMYCIN PHOSPHATE and BENZOYL PEROXIDE GEL, 1% /5% FOR TOPICAL USE ONLY

Rx only

One 50 gram Jar
(after admixing)



NDC 0378-8688-54

CLINDAMYCIN PHOSPHATE and BENZOYL PEROXIDE GEL, 1% /5% FOR TOPICAL USE ONLY

Rx only

One 50 gram Jar
(after admixing)

CLINDAMYCIN PHOSPHATE and BENZOYL PEROXIDE GEL, 1% /5%

Each gram of Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% as dispensed, contains 10 mg (1%) *clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, propylene glycol, potassium hydroxide, and purified water. **Usual Dosage:** Apply twice daily, morning and evening, or as directed by physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry. See package insert for full prescribing information. Use within 3 months after mixing. **Store at room temperature up to 25°C (77°F) [see USP]. Do not freeze. Keep tightly closed.**
Precautions: For external use only. Avoid contact with eyes. Keep out of reach of children. May bleach fabric or hair.
US Patents 5,733,886; 6,117,843



GLUE AREA
NO INK & COATING



3 0378-8688-54 6

NO
COPY
AREA



GLUE AREA
NO INK &
COATING

NO
COPY
AREA



GLUE AREA
NO INK &
COATING

← GRAIN →

FRONT SIDE

CPL NIAGARA

C070319C

CLINDAMYCIN PHOSPHATE SOLUTION

Prior to dispensing, add the solution in the bottle to the gel and stir until homogeneous in appearance (1 to 1½ minutes).
Clindamycin Phosphate and Benzoyl Peroxide Gel, 1% (EUS)/5% can be stored at room temperature up to 25°C (77°F) for 3 months. Place a 3 month expiration date on the labeling immediately following mixing. Not for separate dispensing. See package insert for full prescribing information.
Keep out of reach of children. For external use only. Avoid contact with eyes.

Net Wt. 10 grams clindamycin solution containing 0.8 grams clindamycin as phosphate
Dix by Mylan Pharmaceuticals Inc. Mfg by Contract Pharmaceuticals Ltd.
Morgantown, WV 26505 Buffalo, NY 14213

Rx only

DW M 8688BE2

10

Label Size: 2.875 x 0.625 Part Number: DW-M-8688BE2

1 Color:

Pantone: ● Black DieCut

CPL

100002-0

KTD

(b) (4)

(b) (4)

(b) (4)



NDC 0378-8688-54

**CLINDAMYCIN PHOSPHATE and
BENZOYL PEROXIDE GEL, 1%*/5%**
FOR TOPICAL USE ONLY

One 50 gram Jar
(after admixing)

Each gram of Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%*/5% contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, propylene glycol, potassium hydroxide, and purified water. Dosage and Administration: See package insert for dosage information. Use within 3 months after mixing. Store at room temperature up to 25°C (77°F) [see USP]. Do not freeze. Keep tightly closed. Precautions: For external use only. Avoid contact with eyes. **Keep out of reach of children.** May bleach fabric or hair.

Rx only

Dist. by: Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

Mfd. by: Contract Pharmaceuticals Ltd.
Buffalo, NY 14213

DW-M-8688CD2

Label Size: 5.98 x 1.09 w/ 0.25 CodeStrip Part Number: DW-M-8688CD2

3 Colors:

Pantone: ● Black ● (b) (4) ● (b) (4) DieCut

Please Review this proof and clearly mark any modification and corrections required.

Customer: CPL

GG WO#: 100004-7

CSR: KTD

Did you Check for the Correct:

- Size of Label
- # of Colors & Color Break
- Spelling & Punctuation
- Barcode (including version #)

Please Check One:

- Proof OK as is. Proceed with Order.
- Change as Noted. New Proof Required.

**This Proof is for
Color Break Only**

Please refer to the Pantone
Swatch Guide for accurate color.
This color will not match your
final printed piece.

Customer Sign Off

Date

Please Check a
Rewind Direction


 1 2 3 4
 5 6 7 8

 1 2 3 4
 5 6 7 8

Phone:

(b) (4)

Fax:

(b) (4)

(b) (4)

Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%

Topical Gel: clindamycin (1%) *as clindamycin phosphate, benzoyl peroxide (5%)

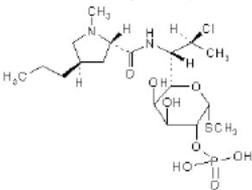
For Dermatological Use Only - Not for Ophthalmic Use
Mix Before Dispensing



Rx only

DESCRIPTION

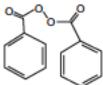
Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% contains clindamycin phosphate, (7S)-chloro-7-deoxylincomycin-2-phosphate. Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-7-deoxylincomycin-2-phosphate. Chemically, clindamycin phosphate is (C₁₈H₃₄ClN₂O₈PS). The structural formula for clindamycin is represented below:



Clindamycin phosphate has a molecular weight of 504.97 and its chemical name is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-pyridyl-L-2-pyrrolidinedicarboxamido)-1-thio-L-threo- α -D-galactooctopyranoside 2-(dihydrogen phosphate).

Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% also contains benzoyl peroxide, for topical use.

Chemically, benzoyl peroxide is (C₁₄H₁₀O₄). It has the following structural formula:



Benzoyl peroxide has a molecular weight of 242.23.

Each gram of **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, polyethylene glycol, potassium hydroxide, and purified water.

CLINICAL PHARMACOLOGY

An *in vitro* percutaneous penetration study comparing **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** and topical 1% clindamycin gel alone, demonstrated here was no statistical difference in penetration between the two drugs. Mean systemic bioavailability of topical clindamycin in **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** is suggested to be less than 1%.

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Less than 2% of the dose enters systemic circulation as benzoic acid. It is suggested that the lipophilic nature of benzoyl peroxide acts to concentrate the compound into the lipid-rich sebaceous follicle.

Microbiology:

The clindamycin and benzoyl peroxide components individually have been shown to have *in vitro* activity against *Propionibacterium acnes* an organism which has been associated with acne vulgaris; however, the clinical significance of its activity against *P. acnes* was not examined in clinical trials with this product.

CLINICAL STUDIES

In two adequate and well controlled clinical studies of 758 patients, 214 used **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%**, 210 used benzoyl peroxide, 168 used clindamycin, and 166 used vehicle. **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** applied twice daily for 10 weeks was significantly more effective than vehicle in the treatment of moderate to moderately severe facial acne vulgaris. Patients were evaluated and acne lesions counted at each clinical visit; weeks 2, 4, 6, 8 and 10. The primary efficacy measures were the lesion counts and the investigator's global assessment evaluated at week 10. Patients were instructed to wash the face with a mild soap, using only the hands. Fifteen minutes after the face was thoroughly dry, application was made to the entire face. Non-medicated make-up could be applied at one hour after the **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** application. If a moisturizer was required, the patients were provided a moisturizer to be used as needed. Patients

were instructed to avoid sun exposure. Percent reductions in lesion counts after treatment for 10 weeks in these two studies are shown below:

| Study 1 | | | |
|--|-----------------------------|------------------------|--------------------|
| Clindamycin Phosphate and Benzoyl Pe oxide Gel, 1%/5% n = 120 | Benzoyl pe oxide n = 120 | Clindamycin n = 120 | Vehicle n = 120 |
| Mean percent reduction in inflammatory lesion counts | | | |
| 46% | 32% | 16% | +3% |
| Mean percent reduction in non-inflammatory lesion counts | | | |
| 22% | 22% | 9% | +1% |
| Mean percent reduction in total lesion counts | | | |
| 36% | 28% | 15% | 0.2% |

| Study 2 | | | |
|---|----------------------------|-----------------------|-------------------|
| Clindamycin Phosphate and Benzoyl Pe oxide Gel, 1%/5% n = 95 | Benzoyl pe oxide n = 95 | Clindamycin n = 49 | Vehicle n = 48 |
| Mean percent reduction in inflammatory lesion counts | | | |
| 63% | 53% | 45% | 42% |
| Mean percent reduction in non-inflammatory lesion counts | | | |
| 54% | 50% | 39% | 36% |
| Mean percent reduction in total lesion counts | | | |
| 58% | 52% | 42% | 39% |

The **Clindamycin Phosphate and Benzoyl Pe oxide Gel, 1%/5%** group showed greater overall improvement than the benzoyl peroxide, clindamycin and vehicle groups as rated by the investigator.

INDICATIONS AND USAGE

Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS

Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS

ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIUM IS ONE PRIMARY CAUSE OF ANTIBIOTIC-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR *Clostridium Difficile* AND STOOL ASSAY FOR *C. difficile* TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPERISTALTIC AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS, AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS**General:**

For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of non-susceptible organisms including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two antibiotics. The clinical significance of this *in vitro* antagonism is not known.

Information for Patients:

Patients using **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** should receive the following information and instructions:

1. **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by physician.
4. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%. To minimize exposure to sunlight, a wide-brimmed hat or other protective clothing should be worn, and a sunscreen with SPF 15 rating or higher should be used.
5. Patients who develop allergic symptoms such as severe swelling or shortness of breath should discontinue **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** and contact their physician immediately. In addition, patients should report any signs of local adverse reactions to their physician.
6. **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** may bleach hair or colored fabric.
7. **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** can be stored at room temperature up to 25°C (77°F) for 3 months. Do not freeze. Discard any unused product after 3 months.
8. Before applying **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** to affected areas wash the skin gently, then rinse with warm water and pat dry.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment.

In a 52 week dermal photocarcinogenicity study in hairless mice, the median time to onset of skin tumor formation was decreased and the number of tumors per mouse increased following chronic concurrent topical administration of Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% with exposure to ultraviolet radiation (40 weeks of treatment followed by 12 weeks of observation).

Genotoxicity studies were not conducted with Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Clindamycin phosphate sulfoxide, an oxidative degradation product of clindamycin phosphate and benzoyl peroxide, was not clastogenic in a mouse micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 grams Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%, based on mg/m²) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C:

Animal reproductive/developmental toxicity studies have not been conducted with Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% or benzoyl peroxide. Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120

times amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

There are no well-controlled trials in pregnant women treated with **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%**. It also is not known whether **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** can cause fetal harm when administered to a pregnant woman.

Nursing Women:

It is not known whether **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** is excreted in human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

During clinical trials, the most frequently reported adverse event in the Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% treatment group was dry skin (12%). The table below lists local adverse events reported by at least 1% of patients in the Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% and vehicle groups.

| Application Site Reaction | Local Adverse Events - all causalities in ≥ 1% of patients | |
|------------------------------|---|--------------------|
| | Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% n = 420 | Vehicle n = 168 |
| Dry Skin | 13 (3%) | 1 (< 1%) |
| Pruritis | 50 (12%) | 10 (6%) |
| Peeling | 8 (2%) | 1 (< 1%) |
| Erythema | 9 (2%) | - |
| Sunburn | 6 (1%) | 1 (< 1%) |
| Sunburn | 5 (1%) | - |

The actual incidence of dry skin might have been greater were it not for the use of a moisturizer in these studies.

Anaphylaxis, as well as allergic reactions leading to hospitalization, have been reported during post-marketing use of clindamycin/benzoyl peroxide products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DOSAGE AND ADMINISTRATION

Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

HOW SUPPLIED AND COMPOUNDING INSTRUCTIONS

| Size (Net Weight) | NDC # | Benzoyl Peroxide Gel | Clindamycin Phosphate Solution (in plastic bottle) |
|----------------------|--------------|-------------------------|---|
| 50 grams | 0378-8688-54 | 40 grams | 10 grams |

Prior to dispensing, add the solution in the bottle to the gel and stir until homogenous in appearance (1 to 1½ minutes). **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%** can be stored at room temperature up to 25°C (77°F) for 3 months. Place a 3 month expiration date on the labeling immediately following mixing.

Store at room temperature up to 25°C (77°F) [See USP].

Do not freeze. Keep tightly closed. Keep out of the reach of children.

US Patents 5,733,886; 6,117,843

Distributed by:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

Manufactured by:

Contract Pharmaceuticals Ltd.
Buffalo, NY 14213

090068
REVISED JUNE 2009
DW-M-CLBZPX:R3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 65-443

LABELING REVIEWS

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **65-443** Dates of Submission: **February 7 and March 28, 2007**

Applicant's Name: **Dow Pharmaceutical Sciences, Inc.**

Established Name: **Clindamycin/Benzoyl Peroxide Gel, 1%/5%**

Labeling Deficiencies:

1. GENERAL COMMENT

The established name for this drug product is "Clindamycin/Benzoyl Peroxide Gel, 1%/5%". Please revise your labels and labeling accordingly.

2. CLINDAMYCIN PHOSPHATE SOLUTION CONTAINER

We note that you have indicated the name of the manufacturer on every piece of labeling save for this one. Please comment.

3. BENZOYL PEROXIDE [FINAL PRODUCT] JAR

"One 50 gram Jar"
"(after admixing)"

4. CARTON

a. See comment under (2) above.

b. Increase the prominence of the established name.

c. Increase the prominence of "Rx ONLY".

5. INSERT

a. TITLE

Place "Rx Only" in conjunction with the established name.

b. DESCRIPTION

i. Structural formula – Improve the depiction of the subscripts.

ii. Third paragraph – "... has a molecular ..." [add "a"]

c. PRECAUTIONS

i. General – Place a blank line-space immediately beneath "Avoid contact with eyes and mucous membranes".

- ii. Carcinogenesis, Mutagenesis, Impairment of Fertility, Fourth paragraph, last sentence - Place "2.5" and "grams" on the same line of text [note "grams" rather than "g"]
- d. HOW SUPPLIED
 - i. "40 grams" and "10 grams" rather than "40g" and "10g"
 - ii. We note that you have represented Dow Pharmaceutical Sciences, Inc. as the manufacturer of this drug product yet your application states that CPL-Niagara is the manufacturer. What is the relationship between these two entities?

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA". The immediate container labels may be submitted either electronically or in hard copy. However, for ease of review, we ask that you submit electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
 Director
 Division of Labeling and Program Support
 Office of Generic Drugs
 Center for Drug Evaluation and Research

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No - ELECTRONIC

Clindamycin Phosphate Solution Container Label:

Final Product Jar Label:

Kit Carton Labeling:

Insert Labeling:

| | SUBMIT | ACCEPTED | ACTION |
|-----------|--------|----------|--------|
| Container | 2-7-07 | 3-28-07 | REVISE |
| Jar | 2-7-07 | 3-28-07 | REVISE |
| Carton | 2-7-07 | 3-28-07 | REVISE |
| Insert | 2-7-07 | 3-28-07 | REVISE |

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: BenzaClin® Topical Gel
NDA Number: 50-756
NDA Drug Name: BenzaClin® (clindamycin-benzoyl peroxide gel)
NDA Firm: Sanofi Aventis US
Date of Approval of NDA Insert and supplement #: 5-23-07 (S-026)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? NO
Other Comments

NOTE TO THE CHEMIST:

The labeling of this drug product states that it must be stored at room temperature and used within three months after mixing. Is this accurate?

FOR THE RECORD:

- Review based on the labeling of BenzaClin® Topical Gel (NDA 50-756/S-026); approved 5-23-07.
- Product Line:
 The innovator markets their product in a carton containing a jar of benzoyl peroxide gel and a bottle of clindamycin phosphate powder – the pharmacist is to add 10 mL of purified water to the clindamycin phosphate powder then once the powder is in solution it is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.
 The applicant proposes to market their product in a carton containing a jar of benzoyl peroxide and a bottle of clindamycin phosphate solution – there is no need to reconstitute the clindamycin phosphate as it is already in solution – this solution is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.

The firm met with the Agency on November 12, 2003 to discuss the submission of a 505(b)(2) for this drug product [see difference from RLD above]. After the meeting the Agency felt that it was appropriate for the firm to submit this application as a 505(j). The Agency indicated to the Sponsor that they would need to demonstrate that their product is bioequivalent to Benzaclin (the RLD) by conducting a three-arm study; the Sponsor’s combination product vs Benzaclin vs the Sponsor’s vehicle. The sponsor’s product should be non-inferior to Benzaclin and superior to vehicle in the treatment of acne vulgaris.

- Patent/ Exclusivities
Patent Data – 50-756

| No | Expiration | Use Code | Use | File |
|------|------------|----------|-----|------|
| None | | | | |

Exclusivity Data – 50-756

| Code/sup | Expiration | Use Code | Description | Labeling Impact |
|----------|------------|----------|--|-----------------|
| None | | | There is no unexpired exclusivity for this product | |

- Storage Conditions:
 NDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.
 ANDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.
 USP – Not USP
 Mixed product must be stored at room temperature and used within three months after mixing.

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

/s/

Adolph Vezza
10/12/2007 08:28:12 AM
LABELING REVIEWER

Lillie Golson
10/12/2007 03:56:08 PM
LABELING REVIEWER

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **65-443**

Date of Submission: **December 20, 2007**

Applicant's Name: **Dow Pharmaceutical Sciences, Inc.**

Established Name: **Clindamycin/Benzoyl Peroxide Gel, 1%/5%**

Labeling Deficiencies:

1. CARTON

- a. Improve the legibility of "Rx only".
- b. It appears that the established name is presented in two different fonts. Please revise accordingly.
- c. Right panel (package right side) – The font size does not look consistent. Please revise accordingly.
- d. Back panel (package back) – See comment under (c) above.

2. INSERT

We remind you that the package insert labeling must be submitted in final print as it will appear in the marketplace.

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA".

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No - ELECTRONIC

Clindamycin Phosphate Solution Container Label:

Final Product Jar Label:

Kit Carton Labeling:

Insert Labeling:

| | SUBMIT | ACTION |
|-----------|----------|---------|
| Container | 12-20-07 | APPROVE |
| Jar | 12-20-07 | APPROVE |
| Carton | 12-20-07 | REVISE |
| Insert | 12-20-07 | REVISE |

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: BenzaClin® Topical Gel

NDA Number: 50-756

NDA Drug Name: BenzaClin® (clindamycin-benzoyl peroxide gel)

NDA Firm: Sanofi Aventis US

Date of Approval of NDA Insert and supplement #: 5-23-07 (S-026)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? NO

Other Comments

NOTE TO THE CHEMIST:

The labeling of this drug product states that it must be stored at room temperature and used within three months after mixing. Is this accurate? Per first chemistry review done by S. Pittinger the firm demonstrated that the mixed product met all specifications after 0, 1, 2 and 3 months from mixing time.

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of BenzaClin® Topical Gel (NDA 50-756/S-026); approved 5-23-07.
2. Product Line:
The innovator markets their product in a carton containing a jar of benzoyl peroxide gel and a bottle of clindamycin phosphate powder – the pharmacist is to add 10 mL of purified water to the clindamycin phosphate powder then once the powder is in solution it is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.
The applicant proposes to market their product in a carton containing a jar of benzoyl peroxide and a bottle of clindamycin phosphate solution – there is no need to reconstitute the clindamycin phosphate as it is already in solution – this solution is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.

The firm met with the Agency on November 12, 2003 to discuss the submission of a 505(b)(2) for this drug product [see difference from RLD above]. After the meeting the Agency felt that it was appropriate for the firm to submit this application as a 505(j). The

Agency indicated to the Sponsor that they would need to demonstrate that their product is bioequivalent to Benzaclin (the RLD) by conducting a three-arm study; the Sponsor's combination product vs Benzaclin vs the Sponsor's vehicle. The sponsor's product should be non-inferior to Benzaclin and superior to vehicle in the treatment of acne vulgaris.

3. Patent/ Exclusivities

Patent Data – 50-756

| No | Expiration | Use Code | Use | File |
|------|------------|----------|-----|------|
| None | | | | |

Exclusivity Data – 50-756

| Code/sup | Expiration | Use Code | Description | Labeling Impact |
|----------|------------|----------|--|-----------------|
| None | | | There is no unexpired exclusivity for this product | |

4. Storage Conditions:

NDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.

ANDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.

USP – Not USP

Mixed product must be stored at room temperature and used within three months after mixing.

5. Main panel: "FOR TOPICAL USE ONLY"

Side panel: **Precautions:** For external use only. Avoid contact with eyes. **Keep out of reach of children.** May bleach fabric or hair.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

7. Contract Pharmaceutical Limited is the manufacturer.

8. This is a FIRST GENERIC.

Date of Review: 1-25-08

Date of Submission: 12-20-07

Primary Reviewer: Adolph Vezza

Date:

Team Leader: Captain Lillie Golson

Date:

cc: ANDA: 65-443
 DUP/DIVISION FILE
 HFD-613/AVezza/LGolson (no cc)
 aev/1/25/08[C:\FIRMSAM\DOWLTRS&REV\65443na2.LABELING.doc
 Review.

Following this page, 5 pages withheld in full - (b)(4) draft labeling

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/s/

Adolph Vezza
1/25/2008 03:01:20 PM
LABELING REVIEWER

Chan Park
1/25/2008 03:05:17 PM
LABELING REVIEWER
Chan Park for Lillie Golson

**APPROVAL SUMMARY
 REVIEW OF PROFESSIONAL LABELING
 DIVISION OF LABELING AND PROGRAM SUPPORT
 LABELING REVIEW BRANCH**

ANDA Number: **65-443**

Date of Submission: **February 27, 2008**

Applicant's Name: **Dow Pharmaceutical Sciences, Inc.**

Established Name: **Clindamycin/Benzoyl Peroxide Gel, 1%/5%**

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No - ELECTRONIC

Clindamycin Phosphate Solution Container Label:

Final Product Jar Label:

Kit Carton Labeling:

Insert Labeling:

| | SUBMIT | ACTION |
|-----------|---------|---------|
| Container | 2-27-08 | APPROVE |
| Jar | 2-27-08 | APPROVE |
| Carton | 2-27-08 | APPROVE |
| Insert | 2-27-08 | APPROVE |

Revisions needed post-approval: NONE

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: BenzaClin® Topical Gel

NDA Number: 50-756

NDA Drug Name: BenzaClin® (clindamycin-benzoyl peroxide gel)

NDA Firm: Sanofi Aventis US

Date of Approval of NDA Insert and supplement #: 5-23-07 (S-026)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? NO

Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

| Established Name | Yes | No | N.A. |
|--|-----|----|------|
| Different name than on acceptance to file letter? | | X | |
| Is this product a USP item? If so, USP supplement in which verification was assured. | | X | |
| Is this name different than that used in the Orange Book? | | X | |
| If not USP, has the product name been proposed in the PF? | | X | |
| Error Prevention Analysis | | | |
| Has the firm proposed a proprietary name? If yes, complete this subsection. | | X | |
| Packaging | | | |

| | | | |
|--|---|---|---|
| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | X | |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | X | |
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | | X | |
| Are there any other safety concerns? Avoid contact with eyes. | X | | |
| Labeling | | | |
| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | X | |
| Has applicant failed to clearly differentiate multiple product strengths? | | | X |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | | X | |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | X | |
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | | X |
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | X | |
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |
| Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? | | X | |
| Do any of the inactives differ in concentration for this route of administration? | | X | |
| Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? | | X | |
| Is there a discrepancy in inactives between DESCRIPTION and the composition statement? | | X | |
| Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported? | | X | |
| Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray? | | | X |
| Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION? | | | X |
| Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) | | | X |
| USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) | | | |
| Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? | | X | |
| Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | | X |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | | X | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | | | |

NOTE TO THE CHEMIST:

The labeling of this drug product states that it must be stored at room temperature and used within three months after mixing. Is this accurate? Per first chemistry review done by S. Pittinger the firm demonstrated that the mixed product met all specifications after 0, 1, 2 and 3 months from mixing time.

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of BenzaClin® Topical Gel (NDA 50-756/S-026); approved 5-23-07.
2. Product Line:
The innovator markets their product in a carton containing a jar of benzoyl peroxide gel and a bottle of clindamycin phosphate powder – the pharmacist is to add 10 mL of purified water to the clindamycin phosphate powder then once the powder is in solution it is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.
The applicant proposes to market their product in a carton containing a jar of benzoyl peroxide and a bottle of clindamycin phosphate solution – there is no need to reconstitute the clindamycin phosphate as it is already in solution – this solution is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.

The firm met with the Agency on November 12, 2003 to discuss the submission of a 505(b)(2) for this drug product [see difference from RLD above]. After the meeting the Agency felt that it was appropriate for the firm to submit this application as a 505(j). The Agency indicated to the Sponsor that they would need to demonstrate that their product is bioequivalent to Benzaclin (the RLD) by conducting a three-arm study; the Sponsor's combination product vs Benzaclin vs the Sponsor's vehicle. The sponsor's product should be non-inferior to Benzaclin and superior to vehicle in the treatment of acne vulgaris. Per Dr. Hixon the Sponsor's three-arm study was satisfactory but the firm 's final product contains propylene glycol (the RLD does not) and this may cause a problem if systemically absorbed.

3. Patent/ Exclusivities

Patent Data – 50-756

| No | Expiration | Use Code | Use | File |
|------|------------|----------|-----|------|
| None | | | | |

Exclusivity Data – 50-756

| Code/sup | Expiration | Use Code | Description | Labeling Impact |
|----------|------------|----------|--|-----------------|
| None | | | There is no unexpired exclusivity for this product | |

4. Storage Conditions:
NDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.
ANDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.
USP – Not USP
Mixed product must be stored at room temperature and used within three months after mixing.
5. Main panel: “FOR TOPICAL USE ONLY”
Side panel: **Precautions:** For external use only. Avoid contact with eyes. **Keep out of reach of children.** May bleach fabric or hair.
6. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.
7. Contract Pharmaceutical Limited is the manufacturer.
8. This is a FIRST GENERIC.

Date of Review: 3-11-08

Date of Submission: 2-27-08

Primary Reviewer: Adolph Vezza

Date:

Team Leader: Captain Lillie Golson

Date:

cc: ANDA: 65-443
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
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Review.

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/s/

Adolph Vezza
3/14/2008 10:21:49 AM
LABELING REVIEWER

Lillie Golson
3/14/2008 03:39:22 PM
LABELING REVIEWER

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **65-443**

Date of Submission: **February 27, 2008**

Applicant's Name: **Dow Pharmaceutical Sciences, Inc.**

Established Name: **Clindamycin/Benzoyl Peroxide Gel, 1%/5%**

Labeling Deficiencies:

GENERAL COMMENT

Upon further consideration, the established name for this drug product should be as shown below:

"Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%"

Please revise your labels and labeling accordingly.

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA".

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No - ELECTRONIC

Clindamycin Phosphate Solution Container Label:

Final Product Jar Label:

Kit Carton Labeling:

Insert Labeling:

| | SUBMIT | ACTION |
|-----------|---------|--------|
| Container | 2-27-08 | REVISE |
| Jar | 2-27-08 | REVISE |
| Carton | 2-27-08 | REVISE |
| Insert | 2-27-08 | REVISE |

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: BenzaClin® Topical Gel

NDA Number: 50-756

NDA Drug Name: BenzaClin® (clindamycin-benzoyl peroxide gel)

NDA Firm: Sanofi Aventis US

Date of Approval of NDA Insert and supplement #: 5-23-07 (S-026)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? NO

Other Comments

NOTE TO THE CHEMIST:

The labeling of this drug product states that it must be stored at room temperature and used within three months after mixing. Is this accurate? Per first chemistry review done by S. Pittinger the firm demonstrated that the mixed product met all specifications after 0, 1, 2 and 3 months from mixing time.

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of BenzaClin® Topical Gel (NDA 50-756/S-026); approved 5-23-07.

2. Product Line:

The innovator markets their product in a carton containing a jar of benzoyl peroxide gel and a bottle of clindamycin phosphate powder – the pharmacist is to add 10 mL of purified water to the clindamycin phosphate powder then once the powder is in solution it is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.

The applicant proposes to market their product in a carton containing a jar of benzoyl peroxide and a bottle of clindamycin phosphate solution – there is no need to reconstitute the clindamycin phosphate as it is already in solution – this solution is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.

The firm met with the Agency on November 12, 2003 to discuss the submission of a 505(b)(2) for this drug product [see difference from RLD above]. After the meeting the Agency felt that it was appropriate for the firm to submit this application as a 505(j). The Agency indicated to the Sponsor

that they would need to demonstrate that their product is bioequivalent to Benzaclin (the RLD) by conducting a three-arm study; the Sponsor's combination product vs Benzaclin vs the Sponsor's vehicle. The sponsor's product should be non-inferior to Benzaclin and superior to vehicle in the treatment of acne vulgaris. Per Dr. Hixon the Sponsor's three-arm study was satisfactory but the firm 's final product contains propylene glycol (the RLD does not) and this may cause a problem if systemically absorbed.

3. Patent/ Exclusivities

Patent Data – 50-756

| | | | | |
|------|------------|----------|-----|------|
| No | Expiration | Use Code | Use | File |
| None | | | | |

Exclusivity Data – 50-756

| Code/sup | Expiration | Use Code | Description | Labeling Impact |
|----------|------------|----------|--|-----------------|
| None | | | There is no unexpired exclusivity for this product | |

4. Storage Conditions:

NDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.
 ANDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.
 USP – Not USP
 Mixed product must be stored at room temperature and used within three months after mixing.

5. Main panel: “FOR TOPICAL USE ONLY”

Side panel: **Precautions:** For external use only. Avoid contact with eyes. **Keep out of reach of children.** May bleach fabric or hair.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

7. Contract Pharmaceutical Limited is the manufacturer.

8. This is a FIRST GENERIC.

9. This review was done to notify the firm that the established name should be “Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%” for this drug product. I left a message for A.J. Acker of the firm informing him of this deficiency.

Date of Review: 5-1-09

Date of Submission: 2-27-08

Primary Reviewer: Adolph Vezza

Date:

Team Leader: Captain Lillie Golson

Date:

cc: ANDA: 65-443
 DUP/DIVISION FILE
 HFD-613/AVezza/LGolson (no cc)
 aev/5/1/09/C:\OldComputer\cdw5106378\C-drive\FIRMSAM\DOWLTRS&REV\65443na3.LABELING.doc
 Review.

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this page is the manifestation of the electronic signature.**

/s/

Adolph Vezza
5/5/2009 02:32:09 PM
LABELING REVIEWER

Lillie Golson
5/6/2009 01:25:15 PM
LABELING REVIEWER

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **65-443** Dates of Submission: **July 1, July 24 and July 30, 2009**

Applicant's Name: **Dow Pharmaceutical Sciences, Inc.**

Established Name: **Clindamycin Phosphate and Benzoyl Peroxide Gel, 1% (base)/5%**

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No - ELECTRONIC

Clindamycin Phosphate Solution Container Label:

Final Product Jar Label:

Kit Carton Labeling:

Insert Labeling:

| | SUBMIT | ACTION |
|-----------|---------|---------|
| Container | 7-24-09 | APPROVE |
| Jar | 7-24-09 | APPROVE |
| Carton | 7-24-09 | APPROVE |
| Insert | 7-30-09 | APPROVE |

Revisions needed post-approval: CONTAINER – "... containing 0.6 grams clindamycin phosphate."
[delete "as"]

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: BenzaClin® Topical Gel

NDA Number: 50-756

NDA Drug Name: BenzaClin® (clindamycin-benzoyl peroxide gel)

NDA Firm: Sanofi Aventis US

Date of Approval of NDA Insert and supplement #: 5-23-07 (S-026)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? NO

Other Comments

NOTE TO THE CHEMIST:

The labeling of this drug product states that it must be stored at room temperature and used within three months after mixing. Is this accurate? Per first chemistry review done by S. Pittinger the firm demonstrated that the mixed product met all specifications after 0, 1, 2 and 3 months from mixing time.

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of BenzaClin® Topical Gel (NDA 50-756/S-026); approved 5-23-07.
2. Product Line:
The innovator markets their product in a carton containing a jar of benzoyl peroxide gel and a bottle of clindamycin phosphate powder – the pharmacist is to add 10 mL of purified water to the clindamycin phosphate powder then once the powder is in solution it is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.
The applicant proposes to market their product in a carton containing a jar of benzoyl peroxide and a bottle of clindamycin phosphate solution – there is no need to reconstitute the clindamycin phosphate as it is already in solution – this solution is mixed into the jar of benzoyl peroxide which results in a net quantity of 50 grams of final product.

The firm met with the Agency on November 12, 2003 to discuss the submission of a 505(b)(2) for this drug product [see difference from RLD above]. After the meeting the Agency felt that it was appropriate for the firm to submit this application as a 505(j). The Agency indicated to the Sponsor that they would need to demonstrate that their product is bioequivalent to Benzaclin (the RLD) by conducting a three-arm study; the Sponsor's combination product vs Benzaclin vs the Sponsor's vehicle. The sponsor's product should be non-inferior to Benzaclin and superior to vehicle in the treatment of acne vulgaris. Per Dr. Hixon the Sponsor's three-arm study was satisfactory but the firm 's final product contains propylene glycol (the RLD does not) and this may cause a problem if systemically absorbed.

3. Patent/ Exclusivities

Patent Data – 50-756

| No | Expiration | Use Code | Use | File |
|------|------------|----------|-----|------|
| None | | | | |

Exclusivity Data – 50-756

| Code/sup | Expiration | Use Code | Description | Labeling Impact |
|----------|------------|----------|--|-----------------|
| None | | | There is no unexpired exclusivity for this product | |

4. Storage Conditions:
NDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.
ANDA – Store at room temperature up to 25°C (68° to 77°F) [See USP]. Do not freeze. Keep tightly closed.
USP – Not USP
Mixed product must be stored at room temperature and used within three months after mixing.
5. Main panel: “FOR TOPICAL USE ONLY”
Side panel: **Precautions:** For external use only. Avoid contact with eyes. **Keep out of reach of children.** May bleach fabric or hair.
6. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.
7. Contract Pharmaceutical Limited is the manufacturer.
8. This is a FIRST GENERIC.
9. The established name is “Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%” for this drug product. Either the “1%” should have an asterisk [“1%*”] and the “*Each gram contains ...” statement should have an asterisk or the strength should be expressed as “1% (base)/5%”.

Date of Review: 8-6-09

Dates of Submission: 7-1-09, 7-24-09 AND 7-30-09

Primary Reviewer: Adolph Vezza

Date:

Team Leader: Captain Lillie Golson

Date:

cc: ANDA: 65-443
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| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
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| ANDA 65443 | ORIG 1 | | CLINDAMYCIN BENZOYL PEROXIDE |
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/s/

ADOLPH E VEZZA
08/07/2009

LILLIE D GOLSON
08/07/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-443

MEDICAL REVIEWS

SAFETY MEMORANDUM
Propylene Glycol Concentration in Topical Clindamycin Products

To: ANDA 65-443

From: John R. Peters
Medical Officer
Office of Generic Drugs

Through: Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Drug Product: Clindamycin Phosphate and Benzoyl Peroxide Gel,
1%/5%

Sponsor: Dow Pharmaceutical Sciences, Inc.

Reference Drug: BenzaClin[®] Topical Gel, 1%/5%; NDA 50-756

Date of Submissions: February 7, 2007
February 11, 2009

Date of Memorandum: April 24, 2009

Recommendation:

Evaluation of medical literature and AERS reports relating to the systemic absorption of topical clindamycin phosphate demonstrates a risk of development of *Clostridium difficile* Associated Disease (CDAD). However, the occurrence of CDAD is relatively infrequent with currently marketed topical clindamycin containing products. Additional information provided by the sponsor in the submission of 2/11/09 (Amendment 0016) provides further evidence that the propylene glycol content of the formulation presented in ANDA 65-443 would not lead to a clinically significant increase in systemic absorption of clindamycin compared to the RLD.

Also, a literature search was undertaken to evaluate the relationship between plasma concentration of clindamycin and CDAD. The reported literature for topical preparations was evaluated for evidence of enhancement of percutaneous clindamycin absorption relative to the concentration of propylene glycol (PG) in the vehicle. This review finds no evidence that the (b) (4) propylene glycol content of the formulation of clindamycin phosphate/benzoyl peroxide gel by Dow Pharmaceutical Sciences, Inc. (Dow) would increase the systemic absorption of clindamycin. Therefore, from the standpoint of clinical safety, approval of this application is recommended.

Resume:

Dow Pharmaceutical Sciences (Dow) submitted ANDA 65-443 on February 7, 2007 for a topical gel formulation of clindamycin phosphate and benzoyl peroxide (1%/5%) called (b) (4) (Test), which is indicated for treatment of acne vulgaris. The reference listed drug (RLD) for this product is BenzaClin[®] Gel (Dermick Laboratories, NDA 50-756), originally approved on December 21, 2000.

Two clinical trials of the RLD demonstrated the safety and superiority of the combination of benzoyl peroxide (BPO) and clindamycin to its individual components alone and to placebo (the vehicle alone) in the treatment of acne vulgaris. Use of this combination product for treatment of acne vulgaris is reported to reduce antimicrobial resistance compared to the use of topical clindamycin alone.¹ Also, the 2 products are synergistic in their effects; the benzoyl peroxide acting in both inflamed and non-inflamed lesions, while the clindamycin acts as a potent antimicrobial in the inflamed lesions.²

In the original Biopharmaceutical Review of the RLD (BenzaClin[®]-NDA 50-756) application a PK study was reported. In that study no measurable levels of clindamycin phosphate or its metabolites were detected. It was noted, however, that there was enhancement of absorption of benzoyl peroxide in the presence of clindamycin. Unfortunately, this PK study was considered to be non-interpretable because of technical problems, and from a biopharmaceutics point of view the NDA was not considered approvable. There are no further clinical or biopharmaceutical data regarding PK studies available in Agency reviews of the RLD. However, a subsequent safety update for BenzaClin[®] dated October 16, 2000 states “This Safety Update reports no adverse events with BenzaClin[®] Gel that would alter the safety profile previously provided.” A “Changes Being Effected” (CBE) report dated March 1, 1999 did not indicate any cases of systemic adverse events. In the clinical review of the RLD (April 9, 1998), there were no reports of subjects on clindamycin discontinuing due to gastrointestinal adverse events. The label indicates that <1% absorption of clindamycin occurs. This corresponded to a plasma concentration of approximately 3-6 ng/mL. This is consistent with that reported for other topical clindamycin products, but there is little data to support or refute the label claim. The scientific literature must be used as a reference point for this issue.

Comparison of Formulations:

The following table summarizes the formulation of the Dow (Test) product compared to the RLD:

¹ James, WD, “Acne”, NEJM, 2005, 352, Pp. 1463-1472.

² Layton, AM, “Acne Vulgaris and Similar Eruptions”, Medicine, 2005, 33:1, Pp. 44-48.

Formulation of the Dow Product

| Component | Function | Test | | Reference BenzaClin® |
|----------------------------|----------------------------------|------------------------------|--------------------|-----------------------------|
| | | %w/w (b) (4) ¹ | gm/50gm (b) (4) | w/w (b) (4) mg/gm |
| Clindamycin Phosphate, USP | Active Pharmaceutical Ingredient | (b) (4) ¹ | (b) (4) | EQ 1% Base (b) (4) mg/gm |
| Benzoyl Peroxide, USP | Active Pharmaceutical Ingredient | (b) (4) ² | (b) (4) | 5% (b) (4) mg/gm |
| Carbomer (b) (4) | (b) (4) | -- | -- | (b) (4) mg/gm |
| Carbomer (b) (4) | | (b) (4) | -- | -- |
| Sodium Hydroxide | | -- | -- | (b) (4) mg/gm |
| Potassium Hydroxide, NF | | (b) (4) | -- | -- |
| Docusate Sodium | | -- | -- | (b) (4) mg/gm |
| Propylene Glycol, USP | | (b) (4) | -- | -- |
| Purified Water, USP | | (b) (4) | -- | (b) (4) mg/gm |

¹ Equivalent to (b) (4) w/w clindamycin

² Based on (b) (4) benzoyl peroxide

³ Estimated from actual amount used in biobatch

Table reproduced from Clinical Review, ANDA 65-443, 1/8/2008, P. 39.

BenzaClin®, the RLD, contains dioctyl sodium sulfosuccinate (docusate sodium), a (b) (4) and skin penetration enhancer. In the Dow formulation, this has been replaced with (b) (4) propylene glycol (PG), a (b) (4) and skin penetration enhancer. These two compounds have rather different effects on the skin due to their chemical structures. (b) (4)

Depending on the chemical nature of the active ingredient, the anticipated penetration of the skin barrier will vary, sometimes dramatically.

Propylene Glycol Effects on Percutaneous Clindamycin Absorption:

Propylene glycol is a widely used pharmaceutical excipient, known to enhance the skin penetration of some drugs. Use of this excipient raises concerns about the relative systemic exposures to clindamycin from the Dow and RLD products. The amount of systemic clindamycin exposure is associated with a risk of *Clostridium difficile* Associated Disease (CDAD). This review addresses this safety concern and includes a review of additional information submitted to ANDA 65-443 on 2/11/09. The sponsor has provided information about 3 other clindamycin products, Acanya® Gel (NDA 50-819, also manufactured by Dow, approved 10/21/08), Clindagel® (NDA 50-782, by Galderma, approved 11/27/00), and Ziana® (NDA 50-802, by Medicis, approved

11/7/06). The submission also included additional information on the penetration enhancement effects of propylene glycol and reports of 2 additional studies demonstrating clindamycin skin penetration in vitro and in vivo. The relevance of this information is addressed in this review.

Propylene glycol is one of the most frequently used co-solvents in dermatology, but its mechanism of action as a penetration enhancer is controversial.³ Penetration enhancement and penetration reduction have both been demonstrated in topical formulations containing propylene glycol. Propylene glycol typically functions as a relatively non-volatile co-solvent in combination with other more volatile solvents. Upon application of a topical formulation containing propylene glycol as a cosolvent, the more volatile solvent(s) evaporate from the surface of the skin, as well as penetrate the skin. The less volatile propylene glycol remains as part of the residual formulation components on the skin surface. Transient *in situ* supersaturation of a drug, which has sufficient inherent solubility in propylene glycol, may result in a mixture of residual formulation with skin surface lipids. This can increase the thermodynamic activity of the drug for enhanced skin penetration. As propylene glycol penetrates the skin it can transport lipophilic substances via solvent drag. Propylene glycol activity as a penetration enhancer is better for drugs that are more soluble in alcohol than in water.⁴ Therefore, propylene glycol is widely used as a vehicle for penetration enhancers that are lipophilic in nature, such as oleic acid.³ Clindamycin phosphate is much more soluble in water than in alcohol and is therefore an unlikely candidate for penetration enhancement by PG at the concentrations evaluated in this memorandum.

Clindamycin phosphate is hydrolyzed on the skin surface to free clindamycin. In 1989 Eller, et. al.⁵ studied systemic absorption of clindamycin using Cleocin T and a formulation called "Vehicle-N", which was Neutrogena. In this study they found a much greater absorption in the Neutrogena vehicle (4-20 ng/mL versus 0.5-6 ng/mL for Cleocin T). Neutrogena is a more lipophilic base composed of glycerin, propylene glycol, and a mixture of alkylated surfactants. Cleocin T is a hydroalcoholic mixture (b)(4)% w/v in isopropyl alcohol/propylene glycol/water). The total systemic exposure is relative to the skin surface area covered by the product.⁶ Earlier studies⁷ of topical clindamycin indicated that the systemic availability of topical clindamycin ranges from 7.5%-8% of the applied dose to a maximum of 12.5%. These authors concluded that "...systemic absorption from these topical clindamycin preparations is minimal, but is highly dependent on the vehicle used." They further suggested that the increase in absorption of

³ Williams, AC, Barry, BW, "Penetration Enhancers", Advanced Drug Delivery Reviews, 2004, 54, Pp. 603-618.

⁴ Trommer, H, Neubert, RHH, "Overcoming the Stratum Corneum: The Modulation of Skin Penetration", Skin Pharmacol Physiol, 2006, 19, Pp. 106-121.

⁵ Eller, MG, Smith, RB, Phillips, JP, "Absorption Kinetics of Topical Clindamycin Preparations", Biopharmaceutics & Drug Disposition, 1989, 10, Pp. 505-512.

⁶ Milstone, EB, McDonald, AJ, Scholhamer, CF, "Pseudomembranous Colitis After Topical Application of Clindamycin", Arch Dermatol, 1981, 117, Pp.154-155.

⁷ Van Hoogdalem, EJ, "Transdermal absorption of topical anti-acne agents in man; review of clinical pharmacokinetic data", J Eur Acad Dermatol Verereol, 1998, 11 (Suppl 1):S13-19; discussion S28-9.

clindamycin in Vehicle-N was due to the nonionic surfactant. Both preparations studied contained propylene glycol and both were hydroalcoholic in nature.

Comment: This is consistent with Dow's assertion that the (b) (4) PG in the (b) (4) formulation is safe and will not increase the plasma concentration of clindamycin.

Potential skin penetration enhancement from propylene glycol is also thought to result from solvation of alpha-keratin within the stratum corneum and occupation of proteinaceous hydrogen bonding sites, thereby reducing drug-tissue binding and thus promoting skin penetration.³ With respect to the potency of propylene glycol as a skin penetration enhancer, it affords only mild enhancement effects at best. Skin penetration enhancement with propylene glycol is associated with lipophilic compounds. Clindamycin phosphate is not a good drug candidate for skin penetration enhancement by propylene glycol, because it is not lipophilic. Clindamycin phosphate has good water solubility. Therefore, percutaneous absorption of clindamycin is not significantly enhanced by propylene glycol concentrations in the range of concentrations considered in this review.

Clinical Background:

Clindamycin phosphate is the water soluble ester of clindamycin and phosphoric acid. It is a minimally active pro-drug that is rapidly hydrolyzed in vivo to the active compound, which is clindamycin base, a bacteriostatic antimicrobial. In the treatment of acne vulgaris the target organism is primarily the *Propionibacterium acnes* in the skin, although other skin pathogens may be present.⁸ Presence of these pathogens is associated with inflammatory lesions in the skin which have been related to direct stimulation of the innate immune response through activation of Toll-like receptor-2 and other chemotactic factors.^{9,10} Topical antimicrobial treatments deliver local "skin" doses of antibiotic well in excess of the MIC of *P. acnes*. Comedonal concentrations of clindamycin following a topical application of 1% solutions averaged 597 µg/g of comedonal material with systemic absorption of <0.5 ng/mL plasma concentration.¹¹ Activation of the innate immune response in the skin further alters the permeability of the skin barrier to systemic absorption. Thus, the penetration enhancers found in the test and RLD products could have a different impact on inflamed skin with acne lesions than on otherwise intact skin.

Clindamycin is excreted in urine and bile. Approximately 10% is excreted unchanged in urine, the rest is metabolized in the liver to N-dimethyl clindamycin and clindamycin sulfoxide.¹² With currently available topical products, it is estimated that up to 7.5%-

⁸ Becker, LE, Bergstresser, PR, Whiting, PR, Clendenning, WE, et. Al., "Topical clindamycin therapy for acne vulgaris. A cooperative clinical study", Arch Dermatol, 1981, 117:8, Pp. 482-485.

⁹ Ryan, KJ, Sherris Medical Microbiology, 4th Edition Chapter 59, "Skin and Wound Infections".

¹⁰ James, WD, "Acne", NEJM, 2005, 352, Pp. 1463-1472.

¹¹ AHFS Drug Information, 2008

¹² Sun, FF, "Metabolism of clindamycin II: Urinary excretion products of Clindamycin n rat and dog", J Pharm Sci, 1973, 62, Pp. 1657-1652.

8.0% of the topically applied clindamycin is absorbed systemically. Earlier reports¹³ suggested as much as 10%-12.5% absorption of clindamycin hydrochloride, but no clindamycin hydrochloride topical product is in current use. With the older product, it was estimated that an average of 2 mg/day was absorbed with facial applications and up to 20 mg/day with combined applications to the face, chest, and back.^{14, 15} This contrasts to the usual oral dose of clindamycin, which is 300 mg twice daily (600-1200 mg/day for serious infections).

Comment: In the medical literature there are many reports of systemic concentrations ranging from 0 (not measurable) up to 20 ng/mL with different excipients in the formulation. Generally, a range of 3-6 ng/mL is reported for topical use of clindamycin in a 1% concentration.

Suppression of normal gastrointestinal flora by clindamycin allowing *C. difficile* overgrowth is believed to be an underlying cause of CDAD, together with prior colonization of the intestine.¹⁶ Even early in the history of use of topical clindamycin there were occasional case reports of *C. difficile* related diarrhea.¹⁷ It is also known that at very low systemic levels of clindamycin (≤ 0.5 ng/mL) there is a noticeable change in the intestinal flora.^{18,19} Numerous studies have demonstrated that a wide range of systemic levels of clindamycin have been associated with a particularly severe colitis, *Clostridium difficile* Associated Diarrhea (CDAD)^{20,21,22,23,24} and other adverse events.^{25,26}

¹³ Stoughton, RB, "Topical Antibiotics for Acne Vulgaris: Current Usage", Arch Dermatol, 1979, 115, Pp.486-489.

¹⁴ Milstone, EB, McDonald, AJ, Scholhamer, CF, "Pseudomembranous Colitis After Topical Application of Clindamycin", Arch Dermatol, 1981, 117, Pp.154-155.

¹⁵ Parry, MF, Rha, CK, "Pseudomembranous colitis caused by topical clindamycin phosphate", Arch Dermatol, 1986, 122, Pp. 583-584.

¹⁶ Gerding, DN, Johnson, S, Harrison's Principles of Internal Medicine, 17th Edition, Chapter 123, "Clostridium difficile-Associated Disease, Including Pseudomembranous Colitis".

¹⁷ Fisher, AA, "Adverse reactions to topical clindamycin, erythromycin, and tetracycline", Cutis, 1983, 32, Pp. 415-28.

¹⁸ Siegle, RJ, Fekety, R, Sarbone, PD, Finch, RN, et. al., "Effects of topical clindamycin on intestinal microflora in patients with acne", J Am Acad Dermatol, 1986, 15:2, Pp. 180-185.

¹⁹ Borglund, E, Hagermark, O, Nord, CE, "Impact of topical clindamycin and systemic tetracycline on the skin and colon microflora in patients with acne vulgaris", Scand J Infect Dis, 1984, Suppl 43:76-81.

²⁰ Krautheim, A, Gollnick, H, "Transdermal Penetration of Topical Drugs Used in the Treatment of Acne", Clinical Pharmacokinetics, 2003, 42:14, Pp. 1287-1304.

²¹ Gerber, M, Walch, C, Loffler, B, Tischendorf, K, et. Al., "Effect of sub-MIC concentrations of metronidazole, vancomycin, clindamycin and linezolid on toxin gene transcription and production in *Clostridium difficile*", Journal of Medical Microbiology, 2008, 57:6, Pp. 776-783.

²² Siegle, RJ, Fekety, R, Sarbone, PD, Finch, RN, et. al., "Effects of topical clindamycin on intestinal microflora in patients with acne", J Am Acad Dermatol, 1986, 15:2, Pp. 180-185.

²³ Akhavan, A, Bershada, S, "Topical Acne Drugs: Review of Clinical Properties, Systemic Exposure, and Safety", American Journal of Clinical Dermatology, 2003, 4:7, Pp.473-492.

²⁴ Barza M, JA Goldstein, Kane, A, et al., "Systemic absorption of clindamycin hydrochloride after topical treatment", J Am Acad Dermatol, 1982, 7, Pp. 208-214.

²⁵ de Groot MCH, van Puijenbroek EP, "Clindamycin and taste disorders", British Journal of Clinical Pharmacology, 2007, 64:4, Pp. 542-545.

In the past several years, there have been reports of a significant increase in *Clostridium difficile* associated diarrhea (CDAD). Some have described it as a new epidemic²⁷ and there are reports of an increase in the severity of the condition due to a mutational change in the toxins produced. The extent of systemic absorption is a significant safety concern, particularly when larger surface areas of skin are treated (face, neck, chest, back). Barza, et.al. (1982)²⁸ described “striking variation from subject to subject in both the concentration and amount of clindamycin excreted in the urine”.

There have been a number of studies which investigated the relative risk of development of CDAD with antibiotic use. Levy, et. al.²⁹ in 2000 reported the prevalence of CDAD to be 12 per 100,000 for all antibiotics in an ambulatory population. Cefuroxime demonstrated the highest relative odds ratio of 7.5 for CDAD, but the authors note that clindamycin and other known high CDAD risk antibiotics are infrequently used in the ambulatory setting, suggesting that the lower rate is relative to the lesser use of the clindamycin in ambulatory patient care. In fact, clindamycin and other high risk antibiotics have not been used in the ambulatory setting specifically because of the concern over CDAD.³⁰ Given the recent reports of a new epidemic of CDAD, it is apparent that the prevalence of colonization and/or exposure to *C. difficile* has been increasing and the disease itself is becoming more serious.^{31,32} Bartlett, et. al.²⁷, suggest that 2-4% of all adults are now colonized, and rates of 20-40% colonization occur in institutional settings. The population at risk is greater now than in the past. Considering the widespread ambulatory use of topical and vaginal clindamycin preparations, any enhancement of systemic absorption needs to be carefully considered due to this increased rate of colonization in the population posing greater risk of CDAD with any use of antibiotic.

In the FDA Adverse Events Reporting System (AERS) a search of all clindamycin topical acne preparations revealed few cases of colitis. The following table relates the reporting of “preferred terms” consistent with or possibly related to CDAD for 4 categories of clindamycin preparations. Ophthalmic and otic preparations were not included in this report.

²⁶ Scissors, B, Schwayder, T, “Topical clindamycin reproducibly causing tinnitus in a 14-year-old boy”, J Am Acad Dermatol 2006, 54:5, Pp. s23-22

²⁷ Bartlett, JG, “Narrative Review: The New Epidemic of *Clostridium difficile*–Associated Enteric Disease”, Annals of Internal Medicine, 2006;145:758-764.

²⁸ Barza, M, Goldstein, JA, Kane, A, Feingold, DS, et. al., “Systemic absorption of clindamycin hydrochloride after topical application”, J Am Acad Dermatol, 1982, 7, Pp. 208-214.

²⁹ Levy, DG, Stergachis, A, McFarland, LV, van Vorst, K, et. al., “Antibiotics and *Clostridium difficile* Diarrhea in the Ambulatory Care Setting”, Clinical Therapeutics, 2000, 22:1, Pp. 91-102.

³⁰ McFarland, LV, “Update on the changing epidemiology of *Clostridium difficile*-associated disease”, Nature Clinical Practice Gastroenterology and Hepatology, 2008, 5:1, Pp. 40-48.

³¹ Bartlett, JG, “Narrative Review: The New Epidemic of *Clostridium difficile*–Associated Enteric Disease”, Annals of Internal Medicine, 2006;145:758-764.

³² Razavi, B, Apisarnthanarak, A, Mundy, LM, “*Clostridium difficile*: Emergence of hypervirulence and fluoroquinolone resistance”, Infection, 2007, 35:5, Pp. 300-307.

Preferred Term AERS Summary for Clindamycin Preparations

| AE | Systemic | Vaginal Suppository | Vaginal Cream | Topical Preparation |
|--|----------|---------------------|---------------|---------------------|
| Total Reports | 12427 | 23 | 365 | 211 |
| Abnormal Feces | 13 | | 2 | |
| Anal Hemorrhage/Anorectal Disorder | 1 | | | 1 |
| Bacterial Stool Infection | 8 | | | |
| Bacterial Sepsis | 3 | | | |
| Clostridial Infection/Colitis/Toxin | 657 | | 9 | 3 |
| Colitis | 503 | | 9 | 4 |
| Colitis, Ulcerative | 81 | | 2 | 1 |
| Diarrhea/Fecal Incontinence/Frequent Bowel Movements | 840 | | 20 | 15 |
| Diarrhea Hemorrhagic/Infectious/Pus in Stool/Melena | 75 | 1 | 3 | 5 |
| Endotoxin Shock | 1 | | | |
| Hematochezia | 14 | | 1 | |
| Inflammatory Bowel Disease | 1 | | | |
| Intestinal Hemorrhage | 1 | | | |
| Irritable Bowel Syndrome | 1 | | | |
| Large Intestine Ulceration/Perforation/Toxic Dilation/Necrosis | 9 | 1 | | 2 |
| Mucous Stools/Mucosal Hemorrhage | 5 | | | 2 |
| Painful Defecation | 1 | | | |
| Peritonitis/Sepsis/Septic Shock | 109 | | | 1 |
| Proctalgia/Proctitis/Rectal Hemorrhage/Rectal Discharge/Tenesmus | 33 | | 1 | |
| Pseudomembranous Colitis | 5 | | | 1 |
| Total Reports Consistent With CDAD Episode | 2371 | 1 | 47 | 35 |

Compiled from AERS using Preferred Term Report and selecting all clindamycin products in each category.

Comment: It must be noted that the AERS only records reported events and does not indicate the actual rate of an adverse event proportional to the total use of the medication. However, the number of reported events that could be consistent with CDAD does indicate a similarity between the vaginal cream and topical preparations of clindamycin. Both of these are proportionally much lower than that of the systemic

product. There is only one marketed vaginal suppository of clindamycin and the much lower reporting is probably related to a lower overall utilization of this product. Interestingly, when expressed as % of total reported AEs, there is not much difference in % of reports consistent with CDAD with use of the vaginal cream or topical product compared to the systemic products (12.9%, 16.6%, and 19.1% respectively). This would seem to suggest that, while many fewer patients report any AEs to vaginal cream or topical clindamycin compared to systemic clindamycin, the proportion of total AE reports that are consistent with CDAD-like problems is very similar regardless of the route of administration.

The plasma concentration of clindamycin appears to be related to the risk of CDAD. Thus, it is important that there be an adequate margin of safety to allow for broad individual variation in the surface area of skin treated and in the systemic absorption of this drug. The product formulation can significantly impact the systemic absorption of clindamycin as was demonstrated clearly in a cross-over study by Chassard, et. al. (2006).³³

Topical clindamycin has rarely been associated with CDAD, and the risk of developing CDAD appears to be lower with clindamycin phosphate, which is absorbed percutaneously to a lesser extent than clindamycin hydrochloride.³⁴ There are only 2 documented case reports in the literature of CDAD following topical application of clindamycin. One case occurred in a patient using clindamycin hydrochloride and one in a patient treated with clindamycin phosphate.^{12, 35, 36} It is important that there be an adequate margin of safety to allow for broad individual variation in the surface area of skin treated and in the systemic absorption of this drug. The product formulation can significantly impact the systemic absorption of clindamycin as was demonstrated clearly in a cross-over study by Chassard, et. al. (2006).³⁷

In order to determine an appropriate risk:benefit for topical clindamycin products it is desirable to consider a “relatively safe” plasma concentration at which minimal or no significant changes to the intestinal flora are identifiable, or at least a level at which no cases of CDAD are known to occur. Unfortunately, there is nothing in the medical literature that clearly identifies such a safe plasma concentration. Changes in intestinal

³³ Chassard, D, Kanis, R, Manour, F, Evene, E, et. al., “A single centre, open-label, cross-over study of pharmacokinetics comparing topical zinc/clindamycin gel (Zindaclin) and topical clindamycin lotion (Dalacin) in subjects with mild to moderate acne”, *Journal of Dermatological Treatment*, 2006, 17, Pp. 154-157.

³⁴ Milestone, EB, McDonald, AJ, Scholhamer, “Pseudomembranous colitis after topical application of clindamycin”, *Arch Dermatol*, 1981, 117, Pp. 154-155.

³⁵ Parry, MF, Rha, CK, “Pseudomembranous colitis caused by topical clindamycin phosphate”, *Arch Dermatol*, 1986, 122, Pp. 583-584.

³⁶ Parry, MF, Rha, CK, “Pseudomembranous colitis caused by topical clindamycin phosphate”, *Arch Dermatol*, 1986, 122, Pp. 583-584.

³⁷ Chassard, D, Kanis, R, Manour, F, Evene, E, et. al., “A single centre, open-label, cross-over study of pharmacokinetics comparing topical zinc/clindamycin gel (Zindaclin) and topical clindamycin lotion (Dalacin) in subjects with mild to moderate acne”, *Journal of Dermatological Treatment*, 2006, 17, Pp. 154-157.

flora have been identified with as little as 0.5 ng/mL³⁸, but it is not known how that impacts on the occurrence of CDAD. As summarized in the table above, topical dermatologic clindamycin products are generally considered to result in a plasma concentration of 0.5-6 ng/mL. Vaginal cream preparations deliver approximately 25 ng/mL versus an average of 270 ng/mL for the vaginal suppository. This compares to 200-400 ng/mL for the 100 mg oral preparation. The usual oral dosage is 300 mg twice daily, and the usual oral plasma concentration is 600-1200 ng/mL. Even with topical use, 0.1% of 73,000 patients (AHFS Drug Information) receiving topical clindamycin experience GI adverse effects including CDAD. While not insignificant, this number does suggest that the risk associated with topical use of clindamycin preparations is quite small. A similar low risk is associated with vaginal clindamycin preparations.

Mean plasma concentrations of clindamycin in a range of 0.5-6 ng/mL have been reported with use of the currently available topical clindamycin products. Becker, et. al.³⁹, in 1981 evaluated the effect of clindamycin therapy in the treatment of acne. They enrolled 358 patients in 3 arms (clindamycin phosphate 1%, clindamycin hydrochloride 1%, and hydroalcoholic vehicle). In that study there were 12 episodes of diarrhea in patients receiving clindamycin, but it was difficult to assign attribution. More recently (2003) Akhavan and Barshad⁴⁰, in a review of all topical acne products, reported that “Clear-cut links to systemic toxicity in humans are practically nonexistent, except in the case of topical clindamycin, which has been associated with diarrhea rarely, and there have been 2 cases of pseudomembranous colitis reported.”

The approved labeling of BenzaClin[®] states that the mean systemic bioavailability of topical clindamycin in BenzaClin[®] Topical Gel is suggested to be less than 1%, producing plasma concentrations of approximately 3-6 ng/mL. The labeling also includes the following warning concerning the use of topical agents containing clindamycin:

“Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis...When significant diarrhea occurs, the drug should be discontinued...”

On February 7, 2007, Dow submitted ANDA 65-443 for Clindamycin Phosphate and Benzoyl Peroxide Gel 1%/5% identifying BenzaClin[®] as the RLD, and providing results of a multicenter, evaluator-blind, randomized, vehicle controlled, parallel group study, comparing the Dow product to the RLD, BenzaClin[®]. This study used the primary

³⁸ Siegle, RJ, Fekety, R, Sarbone, PD, Finch, RN, et. al., “Effects of topical clindamycin on intestinal microflora in patients with acne”, J Am Acad Dermatol, 1986, 15:2, Pp. 180-185.

³⁹ Becker, LE, Bergstresser, PR, Whiting, PR, Clendinning, WE, et. Al., ”Topical clindamycin therapy for acne vulgaris. A cooperative clinical study”, Arch Dermatol, 1981, 117:8, Pp. 482-485.

⁴⁰ Akhavan, A, Bershad, S, “Topical Acne Drugs: Review of Clinical Properties, Systemic Exposure, and Safety”, American Journal of Clinical Dermatology, 2003, 4:7, Pp. 473-492.

| | | | | | |
|-------------------|-----|--------|---------|---|--------------|
| (b) (4) (Test) | Gel | 65-443 | (b) (4) | 1 | Not reported |
|-------------------|-----|--------|---------|---|--------------|

The following table is a composite taken from product labels, clinical, biopharmaceutical, and pharmacologic/toxicologic reviews in the Agency's Division File System (DFS) and Electronic Document Room (EDR). It summarizes the estimated plasma concentrations of a number of the clindamycin containing topical products (current ANDA and RLD are **bolded**):

Propylene Glycol Content of Clindamycin Topical and Vaginal Preparations

| NDA/ ANDA # | Sponsor | Date of Approval | Dosage Form | Strength | Amt of Propylene Glycol | Estimated Plasma Conc. (ng/mL) |
|-------------------------|---------------------------|---------------------|-----------------------------------|-----------------|---------------------------------|---|
| 50-741 | Stiefel | 8/26/2002 | Gel (with Benzoyl Peroxide) | 1%/5% | none | <0.5 |
| 50-537 | Pharmacia/ Upjohn | 7/9/1980 | Solution | 1% | n/a | 0-3 |
| 50-600 | Pharmacia/ Upjohn | 5/31/1989 | Lotion | 1% | none | 0-3 |
| 50-615 | Pharmacia/ Upjohn | 1/7/1987 | Gel | 1% | n/a | 0-3 |
| 50-782 | Galderma | 11/27/2000 | Gel | 1% | (b) (4) % (w/w) | <0.5 |
| 50-801 | Connetics | 10/22/2004 | Topical Foam | 1% | (b) (4) % (w/w) | <3.1 |
| 50-802 | Medicis | 11/7/2006 | Gel (with Tretinoin) | 1.2%/0.02 5% | none | 3.5 |
| 62-811 | Actavis Mid Atlantic | 9/1/1988 | Solution | 1% | none | 0-3 |
| 63-304 | Morton Grove | 7/15/1997 | Solution | 1% | (b) (4) mL/mL (b) (4) % v/v) | n/a |
| 63-329 | Paddock | 9/30/1992 | Solution | 1% | n/a | n/a |
| 64-050 | Perrigo | 11/30/1995 | Solution | 1% | (b) (4) % v/v | n/a |
| 64-108 | Stiefel Labs | 9/27/1996 | Solution | 1% | (b) (4) % v/v | n/a |
| 64-136 | Perrigo | 9/30/1996 | Solution | 1% | (b) (4) g/100 mL | n/a |
| 65-049 | Perrigo | 5/25/2000 | Solution (Pledgets) | 1% | (b) (4) v/v | n/a |
| 65-184 | Taro Pharm | 3/31/2004 | Solution | 1% | none | n/a |
| 50- 756(RLD) | Sanofi Aventis | 12/21/2000 | Gel | 1%/5% | none | 3-6 |
| 65-443 | Dow | In Review | Gel | 1%/5% | (b) (4) w/w | -- |

| | | | | | | |
|--------|----------------------|-----------|---------------------|--------|------|----------------------------|
| 50-793 | KV Pharm | 1/30/2004 | Vaginal Cream | 2% | none | Cmax 6.6 (0.8-39 range) |
| 50-767 | Pharmacia/ Upjohn | 8/13/1999 | Vaginal Suppository | 100 mg | none | 270 (30-670 range) |

In 1983 Franz⁴¹ reported that the percutaneous absorption of clindamycin hydrochloride varied greatly among 14 formulations with different vehicles, all containing propylene glycol. All of the formulations tested contained the same amount of clindamycin hydrochloride (1.2%), and penetration was measured in vitro utilizing cadaveric monkey skin. There was minimal difference in the 24 hour absorption of clindamycin with 3 concentrations of propylene glycol, ranging from 5% to 40%. However, these formulations also differed widely in the concentration of alcohol, which could also impact skin penetration. It was felt that the similarity in absorption between these formulations was relative to the need for a minimum ratio of the water to alcohol concentration required to solubilize the clindamycin. Franz concluded that

“These data appear to confirm the earlier observations of Orr et al, who found that a minimum concentration of water was essential for adequate solubilization of clindamycin hydrochloride. In their work, a minimum of 7.5% water in ethanol, or 11.5% water in isopropanol, was required to achieve a 1.0% concentration of clindamycin hydrochloride when pure drug was used.”

The above-mentioned 1979 study report by Orr, et. al.⁴² discussed the compounding of clindamycin for topical use prior to the FDA approval of a topical commercial product. In this discussion of compounding either clindamycin hydrochloride or clindamycin phosphate, the authors suggest that the ideal vehicle for topical clindamycin would consist of 70% alcohol (isopropanol for the clindamycin phosphate or ethanol for the clindamycin hydrochloride), 10% propylene glycol, and 20% water. Their observations suggest that a 20% water concentration is necessary for optimal solubilization of the clindamycin while the PG serves as a non-volatile, miscible liquid which would be left on the skin and would improve partitioning of the drug into the skin, pores, and comedones. They do not address the plasma concentrations of clindamycin produced by topical products with their vehicle.

The sponsor submitted reports of 2 additional studies to further support a conclusion that the any risk for enhancement of clindamycin absorption by (b)(4) PG content in the formulation is low:

⁴¹ Franz, TJ, “On the bioavailability of topical formulations of clindamycin hydrochloride” J Am Acad Dermatol, 1983, 9, Pp. 66-73.

⁴² Orr, RJ, Lacina, NC Peters, LS, Flynn, GL, “Topical clindamycin for acne. Part 2. Guidelines for extemporaneous compounding”, Am Pharm, 1979, 18, Pp. 23-26.

1. Study Report No. 2104-047: In Vitro Percutaneous Absorption of Clindamycin and Benzoyl Peroxide from Benzaclin, (b) (4) (1/2.5), (b) (4) (1/5), and Duac Topical Gel Using Intact Human Skin from Two Healthy Donors
2. Study Report No. CGEL-005: An Open Label Randomized Study of the Comparative Absorption of Clindagel Versus Cleocin T in Subjects with Acne Vulgaris

Comment: The first of these studies is important in demonstrating that the presence of benzoyl peroxide (BPO) in the formulation does not impact the percutaneous absorption of clindamycin. The in vitro results of clindamycin skin penetration do not predict the plasma concentration of clindamycin in patients utilizing either product, but the results do demonstrate that the absorption of drug is similar regardless of the presence or absence of BPO. This finding allows for a reasonable comparison of the percutaneous absorption of clindamycin with differing PG concentrations, as shown in the second of these studies, with the anticipated absorption of PG in the Dow product in ANDA 65-443.

MOR Summary of Study Report No. 2104-047

Study Title:

“In Vitro Percutaneous Absorption of Clindamycin and Benzoyl Peroxide from Benzaclin, (b) (4) (1/2.5), (b) (4) (1/5), and Duac Topical Gel Using Intact Human Skin from Two Healthy Donors”

Summary of Study 2104-047:

This is an in vitro skin permeation study comparing the penetration of clindamycin and benzoyl peroxide (BPO) in 4 different preparations: Dow’s (b) (4) (1/2.5) (marketed as Acanya Gel), Dow’s (b) (4) (1/5) (pending approval of the current application), BenzaClin[®], and Duac .

Background:

A previous investigation (BenzaClin[®], NDA 50-756) demonstrated that clindamycin skin permeation in the presence of benzoyl peroxide following topical application to cadaveric skin is very low, ~0.5 percent of the applied dose. It has also been shown that benzoyl peroxide has no effect on the absorption or metabolism of topical clindamycin.⁴³

It was hypothesized that the skin permeation of both clindamycin and BPO from the Acanya Gel will be low (2% or less of the applied dose). Penetration of Clindamycin should be independent of the concentration of BPO. The clindamycin penetration profiles

⁴³ Leyden, JJ, Hickman, JG, Harratt, MT, Stewart, DM, Levy, SF, “The efficacy and Safety of a Combination Benzoyl Peroxide/Clindamycin Topical Gel Compared with Benzoyl Peroxide Alone and a Benzoyl Peroxide/Erythromycin Combination Product”, J Cutaneous Med and Surg, 2001, 5:1, Pp. 37-42.

for the 4 formulations tested were expected to be similar. BPO was expected to be converted to benzoic acid, which will quickly partition into the receptor solution.

Comment: Relevant to our question regarding the safety of the (b) (4) % PG in the vehicle, Dow preparations contain either (b) (4) or (b) (4) PG. Neither BenzaClin[®] nor Duac[®] contain any PG.

Methodology:

The in vitro percutaneous absorption of clindamycin, benzoyl peroxide, and benzoic acid was measured following a single topical application of a dose of 5 mg/cm² of formulation to dermatomed human abdominal skin obtained from 2 healthy donors following elective surgery. Percutaneous absorption was evaluated using this human abdominal tissue mounted in Bronaugh flow-through diffusion cells maintained at a constant temperature of 32 °C. Fresh receptor solution, PBS with 0.1% sodium azide and 4% Bovine Serum Albumin, was continuously pumped under the tissue at a flow rate of 1.5 mL/hr and collected in 6-hour intervals. Following the 24-hour duration of exposure, formulation residing on the tissue surface was obtained by tape-stripping and then separating the epidermis from the dermis by blunt dissection.

Concentrations of clindamycin, benzoyl peroxide, and benzoic acid residing in the epidermis, dermis, and receptor solution samples were measured by reversed phase high performance liquid chromatography (HPLC), with ultraviolet (UV) and mass spectroscopic detection (HPLC/UV/MS). One hundred sixty (160) receptor solution samples were assayed. These represent 4 preparations of skin from each of 2 donors (8 skin samples total).

Results:

Only 1 receptor solution contained clindamycin levels greater than the 2.0 ng/mL limit of quantification. Cell ID D4 for (b) (4) (1/5) assayed to contain 2.54 ng/mL at the 12-hour sampling point. None of the other 4 replicate cells containing skin from the same donor contained concentrations of clindamycin greater than 2.0 ng/mL. Likewise, none of the dermis samples for Acanya[®] Gel, (b) (4) (1/5), BenzaClin[®] or Duac[®] contained clindamycin above that level. The percent dose permeated is typically calculated based upon the amount of active ingredient assayed in the receptor solution. Only the levels of clindamycin in the epidermis provided assay values consistently above the 200 ng/sample limit of quantification. Limits of quantification of the assay are summarized in the following table:

Limits of Quantitation

| Analyte | Receptor Solution (ng/mL) | Epidermis (µg /sample) | Dermis (µg /sample) |
|------------------|---------------------------|------------------------|---------------------|
| clindamycin | 2.0 | 0.20 | 0.20 |
| benzoic acid | 200.0 | 40.0 | 40.0 |
| benzoyl peroxide | 400 | 40.0 | 40.0 |

Reproduced from Sponsor's Study 2104-047, P. 13.

The following tables summarize the range of concentration of clindamycin for all preparations for each donor:

Clindamycin Concentration Ranges for All Samples of Donor 1

| | Receptor Phase (ng/mL) | | | | Epidermis (ng/sample) | Dermis (ng/sample) |
|------------------------|------------------------|---------|----------|----------|-----------------------|--------------------|
| | 6 hr | 12 hr | 18 hr | 24 hr | 24 hr | 24 hr |
| BenzaClin [®] | ND*-0.482 | ND | ND | ND | 338-3060 | ND-48 |
| Duac | ND | ND | ND | ND | 230-804 | ND |
| Acanya Gel | ND | ND | ND | ND | 123-336 | ND-12.4 |
| (b) (4) 1/5 | ND-1.91 | ND-2.54 | ND-0.486 | ND-0.595 | 135-3380 | ND |

Taken from Sponsor's Study 2104-047, P. 17.

*ND=none detected

Clindamycin Concentration Ranges for All Samples of Donor 2

| Formulation | Receptor Phase (ng/mL) | | | | Epidermis (ng/sample) | Dermis (ng/sample) |
|------------------------|------------------------|-------|-------|-------|-----------------------|--------------------|
| | 6 hr | 12 hr | 18 hr | 24 hr | 24 hr | 24 hr |
| BenzaClin [®] | ND-0.895 | ND | ND | ND | 512-1086 | ND-85.8 |
| Duac | ND | ND | ND | ND | 604-3080 | ND-135 |
| Acanya Gel | ND | ND | ND | ND | 260-1600 | ND-204 |
| (b) (4) 1/5 | ND-0.455 | ND | ND | ND | 322-1704 | ND-188 |

Taken from Sponsor's Study 2104-047, P. 17.

Comment: The delivery of clindamycin into the epidermis is variable for all of the formulations tested. The percent of the applied dose delivered to the epidermis and dermis was similar for BenzaClin[®], which does not contain PG, and (b) (4) 1/5, which contains (b) (4) % PG. This information has been summarized in the following table:

Mean Clindamycin Concentration in the Epidermis at 24 Hours

| Formulation - | Donor | Epidermis | |
|----------------------------|---------|--------------------|----------------|
| | | ng/cm ² | % Dose Applied |
| BenzaClin [®] Gel | Donor 1 | 1985 | 4 |
| | Donor 2 | 1251 | 3 |
| Duac [®] Gel | Donor 1 | 699 | 2 |
| | Donor 2 | 2354 | 5 |

| | | | |
|-------------------------|---------|------|---|
| Acanya [®] Gel | Donor 1 | 349 | 1 |
| | Donor 2 | 1234 | 3 |
| (b) (4) 1/5 | Donor 1 | 1586 | 3 |
| | Donor 2 | 1324 | 3 |

Taken from Sponsor's Study 2104-047, P. 16.

Comment: The results of this study are in agreement with previous investigators that have shown very low levels of clindamycin skin permeation in the presence of benzoyl peroxide following topical application. Permeation of clindamycin into the dermis appears independent of the amount of BPO present in the formulation. PG in the vehicle does not appear to significantly change clindamycin penetration in (b) (4) or (b) (4) concentrations.

MOR CONCLUSIONS from Study 2104-047

1. Percutaneous absorption of clindamycin from (b) (4) (1/5) Gel is comparable to that of the currently marketed products Acanya[®] Gel, BenzaClin[®] Gel, and Duac[®] Gel within the limits of the assay, which is 2 ng/mL. These findings are consistent with previous studies demonstrating that clindamycin skin penetration in the presence of benzoyl peroxide following topical application is very low.
2. Interpretation of this study is very limited due to the nature of the dermatomed skin preparations, the very small number of samples (only 2 subjects), and to the limited ability of the assay to measure small amounts of clindamycin. The presence of BPO does not seem to affect clindamycin absorption as demonstrated in the epidermal concentrations observed.
3. The sponsor concludes that BPO does not significantly impact the percutaneous absorption of clindamycin. While this study is inadequate for evaluating the actual percutaneous penetration of clindamycin, it is reasonable to infer that the dermal penetration is not significantly effected by BPO. This establishes that it is reasonable to consider a study comparing the percutaneous absorption characteristics of clindamycin topical preparations which do not contain BPO, but have differing concentrations of PG. The in vivo evaluation for clindamycin absorption in the absence of BPO can reasonably be considered in the second study submitted (CGEL-005).

MOR Summary of Study Report No. CGEL-005

Study Title:

“An Open Label Randomized Study of the Comparative Absorption of Clindagel versus Cleocin T in Subjects with Acne Vulgaris”

Summary of Study CGEL-005:

This is a randomized, parallel, comparative treatment study to characterize the systemic absorption of Clindagel[®] and Cleocin T[®] Gel in subjects with acne vulgaris. The study was conducted to support the 2000 approval of the Clindagel[®] NDA 50-782. In this study the safety and absorption of these products were compared regarding skin irritation, adverse event occurrence, urinary excretion of clindamycin, and plasma concentration of clindamycin.

Background:

Cleocin T[®] Gel 1% was approved on January 7, 1987 under NDA 50-615/008. Clindagel[®] was approved on November 27, 2000 under NDA 50-782. Clindagel[®] consists of 1% clindamycin phosphate in a vehicle of methylparaben, Carbomer 941, propylene glycol ((b)(4)%), sodium hydroxide, and purified water. Cleocin T[®] Gel contains 1% clindamycin phosphate in a vehicle of allantoin, carbomer 934P, methylparaben, polyethylene glycol, propylene glycol ((b)(4)), sodium hydroxide, and purified water. This study was designed as a randomized, parallel, comparative treatment study to characterize the systemic absorption of Clindagel[®] and Cleocin T[®] Gel in subjects with acne vulgaris.

Comment: It should be noted that in study 2104-047 the effect of benzoyl peroxide on the percutaneous absorption of clindamycin was negligible. This study (CGEL-005) purports to demonstrate that the ((b)(4))% propylene glycol does not increase clindamycin percutaneous absorption over that of the previously marketed product, Cleocin T Gel that contains ((b)(4)) propylene glycol.

The investigators hypothesized that the skin permeation of clindamycin from the test (Clindagel[®]) and reference (Cleocin T[®] Gel) products would not be affected by the differences in the vehicles. It was also hypothesized that there would be no significant difference in the skin irritation potential of the products. Sensitization potential was not evaluated in this study.

Comment: Relevant to our question regarding the safety of the ((b)(4)) PG in the vehicle, Clindagel contains ((b)(4)) propylene glycol. This is the highest PG content in any approved topical clindamycin product. The propylene glycol content of Cleocin T Gel is ((b)(4)).

Methodology:

This study enrolled 24 subjects previously diagnosed with acne vulgaris (12 female and 12 male). All completed the study. Subjects were randomized into 2 groups; one group was treated with Clindagel[®] and the other with Cleocin T[®] Gel. Those receiving the Cleocin T[®] product were exposed daily to 11.26-27.04 g of test material with a second application 12 hours later. Subjects in the Clindagel[®] group received a single daily application of 36.58-57.43 g of material.

Comment: Note that the study was not blinded. The Clindagel group received a single daily application of material, and the Cleocin T group received twice daily applications. The sponsor's report does not address the difference in acute exposure. Those receiving the Cleocin T product were exposed to roughly half the amount of material at each

application as those receiving the Clindagel. Presumably, the larger amount of Clindagel applied would lead to more skin irritation/sensitization if there were a difference between it and Cleocin T. However the reduced acute exposure of the Cleocin T group may indicate a greater percutaneous absorption proportional to applied dose compared to the Clindagel. This question would need to be evaluated by reviewing the plasma concentrations against time after application. However, regardless of T_{max} , the C_{max} is critical to our question of enhancement of percutaneous absorption by propylene glycol.

Results:

Study endpoints included:

- Skin Irritation/Adverse Events
- Plasma and Urine Concentrations of Clindamycin

Skin Irritation:

Skin Irritation was evaluated in this study but no data was presented that is relevant to the issue of PG effect on clindamycin absorption, which is the primary focus of this review.

Adverse Events:

The adverse event reporting in this study provided no information relative to the issues of clindamycin absorption.

Clindamycin Plasma Concentrations

| ClindaGel [®] (test) | | | | Cleocin T [®] Gel (reference) | | | |
|-------------------------------|-----|------------------------------|------------------------------|--|-----|------------------------------|------------------------------|
| Subject | Day | Time (hour) post application | Plasma concentration (ng/mL) | Subject | Day | Time (hour) post application | Plasma concentration (ng/mL) |
| 1 | 1 | 4 | 0.817 | 2 | 1 | 4 | BLQ* |
| | | 6 | 1.555 | | | 6 | BLQ |
| | | 8 | 2.164 | | | 8 | BLQ |
| | | 12 | 2.106 | | | 12 | BLQ |
| | | 16 | 1.845 | | | 16 | BLQ |
| | | 24 | 1.003 | | | 24 | BLQ |
| 1 | 7 | 4 | 0.758 | 2 | 7 | 4 | 0.525 |
| | | 6 | 2.191 | | | 6 | BLQ |
| | | 8 | 2.115 | | | 8 | BLQ |
| | | 12 | 1.906 | | | 12 | BLQ |
| | | 16 | 1.876 | | | 16 | BLQ |
| | | 24 | 1.155 | | | 24 | BLQ |
| 3 | 1 | 4 | BLQ | 4 | 1 | 4 | 1.001 |
| | | 6 | 0.638 | | | 6 | 1.341 |
| | | 8 | 0.820 | | | 8 | 1.936 |
| | | 12 | 0.565 | | | 12 | 1.072 |

| | | | | | | | |
|----|---|----|-------|----|---|----|-------|
| | | 16 | BLQ | | | 16 | 3.210 |
| | | 24 | BLQ | | | 24 | 1.910 |
| 3 | 7 | 4 | 1.096 | 4 | 7 | 4 | 1.154 |
| | | 6 | 0.919 | | | 6 | 1.342 |
| | | 8 | 0.921 | | | 8 | 1.158 |
| | | 12 | 0.691 | | | 12 | 1.355 |
| | | 16 | 0.623 | | | 16 | 1.253 |
| | | 24 | BLQ | | | 24 | 1.071 |
| 7 | 1 | 4 | BLQ | 5 | 1 | 4 | BLQ |
| | | 6 | 0.617 | | | 6 | 0.785 |
| | | 8 | 0.757 | | | 8 | 0.731 |
| | | 12 | 0.501 | | | 12 | 0.660 |
| | | 16 | BLQ | | | 16 | 0.603 |
| | | 24 | BLQ | | | 24 | BLQ |
| 7 | 7 | 4 | BLQ | 5 | 7 | 4 | BLQ |
| | | 6 | BLQ | | | 6 | BLQ |
| | | 8 | 0.522 | | | 8 | 0.648 |
| | | 12 | 0.598 | | | 12 | 0.902 |
| | | 16 | BLQ | | | 16 | 1.230 |
| | | 24 | BLQ | | | 24 | 0.866 |
| 8 | 1 | 4 | BLQ | 6 | 1 | 4 | 0.701 |
| | | 6 | 1.270 | | | 6 | 1.211 |
| | | 8 | 1.550 | | | 8 | 1.292 |
| | | 12 | 0.626 | | | 12 | 1.674 |
| | | 16 | BLQ | | | 16 | 1.148 |
| | | 24 | BLQ | | | 24 | 1.107 |
| 8 | 7 | 4 | 1.357 | 6 | 7 | 4 | 3.391 |
| | | 6 | 1.516 | | | 6 | 3.316 |
| | | 8 | 1.614 | | | 8 | 2.983 |
| | | 12 | 1.501 | | | 12 | 2.522 |
| | | 16 | 0.922 | | | 16 | 1.461 |
| | | 24 | 0.530 | | | 24 | 1.443 |
| 10 | 1 | 4 | BLQ | 9 | 1 | 4 | BLQ |
| | | 6 | BLQ | | | 6 | 1.377 |
| | | 8 | BLQ | | | 8 | 1.367 |
| | | 12 | BLQ | | | 12 | 1.137 |
| | | 16 | BLQ | | | 16 | 1.711 |
| | | 24 | BLQ | | | 24 | 0.529 |
| 10 | 7 | 4 | BLQ | 9 | 7 | 4 | 1.566 |
| | | 6 | BLQ | | | 6 | 2.130 |
| | | 8 | 0.505 | | | 8 | 3.002 |
| | | 12 | 0.559 | | | 12 | 2.116 |
| | | 16 | 0.643 | | | 16 | 1.663 |
| | | 24 | BLQ | | | 24 | 1.038 |
| 12 | 1 | 4 | 0.965 | 11 | 1 | 4 | BLQ |

| | | | | | | | |
|----|---|----|-------|----|---|----|-------|
| | | 6 | 1.773 | | | 6 | BLQ |
| | | 8 | 1.629 | | | 8 | BLQ |
| | | 12 | 0.886 | | | 12 | 0.566 |
| | | 16 | 1.159 | | | 16 | BLQ |
| | | 24 | BLQ | | | 24 | BLQ |
| 12 | 7 | 4 | 1.269 | 11 | 7 | 4 | 0.507 |
| | | 6 | 1.201 | | | 6 | 0.550 |
| | | 8 | 0.798 | | | 8 | 0.529 |
| | | 12 | 1.061 | | | 12 | 0.570 |
| | | 16 | 0.668 | | | 16 | 0.676 |
| | | 24 | BLQ | | | 24 | 0.636 |
| 14 | 1 | 4 | 0.693 | 13 | 1 | 4 | 0.610 |
| | | 6 | 1.729 | | | 6 | 0.696 |
| | | 8 | 2.314 | | | 8 | BLQ |
| | | 12 | 2.984 | | | 12 | BLQ |
| | | 16 | 3.130 | | | 16 | BLQ |
| | | 24 | 1.830 | | | 24 | BLQ |
| 14 | 7 | 4 | 4.042 | 13 | 7 | 4 | BLQ |
| | | 6 | 4.317 | | | 6 | BLQ |
| | | 8 | 5.299 | | | 8 | BLQ |
| | | 12 | 4.996 | | | 12 | BLQ |
| | | 16 | 4.424 | | | 16 | 0.505 |
| | | 24 | 2.638 | | | 24 | BLQ |
| 16 | 1 | 4 | 1.127 | 15 | 1 | 4 | BLQ |
| | | 6 | 1.117 | | | 6 | BLQ |
| | | 8 | 1.166 | | | 8 | BLQ |
| | | 12 | 1.535 | | | 12 | BLQ |
| | | 16 | 1.055 | | | 16 | 0.926 |
| | | 24 | BLQ | | | 24 | 0.614 |
| 16 | 7 | 4 | 0.779 | 15 | 7 | 4 | 0.711 |
| | | 6 | 0.547 | | | 6 | 1.187 |
| | | 8 | 0.617 | | | 8 | 1.180 |
| | | 12 | 0.545 | | | 12 | 1.334 |
| | | 16 | 0.704 | | | 16 | 1.589 |
| | | 24 | 0.552 | | | 24 | 1.030 |
| 17 | 1 | 4 | BLQ | 19 | 1 | 4 | BLQ |
| | | 6 | 0.532 | | | 6 | BLQ |
| | | 8 | BLQ | | | 8 | BLQ |
| | | 12 | BLQ | | | 12 | BLQ |
| | | 16 | BLQ | | | 16 | BLQ |
| | | 24 | BLQ | | | 24 | BLQ |
| 17 | 7 | 4 | 0.673 | 19 | 7 | 4 | 0.627 |
| | | 6 | 0.944 | | | 6 | 0.766 |
| | | 8 | 0.994 | | | 8 | 0.696 |
| | | 12 | 0.655 | | | 12 | BLQ |

| | | | | | | | |
|----|---|----|-------|----|---|----|-------|
| | | 16 | 0.693 | | | 16 | 0.552 |
| | | 24 | BLQ | | | 24 | 0.601 |
| 18 | 1 | 4 | BLQ | 20 | 1 | 4 | BLQ |
| | | 6 | BLQ | | | 6 | BLQ |
| | | 8 | 0.606 | | | 8 | BLQ |
| | | 12 | 0.834 | | | 12 | BLQ |
| | | 16 | 0.990 | | | 16 | BLQ |
| | | 24 | 0.729 | | | 24 | 0.509 |
| | 7 | 4 | NS** | 20 | 7 | 4 | 1.367 |
| | | 6 | NS | | | 6 | 1.311 |
| | | 8 | NS | | | 8 | 1.343 |
| | | 12 | NS | | | 12 | 0.958 |
| | | 16 | NS | | | 16 | 0.898 |
| | | 24 | NS | | | 24 | 0.737 |
| 22 | 1 | 4 | 0.803 | 21 | 1 | 4 | BLQ |
| | | 6 | 1.606 | | | 6 | BLQ |
| | | 8 | 1.933 | | | 8 | BLQ |
| | | 12 | 1.259 | | | 12 | BLQ |
| | | 16 | 1.194 | | | 16 | BLQ |
| | | 24 | BLQ | | | 24 | BLQ |
| 22 | 7 | 4 | BLQ | 21 | 7 | 4 | BLQ |
| | | 6 | 0.844 | | | 6 | BLQ |
| | | 8 | 1.084 | | | 8 | BLQ |
| | | 12 | 0.765 | | | 12 | BLQ |
| | | 16 | 0.569 | | | 16 | BLQ |
| | | 24 | BLQ | | | 24 | BLQ |
| 23 | 1 | 4 | 0.591 | 24 | 1 | 4 | BLQ |
| | | 6 | 0.629 | | | 6 | 0.640 |
| | | 8 | 1.049 | | | 8 | 1.027 |
| | | 12 | 0.838 | | | 12 | 1.245 |
| | | 16 | 0.904 | | | 16 | 1.486 |
| | | 24 | BLQ | | | 24 | 1.138 |
| 23 | 7 | 4 | 0.875 | 24 | 7 | 4 | 3.370 |
| | | 6 | 1.118 | | | 6 | 3.343 |
| | | 8 | 0.675 | | | 8 | 2.441 |
| | | 12 | 0.788 | | | 12 | 2.228 |
| | | 16 | 0.694 | | | 16 | 1.852 |
| | | 24 | BLQ | | | 24 | 1.162 |

*BLQ=Below Level of Quantification

**NS=No Sample

Comment: This chart was compiled from the Sponsor's Study Report CGEL-005 by combining the Randomization Code for treatment assignment from table 1 P.6 of the study report with the Plasma Concentrations taken from Appendix 6, pp. 540-549. The percutaneous absorption of clindamycin is somewhat variable between subjects, but the

within-subject variability is essentially consistent on Days 1 and 7. The following table summarizes this information relative to the question of comparative percutaneous absorption of clindamycin.

| Clindagel [®] (Test) | | | Cleocin T [®] Gel (RLD) | | |
|--------------------------------------|-------|-------|----------------------------------|-------|-------|
| Maximum Plasma Concentration (ng/mL) | | | | | |
| Subject | Day 1 | Day 7 | Subject | Day 1 | Day 7 |
| 1 | 2.164 | 2.191 | 2 | BLQ* | 0.525 |
| 3 | 0.820 | 1.096 | 4 | 3.210 | 1.355 |
| 7 | 0.757 | 0.598 | 5 | 0.785 | 1.230 |
| 8 | 1.550 | 1.614 | 6 | 1.674 | 3.391 |
| 10 | BLQ | 0.643 | 9 | 1.711 | 3.002 |
| 12 | 1.773 | 1.269 | 11 | 0.566 | 0.676 |
| 14 | 3.130 | 5.299 | 13 | 0.696 | 0.505 |
| 16 | 1.535 | 0.779 | 15 | BLQ | 1.589 |
| 17 | 0.532 | 0.944 | 19 | BLQ | 0.786 |
| 18 | 0.990 | NS | 20 | 0.509 | 1.343 |
| 22 | 1.933 | 1.084 | 21 | BLQ | BLQ |
| 23 | 1.049 | 1.118 | 24 | 1.486 | 3.370 |

*BLQ=Below Level of Quantification

Comment: In this study, the maximum plasma clindamycin concentrations for both products did not exceed the 3-6 ng/mL range, which is the reported maximum range for all currently marketed topical clindamycin products. In the Test group, Subject 14, with a 7 day maximum of 5.299 ng/mL, had the highest of the maximal plasma concentrations in this study. This subject also had the highest reported concentration on Day 1. It is probable that these levels are related to the subject's skin characteristics rather than to an increase in absorption relative to the PG concentration of the product. Overall the plasma concentrations of both tested products were similar and did not exceed levels considered to be safe for currently marketed topical clindamycin products.

Clindamycin Urinary Concentration:

| URINARY EXCRETION OF CLINDAMYCIN ANALYSIS (ng/mL) | | | | | | |
|---|--------------|----------------------------------|-----------------------|----------------------------------|-----------------------|------------------------------------|
| | | Cleocin T [®] (n=12) | | Clindagel [™] (n=11) | | Analysis of Variance P-Value |
| | | Mean | Standard Deviation | Mean | Standard Deviation | |
| Day 1 | Hour 0 – 12 | 4.87 | 6.04 | 6.93 | 4.95 | 0.39 |
| | Hour 12 – 24 | 10.08 | 12.65 | 9.83 | 6.35 | 0.95 |
| | Hour 0 – 24 | 14.95 | 18.54 | 16.76 | 8.76 | 0.77 |
| Day 5 | Hour 0 – 12 | 9.56 | 8.58 | 10.73 | 6.66 | 0.72 |
| | Hour 12 – 24 | 14.16 | 12.04 | 13.21 | 6.87 | 0.82 |
| | Hour 0 – 24 | 23.72 | 19.07 | 23.93 | 12.34 | 0.97 |

Reproduced from Sponsor's Study Report, CGEL-005, Table6, P. 14.

Comment: According to Goldstein, et. al. (1982)⁴⁴, adults will excrete approximately 10% of the absorbed dose of clindamycin via the urine. In their study the excreted amount of clindamycin achieved a rapid state of equilibrium, with the amount excreted on day 7 being equivalent to that of day 3. The mean amount of excreted clindamycin was 150-200 µg, suggesting that there was an overall absorption of 3.8-5% of the dose applied to the skin. They noted one patient in their study to have an inferred absorption of 12.5% of the applied dose. In 1989 Eller, et. al.⁴⁵ studied systemic absorption of clindamycin phosphate and clindamycin hydrochloride. Clindamycin hydrochloride is known to be more actively absorbed than clindamycin phosphate, which must first be hydrolyzed on the skin. The absorption of the clindamycin hydrochloride might be inferred to be higher than the expected absorption for the phosphate. Their findings further noted that an average of 13%, even of the administered IV dose, was ultimately excreted in the urine. Furthermore, they found that 90% of the urinary excretion amount was reached within 12 hours of the dose. This implies a rapid fall in the plasma concentration of clindamycin. The urine findings from the sponsor's study are consistent with the historical findings for clindamycin. The urine excretion of clindamycin is consistent with the reported plasma concentrations noted in the previous tables.

This data is consistent with the FDA Biopharmaceutics Review of NDA 50-782 (Clindagel). The reviewer notes that “The data...suggest that the systemic exposure on day 1 and day 5 was somewhat higher for Clindagel™ compared to Cleocin-T®. An examination of the large variability associated with the mean peak concentrations and AUC 0-24 values indicates that the difference is minimal. The systemic accumulation from repeated applications also appears minimal... the observed plasma concentrations following topical administration of Clindagel™ and Cleocin-T® (0.5 –5.3 ng/mL) were well below the serum levels attained (6000– 29,000 ng/mL) following an intravenous administration of 600 mg to patients with different kinds of infections.” The final conclusions of the FDA Biopharmaceutics Reviewer were:

1. The plasma data from the comparative absorption study demonstrated that the levels (0.5-5.3 ng/mL) of clindamycin attained in the plasma following single and multiple topical applications of Clindagel® and Cleocin-T® to patients with acne vulgaris are well below the serum levels attained after an I.V. administration of an equivalent dose to patients with different kinds of infections.
2. The urinary data demonstrated that <0.04% of the total dose is excreted in the urine for both treatments following single and multiple applications of Clindagel® and Cleocin-T®. This is also consistent with low systemic absorption.
3. The plasma and urinary data demonstrated that systemic exposure to Clindagel® is comparable to that of Cleocin-T® gel under clinical use conditions.

⁴⁴ Goldstein, BM, Feingold, DS, Pechi, PE, “Systemic Absorption of Clindamycin Hydrochloride after Topical Application”, J Am Acad Dermatol, 1982, 1:2, Pp 208-214.

⁴⁵ Eller, MG, Smith, RB, Phillips, JP, “Absorption Kinetics of Topical Clindamycin Preparations”, Biopharmaceutics & Drug Disposition, 1989, 10, Pp. 505-512.

4. The in vitro permeation study was supportive of the in vivo findings in terms of the mean percent of applied dose recovered in the receptor fluid being comparable and relatively low (< 1% in 48 hours) for Clindagel[®] and Cleocin-T[®].

MOR CONCLUSIONS from Study CGEL-005

1. This study showed comparable plasma concentration and urinary excretion of clindamycin for the Clindagel[®] and Cleocin T[®] Gel products, consistent with previously published results. It demonstrates a mean range of 3-6 ng/mL for the maximum blood clindamycin concentrations of both the Cleocin T[®] Gel that has (b) (4) propylene glycol and the Clindagel[®] product that contains a (b) (4) % concentration of propylene glycol. This is consistent with the clindamycin concentrations reported for other currently marketed topical clindamycin products.
2. Absence of increased clindamycin absorption with the Clindagel[®] product containing (b) (4) % propylene glycol suggests that enhancement of clindamycin absorption is unlikely with the (b) (4) % propylene glycol content of the (b) (4) gel product that is the subject of the pending application ANDA 65-443. Although the dosing of Clindagel[®] in the study was once daily compared to twice daily dosing of the reference product, the short half-life of clindamycin would not predict any accumulation of drug in the skin that might lead to higher concentrations with more frequent dosing.

Discussion

Despite the uncertainty regarding a threshold plasma concentration of clindamycin that will significantly increase risk for CDAD, it appears that for clindamycin concentrations below that produced by the vaginal cream (approximately 66 ng/mL) no significant safety signals for CDAD have been reported. This is supported in the medical literature. According to Meadowcroft, et. al.⁴⁶ “Diarrhea occurs in up to 20% of patients receiving systemic therapy, and in less than 1% with clindamycin vaginal cream. Other topical clindamycin formulations implicated in causing CDIC [CDAD] may be systemically absorbed (maximum of 10% for topical acne products).”

Consequently, based on the hydrophilic chemical nature of clindamycin, the characteristics of PG and its theoretical mechanism of action as a penetration enhancer primarily for lipophilic drugs, data and literature reports regarding the PK characteristics of clindamycin and similar plasma concentrations of the various formulations of marketed topical clindamycin preparations, and a review of AERS reports and medical literature relative to the risk of CDAD with various clindamycin preparations, I find nothing to suggest an increased risk for the proposed product, and I recommend approval of ANDA 65-443.

MOR Overall Conclusions

⁴⁶ Meadowcroft, A, Diaz, PR, Latham, GS, “Clostridium difficile Toxin–Induced Colitis After Use of Clindamycin Phosphate Vaginal Cream”, Ann Pharmacother 1998;32:309-11.

1. The presence of up to (b) (4) propylene glycol does not appear to increase the absorption of clindamycin phosphate beyond that of the RLD.
2. There is at least one currently marketed product (Clindagel[®], ANDA 50-782) containing a greater amount of PG (b) (4) in its formulation than the Dow product (b) (4).
3. Addition of benzoyl peroxide to the formulation does not enhance clindamycin absorption in either the Test or RLD products.
4. Review of AERS reveals very few reports of any AEs consistent with possible CDAD associated with use of topical clindamycin products.
5. The presence of (b) (4)% propylene glycol in the proposed product (ANDA 65-443) will not increase the risk for systemic exposure to clindamycin or other related safety considerations.
6. The clindamycin/benzoyl peroxide product that is the subject of ANDA 65-443 is as safe as the RLD and from a clinical perspective should be approved.

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this page is the manifestation of the electronic signature.**

/s/

John Peters
5/11/2009 12:23:53 PM
MEDICAL OFFICER

Dena Hixon
5/11/2009 04:19:29 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-443

CHEMISTRY REVIEWS

ANDA 65-443

**Clindamycin-Benzoyl Peroxide Gel
(Clindamycin 1% and Benzoyl Peroxide 5%)**

Dow Pharmaceutical Sciences, Inc.

**Susan Pittinger
Division 1**

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Chemistry Review Data Sheet

1. ANDA 65-443
2. REVIEW #: 1
3. REVIEW DATE: August 31, 2007
4. REVIEWER: Susan Pittinger
5. PREVIOUS DOCUMENTS: N/A

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Submission

February 7, 2007

Amendment

March 2, 2007

Amendment

March 28, 2007

Acceptable for filing

March 30, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: Dow Pharmaceutical Sciences, inc.

Address: 1330 Redwood Way
Petaluma, CA 94954

Representative: AJ Acker

Telephone: (707) 793-2600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

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

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: The basis for this ANDA is BenzaClin[®] Topical Gel (Clindamycin Phosphate Solution 6% and Benzoyl Peroxide Gel 6.26%). The NDA, 50-756, is held by Sanofi Aventis US. The firm stated that no unexpired patents are listed in the Orange Book. The applicant also stated that there is no unexpired exclusivity.

10. PHARMACOL. CATEGORY: Topical treatment of acne vulgaris

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: Clindamycin 1% and Benzoyl Peroxide 5%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

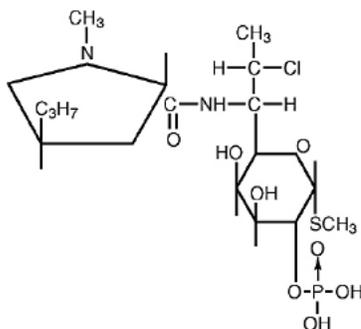
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

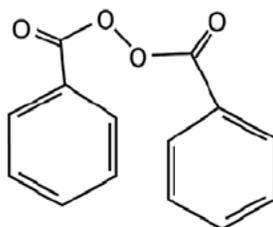
Not a SPOTS product

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

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* -octopyranoside 2-(dihydrogen phosphate). C₁₈H₃₄ClN₂O₈PS MW 504.97



Chemistry Review Data Sheet

Benzoyl Peroxide. C₁₄H₁₀O₄ MW 242.23

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|-------------------------|
| (b) (4) | II | (b) (4) | (b) (4) | 1 | Inadequate | 8/10/07 | Reviewed by S.Pittinger |
| | II | | | 1 | Inadequate | 8/08/07 | Reviewed by S.Pittinger |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 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: N/A

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
| | | |
| | | |

Chemistry Review Data Sheet

| | | |
|--|--|--|
| | | |
| | | |

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|--------------------------------------|-----------------------|-------------|-----------------|
| Microbiology | N/A | | |
| EES | Pending | | |
| Methods Validation | N/A | | |
| Labeling | Pending | | |
| Bioequivalence | Pending | | |
| EA | N/A | | |
| Radiopharmaceutical | N/A | | |

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-443

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not approvable at this point.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance: The Clindamycin Phosphate drug substance is manufactured by (b) (4). DMF (b) (4) describes the synthesis of the drug substance. The DMF was reviewed by S.Pittinger on August 8, 2007 and was found to be inadequate.

The Benzoyl Peroxide drug substance is manufactured by (b) (4), (b) (4). DMF (b) (4) describes the synthesis of the drug substance. The DMF was reviewed by S.Pittinger on August 10, 2007 and was found to be inadequate.

Drug product: Inactive ingredients present in the formulation include Propylene Glycol USP, Carbomer (b) (4), Potassium Hydroxide NF, and Purified Water USP. The product is admixed by the pharmacist before dispensing and filled into a 50 gram jar. An expiration date of (b) (4) months has been requested based on 3-months of accelerated stability data. The stability data support the requested expiration date of (b) (4) months.

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

The drug product is a topical gel for treatment of acne vulgaris. The firm's labeling states to apply the gel twice daily to the affected areas.

C. Basis for Approvability or Not-Approval Recommendation

There are numerous chemistry deficiencies.

Chemistry Assessment Section

[REDACTED] (b) (4)
[REDACTED] . Please explain.

34. Please include a commitment that [REDACTED] (b) (4)

[REDACTED]

35. We note that you did not request a categorical exclusion from the requirement of an environmental assessment or state if you are in compliance with all federal, state and local environmental regulations. Please provide this information.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available drug product room temperature stability data.
2. The Labeling and bioequivalence information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you separately.
3. All facilities referenced in your ANDA should be in compliance with CGMP at the time of approval.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Assessment Section

cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-627/S.Pittinger/

HFD-627/J.Fan, TL/

HFD-617/R.Adigun, PM/

F/T by:

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TYPE OF LETTER: NOT APPROVABLE

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this page is the manifestation of the electronic signature.**

/s/

Susan Pittinger
11/2/2007 02:07:10 PM
CHEMIST

Rosalyn Adigun
11/2/2007 04:09:11 PM
CSO

James Fan
11/5/2007 10:21:03 AM
CHEMIST

ANDA 65-443

Clindamycin-Benzoyl Peroxide Gel (Clindamycin 1% and Benzoyl Peroxide 5%)

Dow Pharmaceutical Sciences, Inc.

**Mahnaz Farahani, Ph.D.
Division 1**

Review # 4, addendum 3

No chemistry reviews numbered 2, 3, 4 or addendums 1 and 2 to chem review 4 were located. Upon consultation with Office of Generic Drugs staff, this review should have been numbered Chemistry Review #2.

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Chemistry Review Data Sheet

1. ANDA 65-443
2. REVIEW #: 4, Addendum 3
3. REVIEW DATE: August 3, 2009
4. REVIEWER: Mahnaz Farahani, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

Previous Documents

Document Date

| | |
|-----------------------|-------------------|
| Original Submission | February 7, 2007 |
| Amendment | March 2, 2007 |
| Amendment | March 28, 2007 |
| Acceptable for filing | March 30, 2007 |
| Amendment | December 18, 2007 |
| Amendment | June 20, 2008 |
| Amendment | July 8, 2008 |
| Telephone Amendment | August 19, 2008 |
| Telephone Amendment | November 6, 2008 |

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

| | |
|----------------------|-------------------|
| Gratuitous Amendment | December 11, 2008 |
| Gratuitous Amendment | January 12, 2009 |
| Gratuitous Amendment | January 29, 2009 |
| Telephone amendment | July 22, 2009 |

7. NAME & ADDRESS OF APPLICANT:

Name: Dow Pharmaceutical Sciences, Inc.

Chemistry Review Data Sheet

Address: 1330 Redwood Way
Petaluma, CA 94954

Representative: AJ Acker

Telephone: (707) 793-2600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

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

9. LEGAL BASIS FOR SUBMISSION: The basis for this ANDA is BenzaClin[®] Topical Gel (Clindamycin Phosphate Solution 6% and Benzoyl Peroxide Gel 6.26%). The NDA, 50-756, is held by Sanofi Aventis US. The firm stated that no unexpired patents are listed in the Orange Book. The applicant also stated that there is no unexpired exclusivity.

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11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: Clindamycin 1% and Benzoyl Peroxide 5%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: X Rx OTC

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

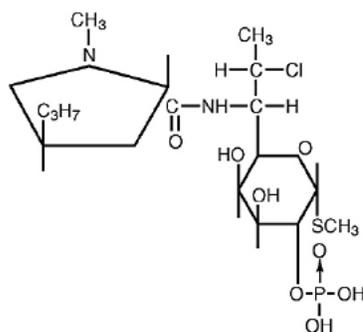
 SPOTS product – Form Completed

 X Not a SPOTS product

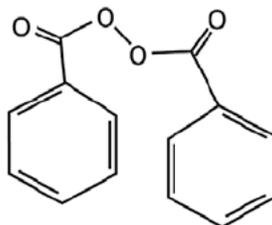
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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* -octopyranoside 2- (dihydrogen phosphate). C₁₈H₃₄ClN₂O₈PS MW 504.97

Chemistry Review Data Sheet



Benzoyl Peroxide. C₁₄H₁₀O₄ MW 242.23



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|-------------------------|
| (b) (4) | II | (b) (4) | (b) (4) | 3 | Adequate | March 12, 2008 | Reviewed by B. Lim |
| | II | | | 1 | Adequate | May 29, 2009 | Reviewed by M. Farahani |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 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

Chemistry Review Data Sheet

- 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: N/A

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
| | | |
| | | |
| | | |
| | | |

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|----------------|---------|--------------|
| Microbiology | N/A | | |
| EES | Acceptable | 4/15/08 | |
| Methods Validation | N/A | | |
| Labeling | Acceptable | 3/14/08 | Adolph Vezza |
| Bioequivalence | Acceptable | 5/11/09 | S H Seung |
| EA | N/A | | |
| Radiopharmaceutical | N/A | | |

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___x___ No If no, explain reason(s) below: Minor Amendment

The Chemistry Review for ANDA 65-443

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance: The Clindamycin Phosphate drug substance is manufactured by (b) (4). DMF (b) (4) describes the synthesis of the drug substance. The DMF was reviewed by M. Farahani on 4/20/08 and was found to be adequate.

The Benzoyl Peroxide drug substance is manufactured by (b) (4), (b) (4). DMF (b) (4) describes the synthesis of the drug substance. The DMF was reviewed by Benjamin Lim 3/12/08 and was found to be adequate.

Drug product: Inactive ingredients present in the formulation include Propylene Glycol USP, Carbomer (b) (4) Potassium Hydroxide NF, and Purified Water USP. The product is admixed by the pharmacist before dispensing and filled into a 50 gram jar. An expiration date of (b) (4) months has been requested based on 3-months of accelerated stability data. The stability data support the requested expiration date of (b) (4) months.

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

The drug product is a topical gel for treatment of acne vulgaris. The firm's labeling states to apply the gel twice daily to the affected areas.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable.

Chemistry Assessment Section

cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/M.Farahani/8/3/09, 8/5/09

HFD-627/J.Fan, TL/8/5/09

HFD-617/N.Patel, PM/8/11/09

F/T by: np

V:\Division I\Team 3\FIRMAM\DOWLTRS&REV\65443.REV04, addendum3.doc

TYPE OF LETTER: APPROVABLE

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---------------------|------------------------|--------------|------------------------------|
| ----- | ----- | ----- | ----- |
| ANDA 65443 | ORIG 1 | | CLINDAMYCIN BENZOYL PEROXIDE |
| ANDA 65443 | ORIG 1 | | CLINDAMYCIN BENZOYL PEROXIDE |
| ANDA 65443 | ORIG 1 | | CLINDAMYCIN BENZOYL PEROXIDE |
| ANDA 65443 | ORIG 1 | | CLINDAMYCIN BENZOYL PEROXIDE |

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

/s/

MAHNAZ FARAHANI
08/11/2009

JAMES M FAN
08/11/2009

NITIN K PATEL
08/11/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 65-443

BIOEQUIVALENCE REVIEWS

**Review of a
Bioequivalence Study
with
Clinical Endpoints**

**ANDA # 65-443
Clindamycin Phosphate
and Benzoyl Peroxide Gel, 1%/5%
Dow Pharmaceutical Sciences, Inc.**

**Sarah H. Seung, Pharm.D.
Clinical Reviewer
Office of Generic Drugs
Date of Review: April 24, 2009**

**Submission dates reviewed:
February 7, 2007 (Refused to Receive)
March 28, 2007
February 11, 2009**

CLINICAL REVIEW

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Review of a Bioequivalence Study with Clinical Endpoints for ANDA 65-443

Executive Summary

A multi-center, evaluator-blind, randomized, vehicle-controlled, parallel-group study demonstrates that Dow Pharmaceutical Sciences, Inc.'s (Dow) Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% is bioequivalent to BenzaClin[®] Topical Gel in the treatment of acne vulgaris. The FDA's statistical analysis shows the 90% Confidence Interval (CI) of the test:reference ratio of mean percent reduction from baseline to Week 10 (rank analysis) in inflammatory lesions to be (0.975, 1.056) and that of non-inflammatory lesion counts to be (0.975, 1.080), within the bioequivalence limits of (0.80, 1.25). According to the sponsor, a total of 1236 patients enrolled into the study. Based on the FDA's analyses, 1182 patients were included in the Intent-To-Treat (ITT) population and 875 patients were included in the Per Protocol (PP) population analyses.

Both test and reference products were also superior to placebo, demonstrating that the study was sufficiently sensitive to discriminate differences between products.

I. Recommendation on Approval

The data submitted to ANDA 65-443, using the primary endpoint of mean percent reduction in inflammatory and non-inflammatory lesion counts from baseline to Week 10 demonstrates bioequivalence of Dow's Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% with the reference listed drug, Sanofi-Aventis US's BenzaClin[®] Topical Gel. Therefore, from a bioequivalence perspective, the test product is recommended for approval.

The sponsor has submitted sufficient data to ensure that the Dow formulation, containing (b) (4) propylene glycol, will not increase the risk of systemic clindamycin exposure and associated adverse events, compared to the RLD.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% is a prescription topical anti-bacterial product indicated for the treatment of acne vulgaris. Dow conducted a clinical endpoint study, enrolling 1236 patients, to establish the bioequivalence of their proposed Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% to the RLD, BenzaClin[®] Topical Gel, in the treatment of acne vulgaris. All patients were randomized to receive either the Dow product (Test), BenzaClin[®] (Reference) or Placebo.

B. Comparative Efficacy

The recommended primary endpoint of this study is the mean percent reduction from Baseline in inflammatory and non-inflammatory lesion count at Week 10.

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According to the FDA's analysis, the mean percent reduction from Baseline in inflammatory lesion count at Week 10 in the PP population was 61.08% in the Test group and 61.49% in the Reference group. The 90% CI for test:reference ratio of the mean percent reduction from Baseline (raw and rank values) in inflammatory lesion count was (0.928, 1.096) and (0.975, 1.056), respectively, which is within the bioequivalence limits of (0.80, 1.25). The mean percent reduction from Baseline in non-inflammatory lesion count at Week 10 in the PP population was 54.54% in the Test group and 52.83% in the Reference group. The 90% CI for test:reference ratio of the mean percent reduction from Baseline (raw and rank values) in non-inflammatory lesion count was (0.964, 1.106) and (0.975, 1.080), respectively, which is within the bioequivalence limits of (0.80, 1.25). Both active products were demonstrated by the FDA's analysis to be superior to placebo with regard to the mean percent reduction from Baseline in inflammatory and non-inflammatory lesion count.

The FDA's analysis also demonstrated that the 90% CI for test:reference ratio of the mean percent reduction from Baseline in inflammatory and non-inflammatory lesion counts is within the bioequivalence limits of (0.80, 1.25) when Sites (b) (6) and (b) (6) were excluded from the PP population. The test and reference products were also demonstrated to be superior to placebo when Sites (b) (6) and (b) (6) were excluded from the ITT analysis.

C. Comparative Safety

The safety data submitted in this ANDA show that the test product did not cause any worse adverse events during this study compared to the reference product in the treatment of acne vulgaris. A total of 1,231 patients received medication. Of these, 497 received the Test product, 490 received the Reference product and 244 received the Placebo. Drug safety was monitored via symptom evaluation and questioning during visits. One death was reported and six patients experienced serious adverse events (all unrelated to the study treatment) during this study. A total of 383 patients reported adverse events during the study (148 in the Test group, 156 in the Reference group and 79 in the Placebo group). The most commonly reported adverse events (AE) were upper respiratory tract infection and nasopharyngitis. Amongst the application site related AEs, application site dryness (0.8% Test and Reference) and application site irritation/burning (1.6% Test vs. 0.6% Reference) were the most commonly reported.

The proposed generic product is qualitatively different from the RLD. It contains (b) (4) propylene glycol, and the RLD contains none. Systemic clindamycin exposure has been associated with severe colitis. Therefore, the potential for increased systemic absorption of clindamycin and associated adverse events has been carefully considered, as documented in a separate memorandum by John R. Peters, M.D. The Office of Generic Drugs (OGD) concludes that the sponsor has submitted sufficient data to ensure that the Dow formulation, containing (b) (4) propylene glycol, will not increase the risk of systemic clindamycin exposure and associated adverse events, compared to the RLD.

Clinical Review

I. Introduction and Background

The OGD has determined that the design of bioequivalence trials for topical acne products should take into consideration the basis of approval for the RLD.

The current standard for NDA approval of a product indicated for treatment of acne vulgaris is statistical superiority over placebo for reduction in both inflammatory and non-inflammatory lesions counts and a statistically larger success proportion on the Physicians Global Assessment (PGA). It is recognized that the change from baseline in total lesion count is strongly influenced by the change in the lesion type that shows the largest effect. The Division of Dermatology and Dental Products (DDDP) has recommended that topical generic products for treatment of acne vulgaris show equivalent performance in reduction of both inflammatory and non-inflammatory lesion types. However, in a consultation dated January 29, 2004, it was agreed that the more subjective Investigator's Global analysis could be removed from the study to simplify future study design for 505(j) applications for the acne indication. The OGD has decided to designate the Investigator Global analysis as a secondary endpoint to support the evaluation of bioequivalence.

The OGD does not require that a generic product must show equivalent performance on an endpoint for which the RLD did not show superiority over placebo. The requirement for demonstration of superiority over placebo in a clinical endpoint bioequivalence study is not intended for establishing efficacy of the generic product. Equivalent efficacy and safety of a generic product is assumed if the product is bioequivalent to the RLD. Superior performance compared to placebo is needed to show that the study design is sufficiently sensitive to demonstrate a difference between products. The study should demonstrate equivalent effectiveness for the endpoint(s) upon which the RLD was approved and also demonstrate that the test product is no worse than the RLD for the additional endpoints for which the RLD did not demonstrate superiority over placebo. Therefore, the firm must show equivalence for both inflammatory and non-inflammatory lesions because the reference product demonstrated statistical superiority over vehicle in regards to percent change from baseline at Week 10 for inflammatory, non-inflammatory and total lesion counts.

Prior to 2004, the OGD requested percent change from baseline in lesion counts as the primary efficacy variable for acne studies. However, the standard for approval of an NDA for acne vulgaris treatment was established as numeric change from baseline in lesion counts. In an attempt to be consistent with the NDA study recommendations, the OGD requested that generic sponsors present the change from baseline as both numerical and percent change. Although most of the ANDAs submitted for acne vulgaris treatments have met the 90% confidence interval criteria for bioequivalence for both numerical change and percent change from baseline, some generic sponsors have communicated that a larger study population is required to meet BE limits for numerical change from baseline than for percent change from baseline. Furthermore, the OGD has observed wider confidence intervals for numerical change from baseline than for percent change from baseline in numerous studies recently submitted with a primary endpoint of change from baseline in lesion counts. The OGD currently believes that it may not be feasible to require that numeric change from baseline

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lesion counts meet the usual BE limits, and we find no clinical or statistical reason to believe that reliance on the percent change from baseline would result in approval of a product that is not therapeutically equivalent. Therefore, the OGD has decided that the previously recommended endpoint of percent change from baseline in lesion counts is the preferred primary endpoint. The numeric change from baseline will be requested as a secondary endpoint to support the evaluation of bioequivalence.

A. Drug Product

1. Drug Established Name: Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%
2. Drug Class: Antibacterial

B. Reference Listed Drug (RLD)

1. RLD Name: BenzaClin[®]
2. NDA Number: 50-756
3. NDA Firm: SANOFI-AVENTIS US
4. Date of Approval: December 21, 2000
5. Approved Indication(s): Topical treatment of acne vulgaris.
6. Dose, Route of Administration and Regimen: The product should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.
7. Description of the reference drug, including pertinent safety or dosing considerations: NDA 50-756 for BenzaClin[®] (clindamycin/benzoyl peroxide) Topical Gel, 1%/5% (Dermik Laboratories), originally called (b)(4) was approved December 2000. Approval of this product was based on two clinical trials that studied the safety and superiority of the combination of benzoyl peroxide and clindamycin to its individual components alone and vehicle in the treatment of acne vulgaris. The studies were conducted for 10 weeks and patients were evaluated at 0, 2, 4, 6, 8 and 10 weeks. The primary endpoints evaluated were mean percent reduction in inflammatory lesion count, non-inflammatory count, total lesion count and the investigator's global assessment. Statistically significant reduction in two of the three lesion counts was acceptable to the Agency. (b)(4) demonstrated statistical superiority over the clindamycin and vehicle in regards to percent change from baseline at Week 10 for inflammatory, non-inflammatory and total lesion counts. However, neither study supported the statistical superiority of (b)(4) to benzoyl peroxide in regards to non-inflammatory lesions. One of the studies also did not show statistical superiority of (b)(4) to benzoyl peroxide in regards to the investigator's global assessment. The reviewer stated that in accordance with Division policy, a trend has been shown

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towards a superiority of the combination over benzoyl peroxide and concluded that there was an adequate demonstration of the effectiveness for this indication.

Benzaclin[®] Topical Gel is a prescription medication and is supplied in a powder form and must be reconstituted with purified water prior to dispensing. The resulting gel contains 1% clindamycin and 5% benzoyl peroxide. Clindamycin is a semi-synthetic antibiotic produced by the parent antibiotic lincomycin.

The labeling for BenzaClin[®] includes the following warning regarding the use of topical clindamycin and the association with severe colitis:

Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis...When significant diarrhea occurs, the drug should be discontinued...

BenzaClin[®] labeling also states that mean systemic bioavailability of topical clindamycin in BenzaClin[®] Topical Gel is suggested to be less than 1%. Peak plasma concentrations are reported to be less than 6 ng/mL. This is far lower than the peak concentrations achieved with systemic administration of clindamycin (C_{max} 1 to 3 mcg/mL in several ANDA BE studies following 300 mg oral dose). Given such limited bioavailability and low peak serum concentrations, it is unlikely that a generic topical formulation with ingredients similar to those in the RLD would result in such an increase in systemic absorption as to change the safety profile in comparison to the RLD. Furthermore, with such low serum concentrations, a pharmacokinetic (PK) study would not likely provide any meaningful information. Therefore the OGD does not require PK studies for generic formulations of topical clindamycin products containing inactive ingredients that are similar to those contained in the RLD. If the inactive ingredients are different, the OGD may request PK studies.

8. Brief Discussion about the indication

Acne vulgaris is a common skin condition that can affect people of all ages, although teenagers develop acne most often. About 10 to 20% of adults may continue to experience some form of acne that occurs when there is an increase in sebum release by sebaceous glands. Small cysts or comedones form in hair follicles due to blockage of the follicular orifice by retention of sebum and keratinous material. The clinical hallmark of acne is the comedone, which may be closed (whitehead) or open (blackhead). Closed comedones (contents not easily expressed) are the precursors of inflammatory lesions while open comedones (filled with easily expressible oxidized, darkened, oily debris) rarely result in inflammatory acne lesions. Comedones are usually accompanied by inflammatory lesions: papules, pustules or nodules.

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C. Regulatory Background

The original February 7, 2007 submission for this ANDA was "Refused to Receive" on March 16, 2007, due to the Chemistry, Manufacturing, Control portion of the submission not being sufficiently complete. Subsequent to the sponsor's amendment, dated March 28, 2007, the ANDA was accepted for filing on March 30, 2007.

1. INDs, Protocols, and/or Control Documents submitted by this sponsor
The Sponsor did not submit any protocol or control document to the OGD for this drug product. The Sponsor did submit an IND (41-733) to DDDDP while pursuing a 505(b)(2) application for a clindamycin/benzoyl peroxide gel. The sponsor was advised that this application can be filed as a 505(j) application.
2. INDs, Protocols, and/or Control Documents submitted by other sponsors
Several INDs, protocols and controls have been submitted by other sponsors for this drug product.
3. Other ANDA submissions for same or related product
This is the first application for this drug product. There are no other pending applications for this drug product.

II. Description of Clinical Data and Sources

A. CRO: Sterling BioConsultants, Inc., Folsom, CA

B. Study Director: Joanna J. Peterkin, M.D

C. Study Period: September 1, 2005 to August 25, 2006

D. Study Centers, Investigators and Enrollment

| Site Number | Investigator | Location | Number enrolled |
|-------------|-----------------------|--|-----------------|
| 101 | Alicia Bucko, D.O. | Academic Dermatology Associates Albuquerque, NM | 128 |
| 102 | Sunil Dhawan, M.D. | East Bay Dermatology Medical Group Fremont, CA | 73 |
| 103 | Michael Jarratt, M.D. | DermResearch Center Austin, TX | 130 |
| 104 | Serena Mraz, M.D. | Solano Clinical Research Vallejo, CA | 149 |
| 105 | Peter Rogge, M.D. | Solano Clinical Research Davis, CA | 154 |
| 106 | Sherry Skinner, M.D. | SFBC Fort Myers Fort Myers, FL | 60 |
| 107 | Stacy Smith, M.D. | Therapeutics Clinical Research San Diego, CA | 109 |
| 108 | Dow Stough, M.D. | Burke Pharmaceutical Research Hot Springs, AR | 72 |

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| | | | |
|-----|-----------------------|---|-----|
| 109 | Leonard Swinyer, M.D. | Dermatology Research Center Salt Lake City, UT | 155 |
| 110 | Hector Wiltz, M.D. | FXM Research Corp Miami, FL | 114 |
| 111 | Suzanne Bruce, M.D. | Center for Skin Research Houston, TX | 57 |
| 112 | Eugene Monroe, M.D. | Advanced Healthcare Milwaukee, WI | 35 |

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission:

February 7, 2007 (This is an e-CTD submission)

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations Report:

A DSI inspection was requested on (b) (6). The inspections (DSI review dated (b) (6)) revealed that two of the three sites inspected had objectionable findings, resulting in Form FDA-483 being issued. For details of the observations, please see Section VI.A of this review. The other site did not receive any Form FDA-483's.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the study report, the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, current Good Clinical Practice (cGCPs) and in compliance with local regulatory requirements. The study protocol, informed consent form and other information to patients, and all appropriate amendments were reviewed and approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC).

D. Evaluation of Financial Disclosure

The sponsor certified that the investigators involved in this study did not have any financial arrangements, significant payments, proprietary interest or equity interest to report as defined in 21 CFR 54.2. However, two principal investigators ((b) (6), M.D. at Site (b) (6) and (b) (6), M.D. at Site (b) (6) and two sub-investigators ((b) (6) M.D. at Site (b) (6) and (b) (6) at Site (b) (6) were reported to be employees of Dow. None are stockholders; however, (b) (6) and (b) (6) hold unexercised stock options in Dow. If exercised, the current value of (b) (6) vested option would be in excess of \$50,000 and (b) (6) less than \$50,000.

Reviewer's comment: *In order to ensure that the outcome of the study has not been biased by the financial interest of the two principal investigators and two sub-*

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investigators, the FDA statistician was requested to conduct appropriate subset analyses to evaluate the potential impact of Sites (b) (6) and (b) (6)

IV. Review of Bioequivalence

A. Brief Statement of Conclusions

The sponsor's study demonstrates the bioequivalence of the test product with the reference product.

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor conducted one clinical study. The sponsor's study was reviewed to evaluate the comparative efficacy and safety of the proposed drug. The electronic submission of the ANDA was reviewed in detail.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

1. **Protocol Number:** DPS-07-07-2005-001

2. **Title:** A Phase III Multi-Center, Randomized, Evaluator-Blind, Vehicle Controlled, Three-Arm Clinical Trial to Evaluate the Bioequivalence of (b) (4) (1/5.0) Gel to BenzaClin[®] Gel, and Superiority to (b) (4) Gel Vehicle, in the Treatment of Acne Vulgaris

3. **Objectives:** To evaluate the bioequivalence of (b) (4) (1/5.0) Gel (Clindamycin 1% and Benzoyl Peroxide 5%) in comparison with BenzaClin[®] Gel and to evaluate the superiority of both to (b) (4) Gel Vehicle in the treatment of mild to severe acne vulgaris

4. **Study Design:** This study was conducted as a multi-center, randomized, evaluator-blind, active-controlled and vehicle-controlled, parallel comparison involving patients with mild to severe acne vulgaris meeting specific inclusion/exclusion criteria. Approximately 1250 patients were to be enrolled into this study [500 patients in the Test (Clindamycin/Benzoyl Peroxide Gel, 1%/5%) group, 500 patients in the Reference (BenzaClin[®] Gel) group, and 250 patients in the Placebo (Clindamycin/Benzoyl Peroxide Vehicle) group]. Patients were enrolled in 12 independent study centers. The duration of treatment was 10 weeks. Patients were evaluated at Screen/Baseline and at Weeks 3, 6 and 10.

a. Treatments

- i. **Test:** (b) (4) (1/5.0) Gel (Clindamycin 1% and Benzoyl Peroxide 5.0%) – Bristol Myers Squibb, Lot #1670WX2-2/166WX3-1
- ii. **Reference:** BenzaClin[®] Gel – Sanofi Aventis/Dermik, Lot #8023536, 8025862, and 8026200
- iii. **Placebo:** Vehicle – Bristol Myers Squibb, Lot # 1675WX1-2/1665WX1-1

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At the time of the manufacturing of the clinical batches, the manufacturing plant site was known as Bristol-Myers Squibb - Buffalo Technical Operations (BMS-BTO). Since then it has changed ownership and is now known as Contract Pharmaceuticals Limited (CPL-Niagara).

b. Drug Application

Topical applications of test materials were made to the face twice daily, morning and evening, for a period of 10 weeks.

Patients were instructed to gently wash their face with a cleanser and warm (not hot) water. After washing, the patients were asked to thoroughly rinse and gently pat their face dry with a cotton towel. After the face had dried completely, the patients applied no more than half an inch of medication (or pea size) to the fingertip. This dose was then to be dotted onto 6 areas (chin, left cheek, right cheek, nose, left forehead, right forehead) on the face. After distributing the dose in this manner, the patient gently rubbed the gel into the skin. This amount of gel was sufficient to cover the entire face, excluding the mouth, eyes, inside the nose, and lips. It was important for patients to treat their entire face (excluding the mouth, eyes and lips) and they were instructed NOT to treat only specific lesions. They were to gently smooth the test material over the face evenly. The test material became invisible almost immediately following application with gentle rubbing. If this did not happen, the investigator instructed the patient on the use of a smaller dosage. The patient was to wash his/her hands after application.

c. Study Population

i. Inclusion Criteria: Patients meeting all of the following criteria were *eligible* for study entry:

- (a) Male or female 12 years of age or older;
- (b) Written and verbal informed consent was obtained. Patients less than 18 years of age signed an assent for the study and a parent or a legal guardian signed the informed consent;
- (c) Patient had a score of 2 (mild), 3 (moderate) or 4 (severe) on the Evaluator's Global Severity assessment at the baseline visit;
- (d) Patients with facial acne inflammatory lesion (papules, pustules, and nodules) count no less than 17 but no more than 40;
- (e) Patients with facial acne non-inflammatory lesion (open and closed comedones) count no less than 20 but no more than 100 (comedones on the nose are included in this count);
- (f) Patients with two or fewer nodules (defined as an inflammatory lesion greater than or equal to 5 mm in diameter);
- (g) Women of childbearing potential who were willing to practice effective contraception for the duration of the study. Females on birth control pills had taken the same type pill for at least three months prior to entering the study and did not change type during the study. Those who used birth control pills in the past discontinued usage at least three months prior to the start of the study. Any female patient who was premenstrual at the start

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- of the study and reached childbearing potential during the study had a pregnancy test performed at the next visit;
- (h) Women of childbearing potential had a negative urine pregnancy test at the baseline visit;
 - (i) Patients were willing to comply with study instructions and return to the clinic for required visits,
 - (j) If a moisturizer or sunscreen was needed during the study, patients used only approved moisturizers, sunscreens, or moisturizer/sunscreen combination products.

Reviewer's comment: *Inflammatory lesions should only include papules and pustules. Nodules should not be included as part of the inflammatory lesion counts. It is unclear if the Sponsor did or did not include nodules in the total inflammatory lesion counts. The study report has contradictory information where one section states that nodules are included and another states that nodules are not included. The Sponsor's datasets report nodules separately from papules and pustules.*

- ii. Exclusion Criteria: Patients meeting any one of the following criteria were *excluded* from the study:
 - (a) Use of an investigational drug or device within 30 days of enrollment or participation in a research study concurrent with this study;
 - (b) Any dermatological conditions on the face that could interfere with clinical evaluations such as acne conglobata, acne fulminans, secondary acne, perioral dermatitis, clinically significant rosacea, gram-negative folliculitis, etc.;
 - (c) Any underlying disease(s) or some other dermatological condition of the face that required the use of interfering topical or systemic therapy or made evaluations and lesion count inconclusive;
 - (d) Patients with a facial beard or mustache that interfered with the study assessments;
 - (e) Evidence or history of cosmetic-related acne;
 - (f) Patient had a history of experiencing significant burning or stinging when applying any facial treatment (e.g., make-up, soap, masks, washes, sunscreens, etc.) to their face;
 - (g) Female patients who were pregnant, nursing mothers, planning a pregnancy during the course of the trial, or became pregnant during the study;
 - (h) Use of estrogens (e.g., Depogen, Depo-Testadiol, Gynogen, Valergen, etc.) for less than 10 weeks immediately preceding study entry; Patients treated with estrogens 12 or more consecutive weeks immediately prior to study entry were not excluded unless the patient expected to change dose, drug or discontinue estrogen use during the study;
 - (i) If female, patient had a history of hirsutism, polycystic ovarian disease or clinically significant menstrual irregularities;

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- (j) History of regional enteritis, ulcerative colitis, inflammatory bowel disease, pseudomembranous colitis, chronic or recurrent diarrhea, or antibiotic-associated colitis;
- (k) Treatment of any type for cancer within the last 6 months;
- (l) Patient used medications and/or vitamins during the study which were reported to exacerbate acne (azathioprine, haloperidol, Vitamin D, Vitamin B12, halogens such as iodides or bromides, lithium, systemic or mid to super-high potency corticosteroids, phenytoin and phenobarbital); Daily vitamins at the FDA prescribed amounts were acceptable;
- (m) History of hypersensitivity or allergic reactions to any of the study preparations as described in the Investigator's Brochure, including known sensitivities to any dosage form of clindamycin, lincomycin or benzoyl peroxide;
- (n) Concomitant use of potentially irritating over-the-counter products that contain ingredients such as benzoyl peroxide, alpha-hydroxy acid, salicylic acid, retinol or glycolic acids;
- (o) Patients that did not undergo the specified washout period(s) for the following *topical* preparations or patients who required the concurrent use of any of the following topical medications:

| | |
|---|---------|
| Topical astringents and abrasives | 1 week |
| Antibiotics* on the facial area | 2 weeks |
| Non-approved moisturizers or sunscreens | 2 weeks |
| Other topical anti-acne drugs | 2 weeks |
| Soaps containing antimicrobials | 2 weeks |
| Anti-inflammatories and corticosteroids on the facial area | 4 weeks |
| Retinoids, including retinol | 4 weeks |

- (p) Patients that did not undergo the specified washout period(s) for the following *systemic* medications or patients who required the concurrent use of any of the following systemic medications:

| | |
|---|----------|
| Corticosteroids (including intramuscular injections)* | 4 weeks |
| Antibiotics* | 4 weeks |
| Other systemic acne treatments | 4 weeks |
| Systemic retinoids | 6 months |

* Study protocol waivers for the use of antibiotics and topical corticosteroids were considered on a case by case basis.

- (q) Patient intended to use a tanning booth or sunbathe during the study;
- (r) Patients who were unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

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Reviewer's comment: Patients with active cystic acne should be excluded.

d. Procedures/Observations

Table 1 – Study Flow Chart (per Sponsor)

| Procedure | Visit 1 Screening Visit | Visit 2 ^a Baseline Day 1 | Visit 3 Week 3 ^b (Day 21 ± 3 days) | Visit 4 Week 6 ^b (Day 42 ± 5 days) | Visit 5 Week 10 ^c (Day 70 -3/+5 days) |
|---|-------------------------------|---|--|--|---|
| Informed Consent/Assent | X | | | | |
| Demographics and Skin Phototype | X | | | | |
| Medical History | X | | | | |
| Inclusion/Exclusion Criteria | X | X | | | |
| Previous Therapies | X | | | | |
| Urine Pregnancy Test | | X | X ^c | X ^c | X |
| Lesion Counts | X | X | X | X | X |
| Evaluator's Global Severity Score | | X | X | X | X |
| Cutaneous Safety Evaluation | | X | X | X | X |
| Tolerability Evaluation | | X | X | X | X |
| Administer Patient Instructions | X | X | | | |
| Weigh Study Containers | | X | X | X | X |
| Test Materials Dispensed | | X ^d | X | X | X |
| Test Materials Collected | | | X | X | X |
| Study Compliance Reviewed | | | X | X | X |
| Concomitant Therapy and Medical History Reviewed | X | X | X | X | X |
| Adverse Events | | | X | X | X |
| End of Study Case Report Form | | | | | X |

^a If no washout was needed, Visits 1 and 2 may have occurred on the same day. If a washout was needed, Visit 2 occurred within one month of Visit 1.

^b All visit dates are in reference to baseline, e.g., Visit 4 occurs 6 weeks ± 5 days after baseline visit.

^c All Week 10 procedures were completed for Patients who terminate early.

^d Dispensed one container of test material at the baseline visit.

^e Urine pregnancy test for all females who had newly reached menarche.

Reviewer's comments: FDA generally accepts a visit window of ± 4 days. Since the primary endpoint is at Visit 5, a visit window of ± 5 days for Visit 4 is acceptable. However, the visit window for Visit 5 (Week 10, Day 70) should be within ± 4 days to be included in the PP population. Therefore, those patients who were outside the visit window of more than 4 days for Visit 5 should be excluded from the PP population.

e. Restrictions -

Precautions: Patients were instructed to continue using the same approved facial

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cleanser and moisturizer and not to change products during the study. At each visit, patients were asked if they have changed their cleansing routine. An approved sunscreen was applied according to the directions on the bottle as needed. Facial makeup could be applied according to the patient's normal daily routine; however, patients were instructed not to wear make-up during study visits, as it may have interfered with the evaluator's assessments. No other products were to be used on the face.

Concomitant medications: As noted in the exclusion criteria, there were mandatory washout periods and restrictions during the study for the topical treatments that have a known beneficial effect for acne vulgaris. In addition there was a mandatory washout period and restrictions during the study for certain systemic drugs as outlined in the exclusion criteria.

Any patients utilizing concomitant therapies that could interfere with the interpretation of study results during the course of the study (including but not limited to those listed under the exclusion criteria) were withdrawn from the study at the discretion of the investigator and sponsor. No other topical treatment (except a cleanser or an approved moisturizer and sunscreen on the face) other than the test material was permitted.

Reviewer's comments:

- *Patients who took any medication for the treatment of acne during the study should be included in the PP population as a treatment failure and LOCF should be used for lesion counts.*
- *Patients who took a restricted concomitant medication that was not for the treatment of acne should be excluded from the PP population but included in the ITT population using LOCF.*

f. Safety measures

The Cutaneous Safety Evaluation, Tolerability Evaluation and Adverse Event (AE) Monitoring were conducted at each visit.

i. **Cutaneous Safety Evaluation**

Scaling

| | |
|--------------|--|
| 0 – None | No Scaling |
| 1 – Mild | Barely perceptible, fine scales present to limited areas of the face |
| 2 – Moderate | Fine scale generalized to all areas of the face |
| 3 – Severe | Scaling and peeling of skin over all areas of the face |

Erythema

| | |
|--------------|--|
| 0 – None | No evidence of erythema present |
| 1 – Mild | Slight pink coloration |
| 2 – Moderate | Definite redness |
| 3 – Severe | Marked erythema, bright red to dusky dark red in color |

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ii. Tolerability Evaluation

Itching

| | |
|--------------|--|
| 0 – None | No itching |
| 1 – Mild | Slight itching, not really bothersome |
| 2 – Moderate | Definite itching that is somewhat bothersome |
| 3 – Severe | Intense itching that may interrupt daily activities and/or sleep |

Burning

| | |
|--------------|---|
| 0 – None | No burning |
| 1 – Mild | Slight burning sensation; not really bothersome |
| 2 – Moderate | Definite, warm burning sensation that is somewhat bothersome |
| 3 – Severe | Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep |

Stinging

| | |
|--------------|--|
| 0 – None | No stinging |
| 1 – Mild | Slight stinging sensation, not really bothersome |
| 2 – Moderate | Definite stinging sensation that is somewhat bothersome |
| 3 – Severe | Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep |

An adverse event (AE) was considered any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the product.

At each visit, the investigators questioned the patient about AEs using an open ended question, taking care not to influence the patient's answers, e.g., "Have you noticed any change in your health since the last visit?" Any AE, whether or not it was related to the test materials, was reported on the AE form along with the date of onset, the severity, and the outcome.

g. Removal of Patients from Therapy or Assessment

Reasons for withdrawal included, but were not limited to the following:

- Acne flare that required treatment with a disallowed therapy;
- Either at the investigator's request, for safety reasons (e.g., severe adverse reactions or unauthorized concomitant therapy), or at the patient's request;
- When the requirements of the protocol were not respected;
- When a concomitant therapy liable to interfere with the results of the study was reported or required by the patient;
- When a patient was lost to follow-up.

Reviewer's comments: *Patients that are discontinued from the study due to lack of treatment effect should be included in the PP population. These patients would be considered failures for the Evaluator's Global Severity Scale and the LOCF should be used for lesion count assessment. Patients*

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discontinued for other reasons should be excluded from the PP population, but included in the ITT population.

h. Endpoints

i. **Primary Endpoints:**

- (a) The sponsor's primary bioequivalence efficacy variable was the absolute change from baseline to Week 10 in inflammatory and non-inflammatory lesion count for the PP population
- (b) The sponsor's primary superiority efficacy variable was the absolute change from baseline to Week 10 in inflammatory and non-inflammatory lesion count for the ITT population

ii. **Secondary Endpoints:**

- (a) Mean percent change from baseline to Week 10 in inflammatory lesion counts
- (b) Mean percent change from baseline to Week 10 in non-inflammatory lesion counts
- (c) Percent of patients who achieved a two-point reduction at Week 10 in the Evaluator's Global Severity Score from baseline

Reviewer's comments:

- *The recommended primary endpoints for this bioequivalence study should be the mean **percent** change from baseline for **both** inflammatory (papules and pustules) and non-inflammatory (open and closed comedones) lesion counts at week 10. Total lesion count assessment is no longer required. The absolute/numeric change from baseline is considered supportive information and is evaluated as a secondary endpoint.*
- *The FDA statistician was requested to analyze the percent change in inflammatory (sum of papules and pustules) and non-inflammatory lesion counts. Analysis of the secondary endpoints is not needed.*

i. Efficacy Variables & Severity Scales

i. **Lesion Counts**

At each visit the evaluator counted the total number of inflammatory lesions on the patient's forehead, right cheek, left cheek, chin and nose. Nodules were counted separately but were included in the total inflammatory lesion count. At baseline, nodules were counted to determine eligibility and were included in the statistical analysis of inflammatory lesion counts. All inflammatory lesions were counted at once rather than counting papules and pustules separately. The evaluator also counted the total number of non-inflammatory lesions on the patient's forehead, right cheek, left cheek, chin and nose. All non-inflammatory lesions were counted at once, except for the nose, which was counted separately. Lesion counts were collected at Baseline, Week 3, Week 6 and Week 10 (or upon discontinuation).

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(a) *Inflammatory lesions* are defined by the sponsor as follows:

Papule – a small, solid elevation less than 5 mm in diameter. Most of the lesion is above the surface of the skin.

Pustule – a small, circumscribed elevation less than 5 mm in diameter that contains yellow-white exudate.

Nodule – an inflammatory lesion greater than or equal to 5 mm in diameter (not included in the count of total inflammatory lesions).

(b) *Non-inflammatory lesions* are defined by the sponsor as follows:

Open comedones (black head) - a lesion in which the follicle opening is widely dilated with the contents protruding out onto the surface of the skin, with compacted melanin cells giving the plug a black appearance.

Closed comedones (white head) - a lesion in which the follicle opening is closed, but the sebaceous gland is enlarged by the pressure of the sebum build up, which in turn causes the skin around the follicle to thin and become elevated with a white appearance.

ii. Evaluator’s Global Severity Score

Certain efficacy determinations were based on evaluator-blinded evaluations of the signs and symptoms of acne vulgaris. The following scores were used to describe the severity grade and subsequent score:

Table 2: Evaluator’s Global Severity Score

| Score | Grade | Description |
|-------|--------------|---|
| 0 | Clear | Normal, clear skin with no evidence of acne vulgaris |
| 1 | Almost clear | Rare, non-inflammatory lesions present with rare, non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red) |
| 2 | Mild | Some non-inflammatory lesions are present with few inflammatory lesions (papules/pustules only; no nodulo-cystic lesions) |
| 3 | Moderate | Non-inflammatory lesions predominate with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulo-cystic lesion |
| 4 | Severe | Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodule-cystic lesions |
| 5 | Very Severe | Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulo-cystic lesions |

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Each patient was evaluated by the same evaluator throughout the study.

The Evaluator's Global Severity Score was dichotomized into "success" and "failure" with a patient considered a success if the Global Severity Score at Week 10 was at least two grades less than baseline.

j. Statistical analysis plan

i. **Patient Populations**

(a) Safety Population – comprised of all randomized patients who received the study medication.

(b) Intent-to-Treat (ITT) Population – The sponsor's ITT population included all patients who:

(c) received at least one dose of study medication and

(d) received at least one post-dose evaluation.

Reviewer's comments:

- *The ITT population should exclude patients that did not meet the inclusion/exclusion criteria.*
- *Patients discontinued for any reason, such as drug-related AEs, should be included in the ITT population, using LOCF.*

(e) Per-Protocol (PP) Population - The sponsor's PP population included all patients who completed the 10-week evaluation without noteworthy study protocol violations.

The PP population excluded patients in the ITT population who met any of the following criteria:

- Had lesion counts or Evaluator's Global Severity Score that did not meet the inclusion criteria;
- Had taken any interfering concomitant medications;
- Did not attend the Week 10 visit, with the exception of a documented lack of treatment effect;
- Had missed more than 1 study visit (excluding the Week 10 visit);
- Had not been compliant with the dosing regimen (e.g., patients could not miss more than five consecutive days of dosing and had to take 80-120% of expected doses);
- Out of visit window at the 10-week visit.

Reviewer's comments: *The sponsor's definition of compliance of 80% to 120% is more stringent than the usual FDA definition of compliance and is acceptable.*

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- ii. **Bioequivalence** (per sponsor) - The Sponsor's primary and secondary tests for demonstrating the statistical bioequivalence of Test and Reference were based on absolute and percent change, respectively, from baseline to Week 10 in inflammatory and non-inflammatory lesions and were established if the 90% confidence interval for the Test/Reference Product group ratio in the inflammatory and non-inflammatory lesion count absolute and percent change was within (0.80, 1.25) in the PP population. The analysis of bioequivalence involved only the active study drugs and was computed from estimates derived from a COVANOVA with factors of product, stratifying baseline variables, and covariate baseline inflammatory and non-inflammatory lesion count, respectively. The ratio statistics for the 90% confidence interval were computed by the methods of Fieller's Theorem based on least squares estimates from the COVANOVA.

A secondary analysis of bioequivalence for the dichotomized Evaluator's Global Severity Score at Week 10 was established if the 90% confidence interval of the difference in success rates was contained within (-0.20, +0.20) in the PP population. The 90% confidence interval was calculated using Wald's method with Yates' continuity correction. The analysis of bioequivalence involved only the active product groups. A last observation carried forward (LOCF) was used to estimate any missing data. Additionally, failure was imputed for the dichotomized Evaluator's Global Severity Score for patients discontinued due to lack of treatment effect.

***Reviewer's comments:** The sponsor's criteria to establish bioequivalence for the FDA's primary endpoints of mean percent reduction from baseline in inflammatory and non-inflammatory lesion count are acceptable. The 90% confidence intervals of the test/reference ratio for the primary endpoint must be within (0.80, 1.25) for continuous variables (mean percent change from baseline). The difference between the products for the Evaluator's Global Severity Score success rate is a secondary endpoint. The FDA statistical consultant was requested to evaluate the appropriateness of the sponsor's method and to verify whether the data are adequate to demonstrate bioequivalence.*

- iii. **Efficacy** - The Sponsor's primary and secondary superiority analyses were conducted for absolute and percent change, respectively, from baseline in lesion counts. These tests for superiority were done for the ITT patients and all three study drugs were included in the COVANOVA analysis. Pairwise contrasts between the vehicle and each active study drug for absolute and percent change from baseline to Week 10 for inflammatory and non-inflammatory lesions were performed to provide comparisons between Test Product and Vehicle groups, as well as the Reference Product and Vehicle groups. An LOCF was used to estimate any missing lesion count data. The COVANOVA included factors of product, stratifying baseline variables, and baseline inflammatory or non-inflammatory lesion count, respectively.

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Also, pairwise comparisons were conducted between the vehicle and each active study drug using the Fisher's Exact test for the proportion of dichotomized Global Severity Scores as a secondary superiority analysis for the ITT patients. An LOCF was used to estimate any missing data. Additionally, failure was imputed for the dichotomized Evaluator's Global Severity Score for patients discontinued due to lack of treatment effect.

Reviewer's comments: *To ensure that the study design is sensitive enough to show a difference between products, the test and reference products should both be statistically superior to placebo ($p < 0.05$, two-sided) with regard to the primary endpoint, using the ITT population. The success rate on the Evaluator's Global Severity Score is a secondary endpoint.*

- iv. **Safety** - All AEs occurring during the study were recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA v 8.1) terminology. Descriptions of AEs included the date of onset, the date the AE ended, the severity of the AE, and the outcome. All reported AEs were summarized by the number of patients reporting AEs, system organ class, severity, seriousness, and relationship to study medication. Each patient was counted only once within a system organ class or a preferred term by using the AEs with the highest severity within each category. Comparisons among treatment groups were made by tabulating the frequency of patients with one or more AEs (classified into MedDRA terms) during the study. The AE rates that occurred at 5% or more within any treatment had a pairwise comparison between treatment groups with the Fisher's Exact test.

5. Study Conduct

a. Compliance

Each patient was instructed on the importance of returning his or her test materials at each visit. The unblinded pharmacist or designated dispenser questioned the patient on history of medication use since the last visit. In order to judge the patient's compliance with the dosing regimen, the pharmacist/dispenser assessed the amount of returned study medication relative to the application area. A patient who deviated significantly from the prescribed dosage was counseled. Any missed doses of test material were noted on the CRF.

Patients were considered compliant if they applied $\geq 80\%$ and $\leq 120\%$ of the expected applications. If they were outside of this range and/or missed more than five consecutive applications of the study drug they were considered non-compliant

Reviewer's comments: *As previously mentioned, the sponsor's definition of compliance is acceptable.*

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b. Randomization

Patients admitted to the trial were stratified by Evaluator's Global Severity Score and skin-tone (segregated according to the Fitzpatrick scale) and randomized to either Test, Reference, or Placebo group. The method of random permuted blocks within strata ensured that for each stratum, equal numbers of patients entered each treatment group as required. Randomization codes were generated centrally by an IWR system ((b) (4)). At each center, patient screening numbers were assigned consecutively starting with the lowest number available. Randomization numbers were assigned by the IWR system.

The study drug kits were randomly selected from the Test, Reference, and Placebo supply depot, having a ratio of 2:2:1. Drug supplies were distributed to the investigational sites through an IWR system in order to maintain the randomization ratio of 2:2:1 within an investigational site. Twelve (12) independent study centers enrolled patients. The randomization schedule remained blinded from those involved in the clinical conduct of the study.

c. Blinding/Packaging

Due to the difference in compounding of the test materials, each site designated an unblinded technician or other designated staff person (who did not perform any patient assessments) to prepare and dispense the test material. Additionally, the Sponsor, Contract Research Organization (CRO), Data Management and Statistical study team members involved in data management and statistical evaluation remained blinded until identification of per-protocol (PP) patients was finished and a database lock memo was issued.

Test materials were supplied in patient kits. Instructions for compounding the individual test materials were provided to the unblinded technician responsible for mixing the study supplies at the clinical sites.

Each patient kit contained:

Test - 4 cartons with each carton containing; (1) 50g plastic jar, (1) 10mL plastic bottle, and a mixing paddle

Reference - 4 cartons with each carton containing; (1) 50g plastic jar, (2) 5mL plastic vials, and a mixing paddle.

Placebo - 4 cartons with each carton containing; (1) 50g plastic jar, (1) 10mL plastic bottle, and a mixing paddle

Both products were white opaque gels in appearance.

Each patient kit contained a single panel label. Each carton in the patient kit carried a double panel label that was comprised of an affixed and a tear-off portion. The affixed portion of the label remained on the carton. The tear-off portion of the label was removed from the carton at the time of dispensing and attached to the appropriate CRF page.

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In the case of a medical emergency, the investigator could break the blind for the patient involved. The investigator was instructed to notify the medical monitor and the sponsor (or designee) immediately in case of such an emergency. The investigator was to record the code break in the patient's source documents.

d. Reserve Samples

All clinical sites participating in the current study were required to maintain a specified number of "sample retains" in accordance with FDA regulations and ICH guidelines for duration of up to 5 years.

e. Study Population

As shown in Table 3, 1236 patients were enrolled in the study, of which 498 patients were randomized to Test, 494 patients were randomized to Reference, and 244 patients were randomized to Placebo. One (1) patient in the Test group and 4 patients in the Reference group were excluded from the safety population because they did not receive medication. Seventeen (17) patients were excluded from the Sponsor's intent-to-treat population in the Test group, 22 patients in the Reference group, and 11 in the Placebo group because they either did not receive medication or did not have any post-baseline evaluations. Nine hundred sixty-two (962) patients were included in the Sponsor's per-protocol population; 390 patients in the Test group, 388 patients in the Reference group, and 184 patients in the Placebo group.

Table 3: Summary of Patient Enrollment and Evaluability (per Sponsor)

| | <u>Test</u> | <u>Reference</u> | <u>Placebo</u> | <u>Total</u> |
|--|-------------|------------------|----------------|--------------|
| Number of Patients Enrolled | 498 | 494 | 244 | 1236 |
| Patient Excluded from Safety Analyses | 1 | 4 | 0 | 5 |
| Patients Included in Safety Analyses | 497 | 490 | 244 | 1231 |
| Patient Excluded from Intent-to-Treat Analyses | 17 | 22 | 11 | 50 |
| Patients Included in Intent-to-Treat Analyses | 481 | 472 | 233 | 1186 |
| Patient Excluded from Per Protocol Analyses | 108 | 106 | 60 | 274 |
| Patients Included in Per-Protocol Analyses | 390 | 388 | 184 | 962 |

Table 4 summarizes patient completion and premature discontinuation from the study, according to the Sponsor.

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Table 4: Summary of Patient Completion/Discontinuation (per Sponsor)

| | <u>Test</u> | <u>Reference</u> | <u>Placebo</u> | <u>Total</u> |
|--|-------------|------------------|----------------|--------------|
| Number of Patients Enrolled | 498 | 494 | 244 | 1236 |
| Number of Patients who Completed the Study | 455 | 450 | 222 | 1127 |
| Reasons for Study Discontinuation | | | | |
| Adverse Event | 3 | 6 | 2 | 11 |
| Patient Request | 15 | 15 | 8 | 38 |
| Protocol Violation | 0 | 0 | 0 | 0 |
| Lost to Follow-Up | 23 | 15 | 12 | 50 |
| Pregnancy | 1 | 1 | 0 | 2 |
| Other* | 1 | 7 | 0 | 8 |

* Patient 101-57 (Reference) was unable to make follow-up visits. Patient 102-41 (Reference) was previously enrolled in this study. Patient 104-88 (Reference) perceived lack of efficacy. Patients 104-103 (Test), 109-72 (Reference), and 109-78 (Reference) were non-compliant with study medication. Patient 106-59 (Reference) discontinued due to SAE. Patient 109-172 (Reference) was lost to follow-up and site confirmed patient dropped off study medication.

Reviewer's Comment: Patient 104-88 should be included in the PP population as treatment failure and LOCF used.

i. Protocol Deviations

Table 5 presents a summary of the primary protocol deviations that disqualified patients from the per-protocol population. Some patients had more than one exclusionary protocol deviation. A primary deviation was identified for each patient according to the following order: missed Week 10 evaluation, missed more than 1 visit, Week 10 evaluation off schedule, prohibited medication usage, not dosing compliant, and failed inclusion exclusion criteria.

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Table 5: Protocol Deviations that Disqualified Patients from the Per-Protocol Population (Per Sponsor)

| | <u>Test</u> | <u>Reference</u> | <u>Placebo</u> |
|--|-------------|------------------|----------------|
| Number of Patients Enrolled | 498 | 494 | 244 |
| Patients Excluded from the Per-Protocol Population | 108 | 106 | 60 |
| Primary Exclusionary Deviation ^a | | | |
| Did Not Receive Medication | 1 | 4 | 0 |
| No Post-Dose Evaluations | 16 | 18 | 11 |
| Did Not Meet the Inclusion/Exclusion Criteria | 1 | 0 | 0 |
| Patient Used a Prohibited Concomitant Medication | 2 | 5 | 1 |
| Patient Missed the Week 10 Visit | 23 | 18 | 9 |
| Patient Missed More than 1 Interim Visit | 1 | 2 | 0 |
| Week 10 Visit Outside +3/-5 Day Visit Window | 63 | 57 | 35 |
| Patient was Non-Dosing Compliant ^b | 1 | 2 | 4 |

^a Patients may have more than one exclusionary deviation. However, patients are included under the most severe deviation reported.

^b Patients were not compliant with the dosing regimen if they applied less than 80% or more than 120% of the expected applications and/or missed more than ten (10) consecutive applications of study drug.

Reviewer's Comments:

- *The following patients should be excluded from both the ITT and PP populations for not meeting inclusion/exclusion criteria:*
 - *Less than 3 months after the start or switch of a contraceptive birth control or hormonal therapy or for an unknown period of time prior to start of study: Patient 101-12, 103-36, 103-41, 103-114, 105-18, 106-52, and 109-59.*
 - *Baseline lesion counts outside the inclusion criteria: combined papules/pustules should be ≥ 17 and ≤ 40 and combined open and closed comedones should be ≥ 20 and ≤ 100 .*
 - *Baseline nodule count ≥ 3 .*
- *The following patients should be excluded from the PP population due to:*
 - *Prohibited concomitant medication use during the study period:*
 - *Systemic antibiotics known to impact the severity of facial acne vulgaris: Azithromycin - 102-34, 103-7, 104-49, 104-52, 104-93, 104-121, 105-47, 105-81, 106-65, 107-150, 109-122, and 109-164; Ciprofloxacin - 107-177; clarithromycin - 103-67; Doxycycline - 105-72; Levofloxacin - 109-148; Sulfamethoxazole/Trimethoprim - 107-96 and 109-160; Tetracycline - 104-129*
 - *Use of a topical steroid: Desonide to the facial area - 102-51.*
 - *Use of a systemic steroid: Medrol pack - 109-74*
 - *Use of a potentially irritating over-the-counter product that contains salicylic acid: Clearasil - 105-50 and 108-26*
 - *All patients who are more than +4 days for Visit 5.*
- *The following patients should be included in the PP population:*
 - *Patient 103-54 withdrew from the study on December 5, 2005 due to patient's perceived lack of treatment effect. Early termination evaluation*

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was performed that day. However the patient is noted to have started Yasmin[®] and minocycline for acne on November 23, 2005. Therefore, this patient should be included in the PP population as treatment failure and lesion counts from Visit 3 (November 14, 2005; last visit prior to start of alternate acne medication) should be carried forward.

- *Patient 108-34 withdrew from the study on November 7, 2005 for worsening of acne. The patient was evaluated on that day and started on Adoxa[®] (doxycycline). This patient should be considered a treatment failure and LOCF used for lesion counts.*
 - *Patient 104-88 is noted to have discontinued the study due to "perceived lack of efficacy". The patient did not start any alternate medications for acne. Therefore, this patient should be included in the PP population as a treatment failure and LOCF used.*
 - *As stated previously, the FDA statistician was requested to conduct appropriate subset analyses to evaluate the potential impact of the investigators' financial interests on study results for sites (b) (6) and (b) (6)*
- f. Baseline Patient Characteristics (per sponsor)
- i. **Demographics:** The treatment groups were similar with respect to gender, age, ethnicity, and race in the ITT and PP populations. Baseline demographics for the PP populations are summarized in Table 6.

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Table 6: Patient Demographic Characteristics for Per-Protocol Patients (per Sponsor)

| | <u>Test</u> | <u>Reference</u> | <u>Placebo</u> | <u>p-Value</u> |
|--|-------------|------------------|----------------|--------------------|
| Number of Patients | 390 | 388 | 184 | |
| Age (years) | | | | |
| Mean | 19.18 | 18.67 | 19.31 | 0.401 ^a |
| Std | 6.19 | 6.17 | 6.28 | |
| Range | 12.1-46.0 | 12.0-48.4 | 12.1-48.2 | |
| Gender | | | | |
| Male | 182 (47%) | 172 (44%) | 93 (51%) | 0.378 ^b |
| Female | 208 (53%) | 216 (56%) | 91 (49%) | |
| Ethnicity | | | | |
| Hispanic/Latino | 120 (31%) | 98 (25%) | 48 (26%) | 0.198 ^b |
| Not Hispanic/Latino | 269 (69%) | 289 (75%) | 136 (74%) | |
| Race | | | | |
| White | 298 (77%) | 295 (76%) | 139 (76%) | |
| Black/African American | 45 (12%) | 45 (12%) | 17 (9%) | |
| American Indian/ Alaskan Native | 10 (3%) | 8 (2%) | 4 (2%) | |
| Asian | 23 (6%) | 29 (7%) | 11 (6%) | |
| Native Hawaiian/ Other Pacific Islander | 6 (2%) | 7 (2%) | 5 (3%) | |
| Other | 24 (6%) | 19 (5%) | 12 (7%) | |
| Fitzpatrick Skin Type | | | | |
| I | 19 (5%) | 13 (3%) | 4 (2%) | 0.134 ^b |
| II | 67 (17%) | 86 (22%) | 34 (18%) | |
| III | 136 (35%) | 122 (31%) | 71 (39%) | |
| IV | 90 (23%) | 103 (27%) | 52 (28%) | |
| V | 53 (14%) | 37 (10%) | 14 (8%) | |
| VI | 25 (6%) | 27 (7%) | 9 (5%) | |

^a p-value from an analysis of variance with factors of treatment and stratifying variables of skin tone and baseline Evaluator's Global Severity Score.

^b p-value from a likelihood ratio Chi-Square test.

- ii. **Baseline Characteristics:** Baseline inflammatory and non-inflammatory lesion counts, and Baseline Evaluator's Global Severity scores are summarized for the PP populations in Table 7.

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Table 7: Analysis of Patient Baseline Characteristics for Per-Protocol Patients (per Sponsor)

| | <u>Test</u> | <u>Reference</u> | <u>Placebo</u> | <u>P-Value</u> |
|-----------------------------------|-------------|------------------|----------------|--------------------|
| Number of Patients | 390 | 388 | 184 | |
| Inflammatory Lesion Count | | | | |
| Mean | 26.4 | 26.4 | 26.9 | 0.862 ^a |
| Std | 6.6 | 6.9 | 6.6 | |
| Range | 17.0-50.0 | 17.0-43.0 | 17.0-40.0 | |
| Non-Inflammatory Lesion Count | | | | |
| Mean | 44.0 | 45.2 | 43.5 | 0.511 ^a |
| Std | 19.0 | 20.2 | 18.0 | |
| Range | 20.0-100.0 | 17.0-113.0 | 20.0-99.0 | |
| Evaluator's Global Severity Score | | | | |
| Clear | 0 (0%) | 0 (0%) | 0 (0%) | 0.913 ^b |
| Almost Clear | 0 (0%) | 0 (0%) | 0 (0%) | |
| Mild | 89 (23%) | 87 (22%) | 41 (22%) | |
| Moderate | 246 (63%) | 247 (64%) | 112 (61%) | |
| Severe | 55 (14%) | 54 (14%) | 31 (17%) | |
| Very Severe | 0 (0%) | 0 (0%) | 0 (0%) | |

^a p-value from an analysis of variance with factors of treatment and stratifying variables of skin tone and baseline Evaluator's Global Severity Score.

^b p-value from a likelihood ratio Chi-Square test.

6. Results

a. Bioequivalence

Table 8 displays the results of the Sponsor's bioequivalence analysis of the co-primary and co-secondary endpoints, absolute and percent change from Baseline in inflammatory and non-inflammatory lesions at Week 10. The bioequivalence analysis was performed on the per-protocol population.

Table 8: Bioequivalence Analysis of Absolute and Percent Change from Baseline in Inflammatory and Non-Inflammatory Lesions at Week 10 (per Sponsor)

| | <u>Test</u> | <u>Reference</u> | <u>Ratio of Means</u> | <u>90% Confidence Limits^a</u> | |
|--------------------------|----------------|------------------|-----------------------|--|--------------|
| | <u>(N=390)</u> | <u>(N=388)</u> | | <u>Lower</u> | <u>Upper</u> |
| Absolute Change | | | | | |
| Inflammatory Lesions | 15.6 | 16.0 | 0.97 | 89.2% | 106.3% |
| Non-inflammatory Lesions | 21.8 | 21.2 | 1.03 | 92.1% | 114.8% |
| Percent Change | | | | | |
| Inflammatory Lesions | 60.4 | 61.3 | 0.99 | 90.7% | 107.0% |
| Non-inflammatory Lesions | 51.4 | 50.6 | 1.01 | 92.6% | 111.3% |

^a Calculated using the methods of Fieller's Theorem based on least squares estimates from an analysis of covariance with factors of treatment, stratifying baseline variables of skin tone and baseline Evaluator's Global Severity Score and corresponding baseline lesion count as covariate. Analyses were restricted to the two active treatments.

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b. Efficacy

Table 9 displays the results of the Sponsor's superiority analysis of the co-primary and co-secondary endpoints absolute and percent change, from Baseline in inflammatory and non-inflammatory lesions at Week 10. The superiority analysis was performed on the intent-to-treat population.

Table 9: Superiority Analysis of Absolute and Percent Change from Baseline in Inflammatory and Non-Inflammatory Lesions at Week 10 (per Sponsor)

| | Test | Reference | Placebo | p-Value ^a | |
|--------------------------|--------------------------|--------------------------|--------------------------|----------------------|-----------------------|
| | (N=481) <u>LSMean</u> | (N=472) <u>LSMean</u> | (N=233) <u>LSMean</u> | Test vs. Placebo | Reference vs. Placebo |
| Absolute Change | | | | | |
| Inflammatory Lesions | 15.3 | 15.7 | 8.4 | <0.001 | <0.001 |
| Non-inflammatory Lesions | 21.7 | 21.0 | 12.4 | <0.001 | <0.001 |
| Percent Change | | | | | |
| Inflammatory Lesions | 59.2 | 60.3 | 32.5 | <0.001 | <0.001 |
| Non-inflammatory Lesions | 51.0 | 49.6 | 27.8 | <0.001 | <0.001 |

^a p-value from pairwise contrasts within an analysis of covariance with factors of treatment, stratifying baseline variables of skin tone and baseline Evaluator's Global Severity Score and corresponding baseline lesion count as covariate.

c. Evaluator's Global Severity Scores

Evaluator's Global Severity Scores were dichotomized to "success" and "failure" with a patient considered a success if the global severity score was at least 2 grades less than Baseline at Week 10. Tables 10 and 11 display the results of the Sponsor's bioequivalence and superiority analyses of the secondary endpoint, success rate of the Evaluator's Global Severity Score at Week 10.

Table 10: Bioequivalence Analysis of Evaluator's Global Severity Score at Week 10 (per Sponsor)

| | Test | Reference | Difference in Success Rates | 90% Confidence Limits ^a | |
|---------|--------------|--------------|-----------------------------|------------------------------------|-------|
| | (N=390) | (N=388) | | Lower | Upper |
| Success | 152 (39.0%) | 151 (38.9%) | 0.06 | -6.0% | 6.1% |
| Failure | 238 (61%) | 237 (61%) | | | |

^a Calculated using Wald's method with Yates' continuity correction.

Table 11: Superiority Analysis of Evaluator's Global Severity Score at Week 10 (per Sponsor)

| | Test | Reference | Placebo | p-Value ^a | |
|---------|------------|------------|------------|----------------------|-----------------------|
| | (N=390) | (N=388) | (N=233) | Test vs. Placebo | Reference vs. Placebo |
| Success | 177 (37%) | 175 (37%) | 32 (14%) | <0.001 | <0.001 |
| Failure | 304 (63%) | 297 (63%) | 201 (86%) | | |

^a p-value from Fisher's Exact test.

D. **Bioequivalence Conclusion**

The FDA's statistical analysis shows the 90% Confidence Interval (CI) of the test:reference ratio of mean percent reduction from baseline to Week 10 (raw and rank values) in inflammatory lesions to be (0.928, 1.096) and (0.975, 1.056), respectively, and that of non-inflammatory lesion counts to be (0.964, 1.106) and (0.975, 1.080), respectively, within the bioequivalence limits of (0.80, 1.25).

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The mean percent reduction from Baseline in inflammatory and non-inflammatory lesion counts of both products were demonstrated by the FDA's analysis to be superior to placebo.

Reviewer's Comment: The sponsor inappropriately included or excluded some patients from the PP population analysis. The FDA statistician was consulted for reanalysis of the sponsor's data.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

This study showed similar adverse events (AEs) with use of the test and reference products.

One death (motor vehicle accident), unrelated to the test product, was reported during the course of the study. Six patients (0 Test, 5 Reference and 1 Placebo) experienced Serious Adverse Events (SAE), none of which were treatment related. Eleven patients (3 Test, 6 Reference, and 2 Placebo) were discontinued from the study due to AEs. The type and frequency of AEs were similar across treatment groups.

B. Description of Adverse Events

Twelve hundred thirty-six (1,236) male and female patients, 12 years of age and older, with mild to severe acne vulgaris were entered into the study. Five patients (105-164, 110-118, 110-120, 110-121, and 111-55) did not receive medication leaving 1,231 evaluable for safety. A summary of the adverse event characteristics is presented in Table 12.

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Table 12: Adverse Event Characteristics (per Sponsor)

| | Test (N=497) | Reference (N=490) | Placebo (N=244) |
|--|-------------------------|------------------------------|----------------------------|
| Number of Events Reported | 204 | 204 | 101 |
| Number of Patients Reporting One or More Events ^a | 148 (30%) | 156 (32%) | 79 (32%) |
| Serious ^b | | | |
| Yes | 0 (0%) | 5 (3%) | 1 (1%) |
| No | 204 (100%) | 198 (97%) | 100 (99%) |
| Severity of Events ^b | | | |
| Mild | 111 (54%) | 122 (62%) | 54 (54%) |
| Moderate | 84 (41%) | 72 (36%) | 38 (38%) |
| Severe | 9 (4%) | 4 (2%) | 8 (8%) |
| Not Reported ^c | 0 | 6 | 1 |
| Relationship to Study Medication ^b | | | |
| Definitely Unrelated | 123 (60%) | 145 (71%) | 69 (68%) |
| Unlikely | 57 (28%) | 44 (22%) | 25 (25%) |
| Possible | 4 (2%) | 3 (1%) | 3 (3%) |
| Probable | 7 (3%) | 5 (2%) | 1 (1%) |
| Definitely Related | 13 (6%) | 7 (3%) | 3 (3%) |

^a Percentages based on number of patients.

^b Percentages based on number of events reported.

^c Severity was not reported on Serious Adverse Events.

The Sponsor reported that in all three treatment groups, the most common adverse events reported were classified to the system organ class Infections and Infestations, with the specific events of upper respiratory tract infection (URI) and nasopharyngitis being the most common events reported. All other events reported in this system organ class were reported by no more than 1.2% of patients in any treatment group. General Disorders and Administration Site Conditions was the second highest category of adverse events with application site dryness and application site irritation ranked the highest events. The remaining events in this category affected <1% of patients in any treatment group. Approximately 2% of patients in all treatment groups experienced adverse events related to Nervous System Disorders; Respiratory, Thoracic, and Mediastinal Disorders; Injury, Poisoning and Complications; and Gastrointestinal Disorders. The remaining adverse events affected 1% or fewer patients in any treatment group.

Reviewer's Comment: *This study was not intended to be adequately powered to detect statistical significance with regard to adverse events.*

1. Local Signs and Symptoms

Table 13 presents frequency tabulations for local skin reaction severity assessed by treatment group for scaling, erythema, itching, burning, and stinging.

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Table 13: Summary of Cutaneous Safety and Tolerability (per Sponsor)

| Safety Measure | Treatment Group | | | | | |
|----------------|-----------------|------------|-------------------|------------|-----------------|------------|
| | Test (N=497) | | Reference (N=490) | | Placebo (N=244) | |
| | Baseline | Week 10 | Baseline | Week 10 | Baseline | Week 10 |
| Scaling | | | | | | |
| None | 457 (92%) | 397 (87%) | 450 (92%) | 402 (89%) | 227 (93%) | 195 (88%) |
| Mild | 39 (8%) | 45 (10%) | 37 (8%) | 39 (9%) | 15 (6%) | 26 (12%) |
| Moderate | 1 (<1%) | 13 (3%) | 3 (1%) | 9 (2%) | 2 (1%) | 0 (0%) |
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (<1%) |
| Not Reported | 0 | 42 | 0 | 40 | 0 | 22 |
| Erythema | | | | | | |
| None | 418 (84%) | 411 (90%) | 423 (86%) | 416 (92%) | 208 (85%) | 190 (86%) |
| Mild | 65 (13%) | 36 (8%) | 61 (12%) | 30 (7%) | 29 (12%) | 27 (12%) |
| Moderate | 14 (3%) | 8 (2%) | 6 (1%) | 4 (1%) | 7 (3%) | 5 (2%) |
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Not Reported | 0 | 42 | 0 | 40 | 0 | 22 |
| Itching | | | | | | |
| None | 445 (90%) | 428 (94%) | 455 (93%) | 430 (96%) | 224 (92%) | 218 (98%) |
| Mild | 42 (8%) | 23 (5%) | 30 (6%) | 18 (4%) | 18 (7%) | 3 (1%) |
| Moderate | 9 (2%) | 4 (1%) | 5 (1%) | 2 (<1%) | 2 (1%) | 1 (<1%) |
| Severe | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Not Reported | 0 | 42 | 0 | 40 | 0 | 22 |
| Burning | | | | | | |
| None | 488 (98%) | 439 (96%) | 481 (98%) | 444 (99%) | 241 (99%) | 220 (99%) |
| Mild | 8 (2%) | 15 (3%) | 9 (2%) | 6 (1%) | 2 (1%) | 1 (<1%) |
| Moderate | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) | 1 (<1%) | 1 (<1%) |
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Not Reported | 1 | 42 | 0 | 40 | 0 | 22 |
| Stinging | | | | | | |
| None | 481 (97%) | 449 (99%) | 475 (97%) | 446 (99%) | 240 (98%) | 220 (99%) |
| Mild | 16 (3%) | 6 (1%) | 14 (3%) | 4 (1%) | 3 (1%) | 1 (<1%) |
| Moderate | 0 (0%) | 0 (0%) | 1 (<1%) | 0 (0%) | 1 (<1%) | 1 (<1%) |
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Not Reported | 0 | 42 | 0 | 40 | 0 | 22 |

Because the test product is a topical treatment, the occurrence of adverse events as they relate to the application site and the skin are of special interest. A similar percent of patients in the Test and Reference groups had an adverse event attributed to the entire system organ class, General Disorders and Administration Site Conditions (see Table 14). Within this system organ class, application site irritation was the most frequently occurring event under this category affecting 1.6% of patients in the Test group and 0.6% of patients in the Reference group. Application site dryness affected patients equally in the two active treatment groups (0.8%). The remaining preferred terms have only very minimal sporadic reporting. A low percentage of patients in both the Test (1.0%), Reference (1.4%) treatment groups experienced adverse events related to the Skin and Subcutaneous Tissue Disorders System Organ Class. Individual adverse events affected two or fewer patients in either active treatment group. The Placebo group reported 1.2% for this system organ class.

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Table 14: Summary of Adverse Events for Administration Site Conditions and Skin and Subcutaneous Disorders (per Sponsor)

| <u>Adverse Event^a</u> | <u>Test (N=497)</u> | <u>Reference (N=490)</u> | <u>Placebo (N=244)</u> |
|--|---------------------|--------------------------|------------------------|
| Administration site conditions | | | |
| Application site dermatitis | 1 (0.2%) | 0 (0.0%) | 1 (0.4%) |
| Application site dryness | 4 (0.8%) | 4 (0.8%) | 2 (0.8%) |
| Application site eczema | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |
| Application site erythema | 2 (0.4%) | 1 (0.2%) | 1 (0.4%) |
| Application site excoriation | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |
| Application site exfoliation | 1 (0.2%) | 0 (0.0%) | 0 (0.0%) |
| Application site irritation | 8 (1.6%) | 3 (0.6%) | 1 (0.4%) |
| Application site oedema | 1 (0.2%) | 0 (0.0%) | 0 (0.0%) |
| Application site pruritus | 1 (0.2%) | 1 (0.2%) | 1 (0.4%) |
| Application site swelling | 1 (0.2%) | 2 (0.4%) | 0 (0.0%) |
| Skin and subcutaneous tissue disorders | | | |
| Acne | 1 (0.2%) | 0 (0.0%) | 0 (0.0%) |
| Dermatitis atopic | 0 (0.0%) | 0 (0.0%) | 1 (0.4%) |
| Dermatitis contact | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |
| Dyshidrosis | 0 (0.0%) | 0 (0.0%) | 1 (0.4%) |
| Eczema | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |
| Hair growth abnormal | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |
| Ingrowing nail | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |
| Pityriasis rosea | 1 (0.2%) | 0 (0.0%) | 0 (0.0%) |
| Rash | 2 (0.4%) | 0 (0.0%) | 1 (0.4%) |
| Scar | 0 (0.0%) | 1 (0.2%) | 0 (0.0%) |
| Urticaria | 1 (0.2%) | 2 (0.4%) | 0 (0.0%) |

^a Counts reflect numbers of patients in each treatment group reporting one or more adverse events that map to the MedDRA system organ class or preferred term. In this summarization patients are only counted once. Percentages of patients in each treatment group are also given.

Reviewer's Comment:

- *According to the sponsor's study report and datasets, application site "irritation" is equivalent to application site "burning."*
- *Patient 112-32 was noted to have mild pityriasis rosea, which would not exclude the patient from the PP population. However, this patient was excluded from the Sponsor's PP population due to out of visit window (+7 days) for Week 10 visit.*
- *The Reference Listed Drug's (RLD) labeling reports that 3% of patients treated with BenzaClin[®] experienced application site reaction, 12% dry skin, 2% pruritus, 2% peeling, 1% erythema and 1% sunburn. The percentage of patients with skin related adverse events during this study is less than that reported in the RLD's labeling.*

2. Deaths

There was one death reported during the study. Patient 103-063 (Reference) was a pedestrian crossing the highway and was struck by a vehicle on [REDACTED] ^{(b) (6)}. The patient was pronounced dead at the scene. The death was deemed accidental and was definitely unrelated to treatment.

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3. Serious Adverse Events

There were six serious adverse events during the study. Of these six events, none were related to study medication. One of the six patients (109-136, A-F) was in the Placebo group, and the remaining five patients were in the Reference group.

- a. Patient 102-074 was hospitalized for static migraine headache.
- b. Patient 102-075 was admitted to the hospital due to exacerbation of signs and symptoms of Multiple Sclerosis.
- c. Patient 103-063 was struck by a motor vehicle and was pronounced dead at the scene.
- d. Patient 104-091 was admitted to an in-patient psychiatric facility for treatment of depression and suicidal ideation.
- e. Patient 106-059 was admitted to the hospital for acute asthma exacerbation.
- f. Patient 109-136 had a routine breast reduction surgical procedure conducted and the patient's physician requested that the patient remain in the hospital overnight for routine observation.

4. Severe Adverse Events

Within the Test group, nine events were considered severe. These included headache, migraine, URI, nasopharyngitis, tooth repair, nail operation, application site irritation, back pain, and hypertension. In the Reference group, four events were considered severe: sinusitis, gastroenteritis, toothache, and tooth extraction. Eight severe events were recorded for patients in the Placebo group. These included: URI, nasopharyngitis, application site dryness, pyrexia, hand fracture, inguinal hernia, pharyngolaryngeal pain, and back pain.

Only two severe AEs were considered related to the study medication. Patient 112-013 (Test) complained of facial burning that was considered probably related to treatment. The dosing was discontinued and no other therapy was administered; the problem resolved. Patient 101-048 (Placebo) complained of facial dryness that was considered definitely related to treatment. The dosing was discontinued, no other therapy was administered and the problem resolved.

5. Adverse Events Resulting in Discontinuation

Table 15 presents the patients who prematurely discontinued from the study due to adverse events. Three Test group patients withdrew from the study due to adverse events: application site irritation (related, 103-93), acne (related, 108-34), and application site irritation/erythema (probable, 112-13). In the Reference group, six patients withdrew from the study due to an adverse event. One was due to the accidental death (unrelated) of Patient 103-63, and one due to depression/suicidal ideation (both unrelated) in Patient 104-91. Additional patients experiencing events leading to withdrawal in the Reference group included: drug hypersensitivity (related, 105-91), application site pruritus/erythema (probable, 107-19), application site eczema (related, 109-16), application site swelling (probable, 111-31). Two patients in the Placebo group discontinued from the study due to adverse events: application site dryness (related, 101-48) and application site pruritus (probable, 102-4).

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Table 15: Summary of Adverse Events Leading to Discontinuation (per Reviewer)

| Patient No. | Age/Gender | MedDRA Preferred Term | Severity | Outcome | Related to Treatment |
|------------------|------------|-----------------------------|----------|--------------|----------------------|
| Test | | | | | |
| 103-93 | 20.0/F | Application site irritation | Moderate | Resolved | Related |
| 108-34 | 19.8/F | Acne | Moderate | Not resolved | Related |
| 112-13 | 16.3/M | Application site irritation | Severe | Resolved | Probable |
| | | Application site erythema | Moderate | Resolved | Probable |
| Reference | | | | | |
| 103-63 | 16.5/M | Accidental death | NA | NA | Unrelated |
| 104-91 | 15.5/F | Depression | Unknown | Unknown | Unrelated |
| | | Suicidal ideation | Unknown | Unknown | Unrelated |
| 105-91 | 20.7/F | Drug hypersensitivity | Moderate | Resolved | Related |
| 107-19 | 29.9/F | Application site pruritus | Mild | Resolved | Probable |
| | | Application site erythema | Mild | Resolved | Probable |
| 109-16 | 21.7/F | Application site eczema | Moderate | Resolved | Related |
| 111-31 | 48.4/F | Application site swelling | Mild | Resolved | Probable |
| Placebo | | | | | |
| 101-48 | 26.3/F | Application site dryness | Severe | Resolved | Related |
| 102-4 | 17.9/M | Application site pruritus | Moderate | Resolved | Probable |

M=Male; F=Female

Reviewer's comments: Patient 108-34 is included in the sponsor's PP population. This patient should be considered a treatment failure and LOCF used for lesion counts.

Reviewer's comments: The adverse events reported in this study do not suggest a different AE profile for this generic product compared to the RLD.

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Division of Scientific Investigations

Division of Scientific Investigations Report:

A DSI inspection was requested on (b) (6). The inspection (DSI review dated (b) (6)) revealed that two (Sites (b) (6) and (b) (6)) of the three sites inspected were issued Form FDA-483 and were rated VAI (Voluntary action indicated).

Although the third site (Site 110) was not issued any Form 483, it was classified as a VAI (Voluntary action indicated). The objectionable findings and the reason for Site 110 being classified as VAI were as follows:

Site (b) (6)

1. Responsibilities were delegated to a sub-investigator who did not have documentation of proper training by the sponsor and who also was removed as a sub-investigator during the study period.
2. Two registered nurses/research clinicians were delegated authority to obtain medical histories, make inclusion and exclusion criteria assessments, obtain patient data regarding previous acne vulgaris therapies and concomitant

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medications. There were no records showing that these clinicians read the protocol or were provided training on the protocol.

3. Patient (b) (6)-2 used Cetaphil brand cleanser during part of the study period.

Site (b) (6)

4. There were no records indicating that the Dial Soap used by Patient (b) (6)-167 throughout the study was not an antibacterial product.
5. Patient (b) (6)-2 was seen outside the study windows for Visits 3 and 5.
6. No records showing the receipt of Kit #5385.

Site 110

7. Although Form 483 was not issued, DSI review of EIR found that the treatment administered to each patient could not be verified because there was no sealed code at the site for FDA to break the blind and the Fisher Automated Clinical Trial System used to randomize patients was not accessible during the inspection.

Reviewer's comments:

- *DSI's review of the EIR revealed that the sub-investigator in observation #1 did not participate in the clinical evaluations. Therefore, observation #1 would have no impact on this study.*
- *For observation #2, the sponsor responded that the principal investigator (PI) personally trained the two clinicians with the protocol. However, the PI failed to document the training. Since the responsibilities given to the two clinicians are common assessments known to registered nurses, the lack of protocol training documentation would have little impact on the study data.*
- *For observation #3, DSI also noted that Cetaphil cleansers contain an ingredient which has an antibacterial effect, methylparaben, in its formulation. This patient's use of Cetaphil cleanser was listed in the study report datasets. Since methylparaben is commonly used for its preservative effects in several cleansers, and not as an antibacterial agent for the consumer, this reviewer has determined that this patient should not be excluded from analysis for this reason.*
- *For observation #4, the sponsor responded that all patients were informed at screening that antibacterial soaps were prohibited during the trial. Based on the patient's reliability and his denial of antibacterial soap usage, the PI believed that the patient was using one of the allowed Dial products. DSI's review of the EIR finds no record indicating an antibacterial Dial soap was used by this patient. Therefore, this patient should not be excluded from analysis for this reason.*
- *For observation #5, the sponsor provided records that Visits 3 and 5 were within the allowed visit windows. DSI found the sponsor's response to be adequate.*
- *For observation #6, the sponsor obtained shipping and receipt information from the clinical shipper for this study as well as Federal Express number for Kit #5385. The site stated that they will retrain site personnel on shipping and receiving.*
- *For observation #7, the following comment should be forwarded to the sponsor:*

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A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow verification of the treatment identity for each patient.

B. Statistics

The FDA statistical analyses support the bioequivalence of the Test and the Reference products. The statistical consultants found that the percent change from baseline for total lesion count was strongly enough skewed that the assumption of normality of distribution was likely not the most appropriate for these data. They therefore conducted the efficacy and equivalence analyses based on the rank values. The analyses showed that the 90% CI for test:reference ratio of the mean percent reduction-from-Baseline in inflammatory and non-inflammatory lesion counts, using the Rank Transformation Method, are (0.975, 1.056) and (0.975, 1.080), which are within the bioequivalence limits of (0.80, 1.25). The mean percent reduction-from-Baseline in inflammatory and non-inflammatory lesion counts of both active products was demonstrated by the FDA's analysis to be superior to placebo, for both raw and rank values. See Tables 16 and 17 below.

Table 16: Equivalence Analysis for the Percent Change from Baseline in Inflammatory and Non-inflammatory Lesion Counts at Week 10 (per FDA Statistician)

| Raw | | | | Rank | | |
|-------------------------|-------------------|-----------------------------|-----------|-----------------------------|-----------|--|
| Test LS mean | Reference LS mean | 90% Confidence Interval (%) | Pass/Fail | 90% Confidence Interval (%) | Pass/Fail | |
| Inflammatory | | | | | | |
| 61.08 | 61.49 | 92.8, 106.3 | Pass | 97.5, 105.6 | Pass | |
| Non-inflammatory | | | | | | |
| 54.54 | 52.83 | 96.4, 110.6 | Pass | 97.5, 108.0 | Pass | |

Table 17: Efficacy Analysis for the Percent Change from Baseline in Inflammatory and Non-inflammatory Lesion Counts at Week 10 (per FDA Statistician)

| | Test vs. Placebo | | | Reference vs. Placebo | | |
|-------------------------|------------------|-----------------|---------|-----------------------|-----------------|---------|
| | Test LS mean | Placebo LS Mean | p-value | Reference LS Mean | Placebo LS Mean | p-value |
| Inflammatory | | | | | | |
| Raw | 59.88 | 33.19 | <0.0001 | 61.17 | 33.13 | <0.0001 |
| Rank | n/a | n/a | <0.0001 | n/a | n/a | <0.0001 |
| Non-inflammatory | | | | | | |
| Raw | 53.53 | 30.30 | <0.0001 | 51.76 | 29.41 | <0.0001 |
| Rank | n/a | n/a | <0.0001 | n/a | n/a | <0.0001 |

The analyses demonstrate that when Sites (b) (6) and (b) (6) are excluded, the 90% CI are still within the bioequivalence limits of (0.80, 1.25) and both active products are demonstrated to be superior to placebo. See Tables 18 and 19 below.

CLINICAL REVIEW

Table 18: Equivalence Analysis for the Percent Change from Baseline in Inflammatory and Non-inflammatory Lesion Counts at Week 10 without Sites (b) (6) and (b) (6) (per FDA Statistician)

| Raw | | | | Rank | |
|-------------------------|-------------------|-----------------------------|-----------|-----------------------------|-----------|
| Test LS mean | Reference LS mean | 90% Confidence Interval (%) | Pass/Fail | 90% Confidence Interval (%) | Pass/Fail |
| Inflammatory | | | | | |
| 59.75 | 60.42 | 91.2, 107.2 | Pass | 97.0, 107.2 | Pass |
| Non-inflammatory | | | | | |
| 52.45 | 51.24 | 94.0, 111.5 | Pass | 95.2, 108.5 | Pass |

Table 19: Efficacy Analysis for the Percent Change from Baseline in Inflammatory and Non-inflammatory Lesion Counts at Week 10 without Sites (b) (6) and (b) (6) (per FDA Statistician)

| | Test vs. Placebo | | | Reference vs. Placebo | | |
|-------------------------|------------------|-----------------|---------|-----------------------|-----------------|---------|
| | Test LS mean | Placebo LS Mean | p-value | Reference LS Mean | Placebo LS Mean | p-value |
| Inflammatory | | | | | | |
| Raw | 58.29 | 33.89 | <0.0001 | 59.54 | 33.78 | <0.0001 |
| Rank | n/a | n/a | <0.0001 | n/a | n/a | <0.0001 |
| Non-inflammatory | | | | | | |
| Raw | 51.82 | 27.94 | <0.0001 | 49.79 | 26.94 | <0.0001 |
| Rank | n/a | n/a | <0.0001 | n/a | n/a | <0.0001 |

VII. Formulation

The components/composition of Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% as dispensed to the patient is as follows:

| Component | Function | Test | | Reference |
|----------------------------|----------------------------------|---------|---------|--------------------------|
| | | %w/w | gm/50gm | |
| Clindamycin Phosphate, USP | Active Pharmaceutical Ingredient | (b) (4) | (b) (4) | EQ 1% Base (b) (4) mg/gm |
| Benzoyl Peroxide, USP | Active Pharmaceutical Ingredient | (b) (4) | (b) (4) | 5% (b) (4) mg/gm |
| Carbomer (b) (4) | (b) (4) | -- | -- | (b) (4) mg/gm |
| Carbomer (b) (4) | (b) (4) | (b) (4) | (b) (4) | -- |
| Sodium Hydroxide | (b) (4) | -- | -- | (b) (4) mg/gm |
| Potassium Hydroxide, NF | (b) (4) | (b) (4) | (b) (4) | -- |
| Docusate Sodium | (b) (4) | -- | -- | (b) (4) mg/gm |
| Propylene Glycol, USP | (b) (4) | (b) (4) | (b) (4) | -- |
| Purified Water, USP | (b) (4) | (b) (4) | (b) (4) | (b) (4) mg/gm |

¹ Equivalent to (b) (4) w/w clindamycin

² Based on (b) (4) benzoyl peroxide

³ Estimated from actual amount used in biobatch

CLINICAL REVIEW

Reviewer's Comment: The proposed generic product is qualitatively different from the RLD. It contains (b) (4) propylene glycol, and the RLD contains none. Systemic clindamycin exposure has been associated with severe colitis. Therefore, the potential for increased systemic absorption of clindamycin and associated adverse events has been carefully considered, as documented in a separate memorandum by John R. Peters, M.D. The OGD concludes that the sponsor has submitted sufficient data to ensure that the Dow formulation, containing (b) (4) propylene glycol, will not increase the risk of systemic clindamycin exposure and associated adverse events, compared to the RLD.

VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA, using the preferred primary endpoint of mean percent reduction in inflammatory and non-inflammatory lesion counts from baseline to Week 10, demonstrate that Dow Pharmaceutical Sciences, Inc.'s Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% is bioequivalent to the reference listed drug Benzaclin[®]. The sponsor has submitted sufficient data to ensure that the Dow formulation, containing (b) (4) propylene glycol, will not increase the risk of systemic clindamycin exposure and associated adverse events, compared to the RLD.

B. Recommendation

This application is recommended for approval from a clinical bioequivalence standpoint.

Sarah H. Seung, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Date

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Date

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs

Date

CLINICAL REVIEW

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:65-443

APPLICANT: Dow Pharmaceutical Sciences, Inc.

DRUG PRODUCT: Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 65-443, using the primary endpoint of mean percent reduction in inflammatory and non-inflammatory lesion counts from baseline to Week 10, are adequate to demonstrate bioequivalence of Dow Pharmaceutical Sciences, Inc.'s Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% with the reference listed drug, Benzaclin[®].

You have submitted sufficient data to ensure that your formulation, containing (b) (4) propylene glycol, will not increase the risk of systemic clindamycin exposure and associated adverse events, compared to the RLD.

A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow verification of the treatment identity for each patient.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are patient to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Sarah H Seung
5/11/2009 04:39:54 PM
BIOEQUIVALENCE CLINICAL END POIN

Dena Hixon
5/11/2009 04:59:58 PM
MEDICAL OFFICER
I concur.

Dale Conner
5/13/2009 05:26:09 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 65-443

STATISTICAL REVIEWS

ANDA 65-443**Drug Product: Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%****Sponsor: Dow Pharmaceutical Sciences, Inc.****Reference Listed Drug: BenzaClin[®] Gel, Sanofi Aventis/Dermik****Submission date: 2/7/2007****Reviewer: Huaixiang Li, Ph.D., DB6/OB/CDER****Requestor: Sarah Seung, Pharm.D., OGD/CDER, 9/26/2007****Objectives of the study**

The primary objective of the study was to establish the bioequivalence of the test product, Dow Pharmaceutical Sciences, Inc. Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%, and the reference product, Sanofi Aventis/Dermik, BenzaClin[®] gel, and to show superiority of the two active treatments to the placebo, a gel vehicle, in the treatment of severe acne vulgaris.

Remarks

The statistical analyses used information from two summary datasets: 'puredata.xpt' and 'pstatus.xpt' submitted on February 7, 2007.

The sponsor mentioned: A majority of patients (949 out of 1236) had the drug immediately after the screening visit, and did not come for a separate baseline visit (thus, for these patients the screening visit was also the baseline visit.) The lesion counts at the screening date, the date of the screening visit, and the date of the baseline visit (these two dates were actually the same for these patients) were recorded, but the lesion counts at baseline were entered as missing values for these patients in the dataset. The rest of the patients did not receive the drug immediately after the screening visit and came to get the drug and have lesion counts evaluated at a separate baseline visit. They had visit dates and lesion counts for both the screening visit and the baseline visit (except for 7 patients for whom the baseline lesion counts were genuinely missing – see below.) We, the FDA medical and statistical reviewers, confirmed these facts by the screening and baseline dates listed in the datasets, together with comments contained in the sponsor's study report.

In the dataset 'puredata.xpt', five variables (paptot1-paptot5) recorded the papules/pustules total and five variables (nintot1-nintot5) recorded open/closed comedones, in both cases at screening, baseline, week 3, week 6, and week 10 visits. Out of a total of 1236 patients in the study, 956 patients had missing records for the paptot2 and nintot2 variables (i.e. the variables corresponding to the baseline visit.) 949 of these 956 patients had the same date for the screening and baseline visits. The other 7 of these 956 patients had different dates for the screening and baseline visits. Of those 7 patients, 110-118 (reference), 110-120 (reference), and 110-121 (test) were already excluded from the sponsor's ITT and PP populations; 102-80 (test), 104-154 (reference), 104-161 (test), and 111-65 (test) were excluded from FDA's ITT and PP populations. The remaining 280

patients (out of 1236) had records for paptot2 and nintot2, since the screening date and baseline date were different and baseline lesion counts were available.

Last observation Carried forward (LOCF): If the patient discontinued or was discontinued due to various reasons, the last lesion count would be carried forward for statistical analysis.

The following adjustments to the submitted datasets were made in accordance with recommendations of the FDA medical reviewers and our (medical and statistical reviewers) best judgment.¹

Exclusion from the FDA's Intent-to-treat (FITT) and Per-Protocol (FPP) populations

- 1) Four patients, 102-80 (test), 104-154 (reference), 104-161 (test), and 111-65 (test), did not have baseline evaluations.

Exclusion from the FDA's Per-Protocol (FPP) population

- 1) Three patients, 103-36 (test), 103-114 (test), and 106-52 (placebo), started or switched birth control or hormonal therapy, etc. less than three months before the study.
- 2) Seven patients (2:5:0 for test:reference:placebo) had baseline lesion counts out of inclusion criteria - [17,40] for papules/pustules total and [20,100] for open/closed comedones².
- 3) Eight patients (2:4:2 for test:reference:placebo) did not have a week 10 visit (early discontinuation).
- 4) Forty-four patients (13:25:6 for test:reference:placebo) were out of visit window (day 70±4) at the week 10 visit.
- 5) Twenty-three patients (8:9:6 for test:reference:placebo) used prohibited concomitant medication prior to and/or during the study.

Inclusion in the FDA's Per-Protocol (FPP) population

Two patients, 103-54 (placebo) and 104-88 (reference), were included in the FPP population using LOCF (Last Observation Carried Forward) because they were discontinued due to lack of treatment effect³.

Study Design

This was a 3 arm parallel double-blind study for patients with signs and symptoms of acne vulgaris. The three gels were the test product, Dow Pharmaceutical Sciences, Inc., Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%, the reference product, Sanofi Aventis/Dermik, BenzaClin[®] gel, and the placebo, a gel vehicle.

¹ Please see the details in the FDA medical reviewer's report and summary table on page 5 of this report.

² All patients had baseline nodule count < 3.

³ Patient, 108-34 (test) was already included in the sponsor's PP population.

1236 patients were enrolled and randomly assigned to the three treatment groups in the study with a ratio of 2:2:1 (498:494:244 for test:reference:placebo). At the screening/baseline visit(s), inflammatory (papules and pustules total) and non-inflammatory (open and closed comedones) lesion counts were recorded. For inclusion in the study, the patient had to be 12 years of age or older, and to have a minimum of 17, but no more than 40 inflammatory lesions and a minimum of 20, but no more than 100 non-inflammatory lesions. The eligible patient was instructed to apply the study gel onto the face twice daily for 10 weeks. Patients returned for clinical evaluations at week 3, week 6, and week 10.

Outcome Variables at Week 10 (Day 70±4)

The primary efficacy variables were the percent change from baseline of inflammatory (papules and pustules total) and non-inflammatory (open and closed comedones) lesion counts at week 10. The secondary variables were the change from baseline of inflammatory and non-inflammatory lesion counts at week 10. If B is the lesion count at baseline and T is the lesion count at week 10, then percent change from baseline is defined as $100 \cdot (B-T)/B$ and change from baseline is defined as B-T.

In those cases where the screening visit and baseline visit coincided (see discussion above under "Remarks"), the screening visit lesion count was used as the baseline count B for computation of percent change from baseline and change from baseline.

Statistical Analysis Methods

Subset analyses deleting centers (b) (6) and (b) (6)

This study was carried out in 12 centers with varying numbers of patient from 35 to 155 per center. The table in the FDA medical report shows the distribution of the numbers of patients in the centers for the enrollment population. There are even smaller numbers of patients in some centers for the FITT and FPP population. The treatment and center factors were included in the statistical analysis GLM model⁴.

Based on the FDA medical reviewer's comments: *"Two principal investigators and two sub-investigators at Sites (b) (6) and (b) (6) were reported to be employees of the sponsor. Two of them held unexercised stock options in the sponsor. If exercised, one would have a vested option of less than \$50,000, and the other would be in excess of \$50,000. In order to ensure that the outcome of the study has not been biased by the financial interest of these two individuals, please conduct appropriate subset analyses to evaluate the impact of Sites (b) (6) and (b) (6) on the study results"*. The additional analysis was carried out for the FITT and FPP populations without centers (b) (6) (b) (6) patients enrolled: (b) (6) for test:reference:placebo) and (b) (6) (b) (6) patients enrolled: (b) (6) for test:reference:placebo).

⁴ There were some statistically significant center-by-treatment effects in the statistical model. There were always statistically significant center effects in the statistical model, however, the assessments of treatment effects with center in the model were similar to those with center and center-by-treatment in the model.

Efficacy Analysis

All treatment arms should be similar for lesion counts at the enrollment visit.

The comparisons for the percent change and change from baseline of inflammatory (papules and pustule total) and non-inflammatory (open and closed comedones) lesion counts were made between treatment arms at the (two-sided) 5% level of significance. The efficacy analysis for each active treatment was tested separately by comparing with the placebo. The active treatment should be more distinguishable from placebo as the study progresses.

Equivalence Analysis

The compound hypothesis to be tested is:

$$H_0: \mu_T / \mu_R < \theta_1 \text{ or } \mu_T / \mu_R > \theta_2$$

versus

$$H_A: \theta_1 \leq \mu_T / \mu_R \leq \theta_2$$

In accordance with the standard in OGD for equivalence analyses for continuous endpoints, $\alpha=0.05$, $\theta_1=0.80$, and $\theta_2=1.25$. For analysis of untransformed endpoints (i.e. percent change from baseline for lesion count or change from baseline for lesion count analyzed as calculated) the 90% confidence interval (corresponding to two one-sided tests at level $\alpha=0.05$, as described by Sasabuchi) based on Fieller's method is calculated for the equivalence test. The null hypothesis H_0 is rejected if the 90% confidence interval for μ_T / μ_R is contained in the [0.80, 1.25] interval. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products. Calculation of the 90% confidence intervals, using Fieller's method, was facilitated by using the GLM procedure in SAS[®], including the variables treatment and center in the model.

Rank Transformation analyses: We found that the distribution of values of the percent change from baseline for total lesion count was strongly enough skewed that the assumption of normality of distribution was likely not the most appropriate for these data. We conducted the efficacy and equivalence analyses based on the rank values. The results were obtained from rank assignment by using the SAS[®] RANK procedure and fitting general linear models, containing the variables treatment and center, by using the SAS[®] GLM procedure. For equivalence analyses, pre-multiplying all of the Reference product observations by a constant (call it c) prior to taking ranks permitted testing the null hypothesis $H_0: \text{median}(\text{Test})/\text{median}(\text{Ref.}) = c$. The set of c values for which this hypothesis was not rejected at the $\alpha = 0.10$ two-sided level of significance constitutes a 90% confidence set for $\text{median}(\text{Test})/\text{median}(\text{Ref.})$. If this confidence set was contained in the interval [0.80, 1.25], the equivalence test was passed for the Rank analysis⁵.

Analysis Populations

⁵ Although the change from baseline of lesion counts was not strongly skewed, we also performed a rank transformation analysis of this variable as an additional confirmatory analysis.

Two analysis populations were defined in the FDA medical reviewer’s report:

Intent-to-treat population (ITT) – All subjects randomized to treatment and treated, with at least one post-baseline visit.

Per-protocol population (PP) – All subjects in the ITT population who completed the study and were evaluable for the analyses based on the protocol and FDA medical and statistical reviewer’s best judgment.

According to the best judgment of the FDA medical and statistical reviewers , the determination of clinical equivalence of the two active treatments was to be assessed using the FDA’s Per Protocol population (FPP), while the superiority comparison of the two active treatments to placebo was to be assessed using the FDA’s Intent-to-treat population (FITT).

Statistical Analysis Results

1236 patients were enrolled. The FITT population included 1182 patients. The FPP population included 875 patients.

The following table shows the number of patients in each population per treatment arm[&]

| | Test | Reference | Placebo | Total |
|--|------------|------------|------------|-------------|
| Enrollment | 498 | 494 | 244 | 1236 |
| Did not receive medication | 1 | 4 | | 5 |
| No post-dose evaluation | 16 | 18 | 11 | 45 |
| <i>Sponsor’s ITT population (ITT)</i> | <i>481</i> | <i>472</i> | <i>233</i> | <i>1186</i> |
| Missed more than one visit | 1 | 2 | | 3 |
| Failed inclusion criteria | 1 | | | 1 |
| Missed week 10 visit | 23 | 18 | 9 | 50 |
| Non-dosing compliant | 1 | 2 | 4 | 7 |
| Off-schedule week 10 visit | 63 | 57 | 35 | 155 |
| Took prohibited medicine | 2 | 5 | 1 | 8 |
| <i>Total exclusion from sponsor’s PP population</i> | <i>108</i> | <i>106</i> | <i>60</i> | <i>274</i> |
| <i>Sponsor’s PP population (PP)</i> | <i>390</i> | <i>388</i> | <i>184</i> | <i>962</i> |
| <u>Exclusion from the FITT and FPP populations</u> | | | | |
| No baseline evaluation* ¹ | 3 | 1 | | 4 |
| FDA’s ITT population (FITT) | 478 | 471 | 233 | 1182 |
| <u>Exclusion from the FPP population</u> | | | | |
| Birth control or hormonal therapy started/switched less than three months before the study* ² | 2 | | 1 | 3 |
| Baseline lesion counts out of inclusion criteria | 2 | 5 | | 7 |
| Missing week 10 visit | 2 | 4 | 2 | 8 |
| Out of the visit window (day 70±4) at week 10 visit | 13 | 25 | 6 | 44 |
| Prohibited concomitant medication use | 8 | 9 | 6 | 23 |
| <u>Inclusion in the FPP population</u> | | | | |
| Discontinued due to lack of treatment effect** | | +1 | +1 | +2 |
| <i>Total exclusion from FDA’s PP population</i> | <i>138</i> | <i>149</i> | <i>74</i> | <i>361</i> |
| FDA’s PP population | 360 | 345 | 170 | 875 |

&: Patient(s) may have multiple reasons to be excluded from the FITT and FPP populations.

*1: Four patients: 102-80 (test), 104-154 (reference), 104-161 (test), and 111-65 (test).

*2: Three patients: 103-36 (test), 103-114 (test), and 106-52 (placebo).

** : Two patients: 103-54 (placebo) and 104-88 (reference).

Demographics and baseline

The table below shows the age, gender, and race distribution for the FITT population. The age, gender, and race of patients were comparably distributed among the three treatment groups for the FITT and FPP populations with/without centers (b) (6) and (b) (6)

| | Test | Reference | Placebo | Total |
|--------------------------------|------------------|------------------|------------------|------------------|
| Age (years) | | | | |
| Mean (standard deviation) | 19.2 (6.15) | 18.9 (6.12) | 19.7 (6.63) | 19.2 (6.24) |
| Median (range) | 17.1 (12.1-46.0) | 16.8 (12.0-48.4) | 17.2 (12.1-48.2) | 17.1 (12.0-48.4) |
| Gender | | | | |
| Male | 226 | 206 | 118 | 550 |
| Female | 252 | 265 | 115 | 632 |
| Race* | | | | |
| White | 353 | 344 | 169 | 866 |
| Black/African American | 45 | 49 | 19 | 113 |
| American Indian/Alaskan Native | 5 | 3 | 4 | 12 |
| Asian | 23 | 29 | 13 | 65 |
| Native Hawaiian/Pacific Island | 5 | 6 | 5 | 16 |
| Other | 46 | 40 | 23 | 109 |

*: Patient 105-145 (test) missed race record in the data set.

An analysis for homogeneity of the inflammatory and non-inflammatory lesion counts for the FITT and FPP populations with/without centers (b) (6) and (b) (6) at the baseline visit was performed. There were no statistically significant differences among treatment arms for these populations at the baseline visit.

Efficacy and equivalence Analyses

We analyzed the data for efficacy and equivalence for the percent change and change from baseline of lesion counts at week 10 (day 70±4).

In the results that follow, analyses of untransformed observations are designated as “Raw”, while analyses using the Rank Transformation are designated as “Rank”.

Primary endpoint:

Percent change from baseline of inflammatory and non-inflammatory lesion counts at week 10

Table 1.1: Efficacy analysis for the percent change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FITT population.

| Variable | Test vs. placebo | | | Ref. vs. placebo | | |
|------------------|-------------------|-----------------|---------|-------------------|-----------------|---------|
| | Test Drug LS Mean | Placebo LS Mean | p-value | Ref. Drug LS Mean | Placebo LS Mean | p-value |
| Inflammatory | | | | | | |
| Raw | 59.88 | 33.19 | <0.0001 | 61.17 | 33.13 | <0.0001 |
| Rank | n/a | n/a | <0.0001 | n/a | n/a | <0.0001 |
| Non-inflammatory | | | | | | |
| Raw | 53.53 | 30.30 | <0.0001 | 51.76 | 29.41 | <0.0001 |
| Rank | n/a | n/a | <0.0001 | n/a | n/a | <0.0001 |

The test and reference treatments were statistically significantly better than placebo for the percent change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FITT population.

Table 1.2: Equivalence Analysis for the percent change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP populations

| Raw | | | | Rank | |
|------------------|--------------|-----------------------------|-----------|-----------------------------|-----------|
| Test LS mean | Ref. LS mean | 90% Confidence Interval (%) | Pass/Fail | 90% Confidence Interval (%) | Pass/Fail |
| Inflammatory | | | | | |
| 61.08 | 61.49 | 92.8, 106.3 | Pass | 97.5, 105.6 | Pass |
| Non-inflammatory | | | | | |
| 54.54 | 52.83 | 96.4, 110.6 | Pass | 97.5, 108.0 | Pass |

The equivalence test was passed for the percent change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP population.

Secondary endpoints:

Change from baseline of inflammatory and non-inflammatory lesion counts at week 10

Table 2.1: Efficacy analysis for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FITT population

| Variable | Test vs. placebo | | | Ref. vs. placebo | | |
|------------------|-------------------|-----------------|---------|-------------------|-----------------|---------|
| | Test Drug LS Mean | Placebo LS Mean | p-value | Ref. Drug LS Mean | Placebo LS Mean | p-value |
| Inflammatory | | | | | | |
| Raw | 15.45 | 8.66 | <0.0001 | 15.62 | 8.52 | <0.0001 |
| Rank | n/a | n/a | <0.0001 | n/a | n/a | <0.0001 |
| Non-inflammatory | | | | | | |
| Raw | 23.71 | 14.12 | <0.0001 | 23.21 | 13.61 | <0.0001 |
| Rank | n/a | n/a | <0.0001 | n/a | n/a | <0.0001 |

The test and reference treatments were statistically significantly better than placebo for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FITT population.

Table 2.2: Equivalence Analysis for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP populations

| Raw | | | | Rank | |
|------------------|--------------|-----------------------------|-----------|-----------------------------|-----------|
| Test LS mean | Ref. LS mean | 90% Confidence Interval (%) | Pass/Fail | 90% Confidence Interval (%) | Pass/Fail |
| Inflammatory | | | | | |
| 15.55 | 15.81 | 91.2, 106.2 | Pass | 94.9, 106.8 | Pass |
| Non-inflammatory | | | | | |
| 24.20 | 23.39 | 94.4, 113.5 | Pass | 94.7, 112.5 | Pass |

The equivalence test was passed for the change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP population.

Additional analysis for the population without sites (b) (6) and (b) (6)

Table 3.1: Efficacy analysis for the percent change and change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FITT population without centers (b) (6) and (b) (6)

| Variable | Test vs. placebo | | | | Ref. vs. placebo | | | |
|-----------------------|-------------------|-----------------|---------|---------|-------------------|-----------------|---------|---------|
| | Raw | | | Rank | Raw | | | Rank |
| | Test Drug LS Mean | Placebo LS Mean | p-value | p-value | Ref. Drug LS Mean | Placebo LS Mean | p-value | p-value |
| Percent change | | | | | | | | |
| Inflammatory | 58.29 | 33.89 | <0.0001 | <0.0001 | 59.54 | 33.78 | <0.0001 | <0.0001 |
| Non-inflammatory | 51.82 | 27.94 | <0.0001 | <0.0001 | 49.79 | 26.94 | <0.0001 | <0.0001 |
| Change | | | | | | | | |
| Inflammatory | 15.11 | 9.03 | <0.0001 | <0.0001 | 15.28 | 8.84 | <0.0001 | <0.0001 |
| Non-inflammatory | 23.83 | 14.09 | <0.0001 | <0.0001 | 23.48 | 13.37 | <0.0001 | <0.0001 |

The test and reference treatments were statistically significantly better than placebo for the percent change and change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FITT population without centers (b) (6) and (b) (6)

Table 3.2: Equivalence Analysis for the percent change and change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP population without centers (b) (6) and (b) (6)

| | Raw | | | | Rank | |
|-----------------------|--------------|--------------|-----------------------------|-----------|-----------------------------|-----------|
| | Test LS mean | Ref. LS mean | 90% Confidence Interval (%) | Pass/Fail | 90% Confidence Interval (%) | Pass/Fail |
| Percent change | | | | | | |
| Inflammatory | 59.75 | 60.42 | 91.2, 107.2 | Pass | 97.0, 107.2 | Pass |
| Non-inflammatory | 52.45 | 51.24 | 94.0, 111.5 | Pass | 95.2, 108.5 | Pass |
| Change | | | | | | |
| Inflammatory | 15.26 | 15.69 | 88.8, 106.6 | Pass | 93.8, 108.7 | Pass |
| Non-inflammatory | 24.16 | 23.79 | 90.9, 113.6 | Pass | 90.0, 112.4 | Pass |

The equivalence test was passed for the percent change and change from baseline of inflammatory and non-inflammatory lesion counts (raw and rank values) at week 10 for the FPP population without center (b) (6) and (b) (6)

Comments on the Sponsor’s Analysis

As described in the FDA medical review’s report, the sponsor analyzed the percent change and change from baseline of inflammatory and non-inflammatory lesion counts at week 10 for their ITT and PP populations using the methods of Fieller’s Theorem based on least squares estimates from the analysis of covariance with factors of treatment, stratifying baseline variables of skin tone (Fitzpatrick skin typing test) and baseline

Evaluator’s Global Severity Score and corresponding baseline lesion count. The sponsor’s statistical analysis shows: 1) Test and reference treatments were statistically significantly better than placebo for the percent change and change from baseline of inflammatory and non-inflammatory lesion counts at week 10 for their ITT population. 2) The 90% Confidence Interval (CI) for the test/reference ratio of mean percent reduction from baseline for inflammatory lesion count to be (0.91, 1.07) and that of non-inflammatory lesion count to be (0.93, 1.11) at Week 10, within the bioequivalence limits of [0.80, 1.25]. There was no detail provided as to how the sponsor obtained the 90% confidence interval using the ANCOVA model.

According to the best judgment of the FDA medical and statistical reviewers, our statistical analysis was carried out for the inflammatory and non-inflammatory lesion counts using our traditional ANOVA model. An analysis for homogeneity of the stratifying baseline variables of skin tone and Evaluator’s Global Severity Score was performed. There were no statistically significant differences between treatment arms.

Safety

Please see the details in the OGD medical reviewer’s report.

Conclusion

Primary endpoints: Percent change from baseline of inflammatory (papules and pustules total) and non-inflammatory (open and closed comedones) lesion counts at week 10

The test and reference treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the FPP population for percent change from baseline of lesion counts (raw and rank values). This was also true when centers (b) (6) and (b) (6) were deleted from the dataset.

Secondary endpoints: Change from baseline of inflammatory (papules and pustules total) and non-inflammatory (open and closed comedones) lesion counts at week 10

The test and reference treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the FPP population for change from baseline of lesion counts (raw and rank values). This was also true when centers (b) (6) and (b) (6) were deleted from the dataset.

Huaixiang Li, Ph.D.
 Mathematical Statistician, DB6/OB

Donald J. Schuirmann
 Expert Mathematical Statistician, DB6/OB

Stella G. Machado, Ph.D.
 Director, DB6/OB

cc:
 HFD-600 Dena R Hixon, Sarah Seung, Debra M Catterson
 HFD-705 Stella G. Machado, Donald J. Schuirmann, Huaixiang Li, DB6/OB
 Lillian Patrician, OB

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/s/

Huaixiang Li
11/6/2007 04:13:24 PM
BIOEQUIVALENCE STATISTICIAN

Donald Schuirmann
11/6/2007 04:18:56 PM
BIOMETRICS

Stella Machado
11/7/2007 10:12:36 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 65-443

OTHER REVIEWS

MEMORANDUM TO ANDA 65-443
Clindamycin Topical Product Formulations

Through: Dena R. Hixon, MD
Associate Director for Medical Affairs
Office of Generic Drugs

From: James L. Osterhout, PhD

Drug Product: Clindamycin Phosphate Topical Products

Sponsor: Dow Pharmaceutical Sciences, Inc.

Reference Drug: BenzaClin® Topical Gel, 1%/5%; NDA 50-756

Date of Submission: February 7, 2007

Date of Memorandum: 16 March 2009

Introduction

Systemic absorption of topically applied clindamycin has been associated with the onset of *Clostridium difficile* associated diarrhea (CDAD). There have been case reports after application of clindamycin hydrochloride¹ as well as clindamycin phosphate.² However, it is thought that clindamycin phosphate is systemically absorbed from topical dosage forms to a lesser extent.³ CDAD is thought to result from small amounts of clindamycin released into the blood exerting antimicrobial activity on normal intestinal flora, reducing competitive growth and allowing *C. difficile* to overgrow.

The studies in scientific literature on the individual bioavailability of topical clindamycin have results that differ widely, with a range of 7.5% to 10%.^{4 5} Goodman and Gilman's *The Pharmacological Basis of Therapeutics* cites an average bioavailability of 3%. The range of values may be due to the variability of the surface area treated or other factors such as the product formulation. Some inactive ingredients found in topical dosage forms could enhance the penetration of clindamycin and result in greater systemic absorption. The resulting increase in blood clindamycin levels may theoretically increase the likelihood of CDAD. Therefore, the inactive ingredients that might have penetration enhancement potential when used in topical clindamycin products will be reviewed to assess their penetration enhancing potential.

In addition, this review compiled the formulations of all topical products that contain clindamycin either as a single active ingredient or in combination with a second active ingredient. The formulations are given in the Appendix, starting on Page 10.

¹ Arch Dermatol, 1981, Vol. 117, 154-5

² Arch Dermatol, 1986, Vol. 122: 583-4

³ Pharmazie 60: 350-353 (2005)

⁴ Biopharmaceutics & Drug Disposition (1989) Vol. 10, 505-512

⁵ J Eur Acad Dermatol Verereol, 1998, 11 (Suppl 1):S13-19; discussion S28-9

Background

General Information

The main Reference Listed Drugs (RLDs) of concern in this review are Cleocin T®, manufactured by Pharmacia and Upjohn, and BenzaClin® manufactured by Sanofi Aventis US. However, all the clindamycin topical products will bear scrutiny.

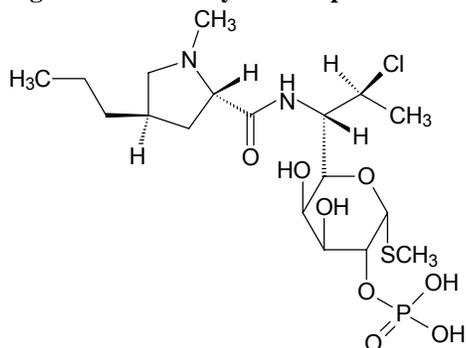
Cleocin T® Topical Solution and Cleocin T® Topical Lotion contain clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per milliliter. Cleocin T® Topical Gel contains clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per gram. Each Cleocin T® Topical Solution pledget applicator contains approximately 1 mL of topical solution.

The solution contains isopropyl alcohol 50% v/v, propylene glycol, and water. The gel contains allantoin, carbomer 934P, methylparaben, polyethylene glycol 400, propylene glycol, sodium hydroxide, and purified water. The lotion contains cetostearyl alcohol (2.5%); glycerin; glyceryl stearate SE (with potassium monostearate); isostearyl alcohol (2.5%); methylparaben (0.3%); sodium lauroyl sarcosinate; stearic acid; and purified water.

BenzaClin® contains, as dispensed in 1 gram, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. Clindamycin is hydrophilic (polar molecule). Clindamycin's short half-life of 2.7 hours after topical application indicates that the skin does not provide any substantial reservoir for the drug and that accumulation in the blood with normal dosing is not likely.

Figure 1: Clindamycin Phosphate



Polar molecules are those which have a permanent electric dipole moment. What this means is that although the molecule may have an overall neutral charge, one part of it is more negative than the other. Using water for example, the oxygen is more electronegative and so this end of

the molecule is more negatively charged. So, a hydrophilic molecule is also called a polar molecule.

The effect the inactive ingredient has on a specific drug will depend on the chemical nature of drug in the formulation, as well as the other inactives in the formulation. In this review we are focusing on how the inactive ingredients act toward large polar molecules such as clindamycin.

Inactive ingredient effects on skin penetration are often described by the damage they do to the skin and how well they make the drug available, but they also can affect penetration by changing the level of hydration in the stratum corneum. This is referred to as the lipid protein partitioning theory.⁶ A number of mechanisms for promotion of skin permeability have been proposed. These include increasing drug solubility in skin; dissolving skin lipids; altering the conformation or denaturing skin proteins, disruption of water structure in skin, and increasing membrane fluidity.

Review History

In the RLD label, in Section OVERDOSAGE, it states; topically applied CLEOCIN T can be absorbed in sufficient amounts to produce systemic effects.

In the Bioequivalence review of ANDA 65-184, the reviewer made the following assessment:

“The content of Propylene Glycol in the test formulation is (b) (4)% greater than that of the RLD product. However, the amount of Propylene Glycol has been found to exceed that of the RLD product in several approved ANDAs, (see Relevant OGD or DBE History on page 2 of this review). The amount of Propylene Glycol in the current test product, therefore, is considered not to affect the safety of the proposed drug product.”

Information From the Material Safety Data Sheet (MSDS) for Clindamycin Phosphate:

| | |
|------------------------|---|
| Solubility: | Freely soluble in water; slightly soluble in dehydrated alcohol; very slightly soluble in acetone; practically insoluble in chloroform; in benzene, and in ether. |
| pH: | 3.5 – 4.5 (10 mg/mL in Water) |
| Hygroscopicity: | Clindamycin Phosphate USP is hygroscopic |

In Chemistry Review Number 1 of NDA 50-801⁷ (Section P.2.1.2 – Excipients), the reviewer refers to the pharmaceutical function of propylene glycol as a “skin penetrant” in addition to the usual moisturizer/humectant function.

A safety memorandum to Dow’s ANDA 65-443 examined the relative systemic exposures to clindamycin of the Dow ANDA and RLD products. The Dow product contains (b) (4) propylene

⁶ A.C. Williams, B.W. Barry, Penetration enhancers, Adv. Drug Deliv. Rev. 56 (2004) 603– 618

⁷ Renamed from NDA 21-709 due to numbering convention specified in Federal Register for antibiotics.

glycol and the RLD contains none. The medical officer concluded that it was unlikely, given the available information, that the Dow formulation of Clindamycin and Benzoyl Peroxide would pose a significant safety risk compared to the RLD and other currently approved products.

Inactive Ingredients Found in Topical Clindamycin Products

Surfactants

Surfactants such as sodium laureth sulfate, disodium lauryl sulfosuccinate, and other related ionic surfactants have been shown to be penetration enhancers for numerous drug entities. The amount of literature available for these products is exhaustive. It is clear that inclusion of surfactant can enhance the penetration of clindamycin specifically.⁸ Given the extent of evidence that surfactants enhance the penetration of numerous types of molecules, both lipophilic and hydrophilic, and specifically clindamycin, any changes greater than 5% proportional to the RLD in any surfactant should be considered too large to support a waiver of the in vivo bioequivalence study requirement for clindamycin topical products, without additional information to ensure the differences in the surfactant concentrations do not affect the safety, effectiveness, or systemic absorption of the active ingredient compared to the RLD.

Changes in surfactant concentration should be considered in all other topical clindamycin submissions; indeed in all other topical products.

Isopropyl Alcohol and Ethanol

Small molecular weight alcohols in general enhance the penetration of drugs through the perturbation of the skin structure, allowing the drug to bypass the normal barriers of the stratum corneum and penetrate through the epidermis.⁹

It was demonstrated that ethanol could enhance the skin flux of compounds primarily by a) increasing the drug solubility in the donor phase; b) increasing skin lipid fluidity, and c) forming new pores in the stratum corneum.¹⁰ Thus, alcohol's action on skin with higher lipid content would make the active substance penetrate more easily.^{11 12}

However, ethanol's use as a penetration enhancer relies predominantly on a bulk aqueous ethanol vehicle to increase the flux of the drug across the skin due to a solvent drag effect.¹³ This effect is changed little by small differences in the alcohol content. Only large changes in the alcohol content, changes greater than 5% w/w, should be considered too large to support a waiver of the in vivo bioequivalence study requirement for clindamycin topical products without additional information to insure the differences in the alcohol concentrations do not affect the safety, effectiveness, or systemic absorption of the active ingredient compared to the RLD.

⁸ Biopharmaceutics & Drug Disposition (1989) Vol. 10, 505-512

⁹ Pharm Res 1987; 4: 59s

¹⁰ Int. J. Pharm. 1998, 163, 167-176.

¹¹ Drug Dev. Ind. Pharm. 1996, 22 (7), 653-658.

¹² Int. J. Pharm. 1997, 159, 105-114.

¹³ J. Pharm. Sci. 1989, 78, 402-407

Changes in alcohol concentration should be considered in all other topical clindamycin submissions; indeed for all other topical products.

Propylene Glycol

The safety memorandum to ANDA 65-443 addresses the effects propylene glycol may have on clindamycin systemic absorption from topical dosage forms. The recommendation was that the amount of propylene glycol in ANDA 65-443 would not pose a significant safety risk compared to the RLD and other currently approved topical clindamycin products.

Review of the scientific literature for propylene glycol enhancement is extensive. It has been identified as a penetration enhancer and can act in numerous ways depending on the chemistry of the drug and the other inactive ingredients in the formulation.^{14 15} However, there is no direct evidence that it enhances clindamycin penetration. Furthermore, the amounts of propylene glycol needed in the formulation to enhance penetration, which could be in the range of 20-40% w/w, may be well above those seen in the marketed topical clindamycin products (maximum of (b) (4) % w/w).

Propylene glycol has been shown to inhibit the activity of cytochrome P450 isozyme 2E1 (CYP2E1).¹⁶ However, clindamycin metabolism is mediated by the N-demethylase and s-oxidase activity of CYP3A4/5 in the liver.¹⁷ Therefore, if there was systemic absorption of clindamycin, its metabolism would not be affected by concurrent systemic absorption of propylene glycol in the topical dosage form.

Carbomers

Carbomers are considered thickening agents. They are polymers of acrylic acid and form hydrogel in water or alkaline solution, due to hydration of the carboxyl groups. They exhibit high viscosity at low concentrations. Moreover, they are quite stable to heat with negligible batch-to-batch variability. They are also unaffected by aging, do not support bacterial or fungal growth, and are nonirritating.¹⁸

Drug release related to carbomers is entirely due to the viscosity of the vehicle the carbomer is used to make. The greater the carbomer concentration the greater the viscosity, and the lesser the rate the drug is released from the vehicle.¹⁹ Thus, carbomer does not enhance drug penetration, but controls the rate of drug release. Changing the amounts and type of carbomer (ex: (b) (4), (b) (4)) over a range of (b) (4) to (b) (4) % will affect the viscosity and thus the drug release rate. However, this finding was in release systems using artificial membranes. When skin is used, the effect that the carbomer has on release rate is drastically diminished.¹⁸

¹⁴ European Journal of Pharmaceutical Sciences, 7 (1998) 129–135

¹⁵ International Journal of Pharmaceutics 116 (1995) 19-30

¹⁶ Advanced Drug Delivery Reviews 59 (2007) 1482–1503

¹⁷ Drug Metabolism and Disposition Vol. 31 No. 7 878-887.pdf

¹⁸ Drug Dev. Ind. Pharm., 30: 637-647

¹⁹ Pak. J. Pharm. Sci., Vo.21, No.1, January 2008, pp.12-16

Conversely, there is evidence that carbomers may enhance penetration when applied as a thin layer due to the humectant properties of the gel as well.²⁰ However, this is a phenomenon seen with almost any other compound used to make a gel or cream vehicle. The amounts used in vehicles range from (b) (4)% to (b) (4)% in all cases of topical clindamycin products. The overall effect of carbomer on drug penetration and for clindamycin penetration in particular, is minimal and changes in the amount or removal of carbomers from the formulation should not change the systemic absorption of clindamycin.

Allantoin

Allantoin is a diureide of glyoxylic acid. Manufacturers cite several beneficial effects for allantoin as an active ingredient in over-the-counter cosmetics. However, there is no evidence in the literature that it promotes penetration of drugs through the skin. It is possible it could act minimally to enhance penetration of drugs into skin through its general humectant properties.

Polyethylene Glycol 400

Polyethylene glycol (PEG) refers to an oligomer or polymer of ethylene oxide and usually refers to oligomers with a molecular mass from 300 to 20,000 g/mol. Similar to the carbomers it is used as a thickening agent, and does not seem to enhance penetration other than through the general humectant properties it possesses.²¹

Parabens

Methylparaben, and propylparaben are esters of para-hydroxybenzoic acid, from which the name is derived. Parabens are effective preservatives in many types of formulas such as shampoo and creams. These compounds, and their salts, are used primarily for their bacteriocidal and fungicidal properties. There is no evidence in literature that these preservatives act as drug penetration enhancers.

Fatty Alcohols

Stearyl, isostearyl, cetostearyl and cetyl alcohol are fatty alcohols. Glyceryl stearate, an esterification of glycerin and stearic acid, is a very similar compound that acts in a similar fashion as fatty alcohols. They are a solid wax at room temperature which is insoluble in water and have been used as an emollient, emulsifier, and thickener in ointments. There is reference to these compounds being penetration enhancers in numerous non-scientific publications and manufacturer information, all of which do not cite peer-reviewed scientific data. In the book “Percutaneous Penetration Enhancers”, Eric W. Smith and Howard I. Maibach mention one study that shows fatty alcohols may enhance penetration of melatonin, but this study used 60% ethanol as a vehicle with the fatty alcohols at 5%, and there is no reference to the data. Another study investigated enhanced naloxone skin penetration in cadaver skin using 10% fatty alcohol in

²⁰ Journal of Investigative Dermatology (2001) 117, 147–150

²¹ J Pharm Sci. 1986 Jan;75(1):26-8.

a propylene glycol vehicle. Addition of stearyl and cetyl alcohol did not significantly enhance the penetration of naloxone.²²

The clindamycin topical foam and lotion products use fatty alcohols in the range of (b) (4) to (b) (4) w/w in the formulation. It is unlikely that small changes in the fatty alcohol content of topical clindamycin products will affect clindamycin systemic absorption.

Polysorbates

Polysorbates, also referred to as Tweens, are derived from polyethylene glycolated sorbitan esterified with fatty acids. They are considered a nonionic surfactant and emulsifier. They are weak surfactants when compared to ionic surfactants such as sodium laureth sulfate. Studies on polysorbate penetration enhancement are limited. One study did not show any significant enhancement of penetration with Tween 20 over the control for 4 different drugs with various lipophilicities.²³ Other research suggested polysorbate 60 may enhance penetration of lidocaine, but this was in the presence of propylene glycol, which is a known strong penetration enhancer.²⁴ Another study investigated enhanced naloxone skin penetration in cadaver skin using 10% polysorbate in a propylene glycol vehicle. Addition of polysorbate (Tween 20) did not significantly enhance the penetration of naloxone.²⁵

The clindamycin topical foam products use (b) (4) % w/w polysorbate in the formulation. It is unlikely that small changes in the polysorbate content of topical clindamycin products will affect clindamycin systemic absorption.

Dimethicone

Dimethicone is optically clear, and is generally considered to be inert, non-toxic and non-flammable. It is one of several types of silicone oil (polymerized siloxane). In topical formulations it is considered a skin protectant. There is little evidence in the literature that dimethicones significantly enhance drug penetration. In one study, use of the various molecular weight dimethicones lead to modest changes in the amount of terpenes found in the epidermis. The authors suggest that the emulsion formed by the dimethicones held the drug in a reservoir at the skin, regulating its release. The vehicles in this study used 15% dimethicone with various waxes and water to form an emulsion.²⁶ Another study examining the enhanced penetration of methyl nicotinate in vivo (upper arm application) with various vehicles found no enhancement with addition of dimethicone.²⁷ Furthermore, a study that investigated the effects of dimethicone on the stratum corneum using wide angle x-ray diffraction and polarized light microscopy revealed that they do not change either the microstructure of excised human stratum corneum or the biphasic lamellar/inverse hexagonal structure.

²² International Journal of Pharmaceutics, 33 (1986) 225-234

²³ International Journal of Pharmaceutics 202 (2000) 133-140

²⁴ Int J Pharm 1993; 95: 161.

²⁵ International Journal of Pharmaceutics, 33 (1986) 225-234

²⁶ Journal of Controlled Release 63 (2000) 7-17

²⁷ Journal of Pharmaceutical Sciences Volume 84 Issue 2, Pages 195 - 198

Dimethicone is used in one combination product, a benzoyl peroxide/clindamycin gel, at (b) (4) % w/w. It is unlikely that small changes in the dimethicone amount in clindamycin topical products will affect clindamycin systemic absorption.

Poloxamer

Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene. Because of their amphiphilic structure, they can be used to increase the water solubility of hydrophobic substances or increase the miscibility of substances with different hydrophobicities.

Poloxamers are generally used to supplement or create a hydrogel base vehicle and of themselves have not been studied as penetration enhancers. In one study they are used at 25% w/v in water as the gel base vehicle that penetration enhancers were added to for evaluation.²⁸ This trend is seen in further research where they are used as a base vehicle for iontophoresis enhancement of insulin penetration, as well as a base for evaluation of penetration enhancers on insulin skin penetration.²⁹

There is no evidence to suggest poloxamer will enhance systemic absorption of clindamycin from topical formulations.

Conclusions

Many of the skin penetration studies published and referenced in the literature and this review are performed on artificial membranes. Other studies are performed on systems that use real skin from animals or cadavers, but the skin is excised and placed in a reservoir system for analysis. In either case, the results from these studies need to be taken only as evidence of a possible enhancement by the chemical entity under study.

Furthermore, many of the penetration enhancement studies are on a drug other than clindamycin. Therefore, the penetration enhancement may not apply to clindamycin specifically. An in vivo study in humans assessing the chemical entity's penetration enhancement of clindamycin would be needed for confirmation. Ideally, this study would not only assess the blood levels over time but the local bioavailability as well, because clindamycin has been shown to accumulate in the intestines and exert antimicrobial activity for days after dosing³⁰.

Given this lack of specific data, many of the compounds used to formulate the various clindamycin topical products can only be assessed by consensus of data and corroborative scientific rationale. It is especially important to look at penetration enhancement of molecules that are hydrophilic and large, similar to clindamycin. Using this method of investigation, it is

²⁸ International Journal of Pharmaceutics 146 (1997) 255-262

²⁹ Journal of Controlled Release 89 (2003) 127-140

³⁰ Antimicrobial Agents and Chemotherapy, Dec. 1981, p. 736-740

clear that the majority of the inactive ingredients used in the currently marketed clindamycin topical formulations will not affect systemic absorption of clindamycin.

However, using this same method of investigation it is clear that some inactive ingredients, such as surfactants and alcohols, and propylene glycol at higher concentrations, have the potential to enhance the systemic absorption of clindamycin from topical dosage forms and should be carefully evaluated in all new ANDA submissions for topical clindamycin products.

Reviewer: _____ Date: _____
James L. Osterhout, Ph.D.
Clinical Reviewer

Concur: _____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Appendix

Table 1: Topical Clindamycin Products

| Appl No | TE Code | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary Name | Applicant |
|------------------------|---------|-----|--|------------------------|---------------|-----------------------|----------------------|
| 050819 | | Yes | BENZOYL PEROXIDE; CLINDAMYCIN PHOSPHATE | GEL; TOPICAL | 2.5%;1.2% | ACANYA | DOW PHARM SCI |
| 050756 | BT | Yes | BENZOYL PEROXIDE; CLINDAMYCIN PHOSPHATE | GEL; TOPICAL | 5%;EQ 1% BASE | BENZAACLIN | SANOFI AVENTIS US |
| 050741 | BT | Yes | BENZOYL PEROXIDE; CLINDAMYCIN PHOSPHATE | GEL; TOPICAL | 5%;EQ 1% BASE | DUAC | STIEFEL |
| 050801 | | Yes | CLINDAMYCIN PHOSPHATE | AEROSOL, FOAM; TOPICAL | 1% | EVOCLIN | STIEFEL LABS INC |
| 064160 | AB | No | CLINDAMYCIN PHOSPHATE | GEL; TOPICAL | EQ 1% BASE | CLINDAMYCIN PHOSPHATE | ALTANA |
| 050782 | BT | No | CLINDAMYCIN PHOSPHATE | GEL; TOPICAL | EQ 1% BASE | CLINDAGEL | GALDERMA LABS LP |
| 050615 | AB | Yes | CLINDAMYCIN PHOSPHATE | GEL; TOPICAL | EQ 1% BASE | CLEOCIN T | PHARMACIA AND UPJOHN |
| 065067 | AB | No | CLINDAMYCIN PHOSPHATE | LOTION; TOPICAL | EQ 1% BASE | CLINDAMYCIN PHOSPHATE | ALTANA |
| 050600 | AB | Yes | CLINDAMYCIN PHOSPHATE | LOTION; TOPICAL | EQ 1% BASE | CLEOCIN T | PHARMACIA AND UPJOHN |
| 062811 | AT | No | CLINDAMYCIN PHOSPHATE | SOLUTION; TOPICAL | EQ 1% BASE | CLINDAMYCIN PHOSPHATE | ACTAVIS MID ATLANTIC |
| 065254 | AT | No | CLINDAMYCIN PHOSPHATE | SOLUTION; TOPICAL | EQ 1% BASE | CLINDAMYCIN PHOSPHATE | ALTANA |
| 064159 | AT | No | CLINDAMYCIN PHOSPHATE | SOLUTION; TOPICAL | EQ 1% BASE | CLINDAMYCIN PHOSPHATE | FOUGERA |
| 063304 | AT | No | CLINDAMYCIN PHOSPHATE | SOLUTION; TOPICAL | EQ 1% BASE | CLINDAMYCIN PHOSPHATE | MORTON GROVE |
| 063329 | AT | No | CLINDAMYCIN PHOSPHATE | SOLUTION; TOPICAL | EQ 1% BASE | CLINDA-DERM | PADDOCK |
| 064050 | AT | No | CLINDAMYCIN PHOSPHATE | SOLUTION; TOPICAL | EQ 1% BASE | CLINDAMYCIN PHOSPHATE | PERRIGO NEW YORK |
| 050537 | AT | Yes | CLINDAMYCIN PHOSPHATE | SOLUTION; TOPICAL | EQ 1% BASE | CLEOCIN T | PHARMACIA AND UPJOHN |
| 065184 | AT | No | CLINDAMYCIN PHOSPHATE | SOLUTION; TOPICAL | EQ 1% BASE | CLINDAMYCIN PHOSPHATE | TARO PHARM INDS |
| 064136 | AT | No | CLINDAMYCIN PHOSPHATE | SWAB; TOPICAL | EQ 1% BASE | CLINDETS | PERRIGO |
| 065049 | AT | No | CLINDAMYCIN PHOSPHATE | SWAB; TOPICAL | EQ 1% BASE | CLINDAMYCIN PHOSPHATE | PERRIGO NEW YORK |
| 050537 | AT | No | CLINDAMYCIN PHOSPHATE | SWAB; TOPICAL | EQ 1% BASE | CLEOCIN | PHARMACIA AND UPJOHN |
| 050802 | | Yes | CLINDAMYCIN PHOSPHATE; TRETINOIN | GEL; TOPICAL | 1.2%;0.025% | ZIANA | MEDICIS |

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this page is the manifestation of the electronic signature.**

/s/

James L. Osterhout
5/7/2009 08:24:35 PM
BIOEQUIVALENCE CLINICAL END POIN

Dena Hixon
5/8/2009 12:54:06 PM
MEDICAL OFFICER
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 65-443

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

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07 February 2007

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Handwritten notes:
GJR
- (Amulya)
15 March 2007

Subject: **Abbreviated New Drug Application No. 065443**
Product: Clindamycin-Benzoyl Peroxide Gel
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc.

Dear Mr. Buehler:

Pursuant to §505(j) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, §314.94, Dow Pharmaceutical Sciences, Inc. (DPSI) herewith submits an Abbreviated New Drug Application (ANDA) for Clindamycin-Benzoyl Peroxide Gel.

The drug product, Clindamycin-Benzoyl Peroxide Gel, is indicated for the topical treatment of acne vulgaris. Clindamycin-Benzoyl Peroxide Gel consists of 2 component products, Clindamycin Phosphate Solution, (b)(4)% and Benzoyl Peroxide Gel, (b)(4)%. Clindamycin Phosphate Solution, (b)(4)% is added to Benzoyl Peroxide Gel, (b)(4)% by the pharmacist prior to dispensing. This "admixing" step yields Clindamycin (1%)-Benzoyl Peroxide (5%) Gel.

The reference listed drug is BenzaClin® Topical Gel which contains clindamycin 1% as clindamycin phosphate and benzoyl peroxide 5%.

DPSI held a Type B EOP2 meeting with the Agency on 12 November 2003 to discuss the submission of a 505(b)(2) for Clindamycin-Benzoyl Peroxide Gel. At the meeting the Agency advised DPSI, per 21 CFR 314.101 (d)(9), that it was appropriate the proposed submission be submitted as a 505(j). The following explication can be found in the FDA Meeting Minutes dated December 10, 2003:

"The Sponsor's 1% clindamycin/5% benzoyl peroxide (BP) product has the same active ingredients, strength, dosage form, route of administration and conditions of use as Benzaclin. Therefore, it would appear more appropriate that the application for this product be filed as a

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OGD / CDER

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505(j) application with Benzaclin as the reference listed drug (RDL). The Sponsor would need to demonstrate that their product is bioequivalent to Benzaclin by conducting a three-arm study: the Sponsor's combination product vs Benzaclin vs the Sponsor's vehicle. The sponsor's product should be non-inferior to Benzaclin and superior to vehicle in the treatment of acne vulgaris."

In accordance with MAPP document 5240.3, entitled, "Review Order of Original ANDA's, Amendments and Supplements" (October 18, 2006), DPSI believes that this application is eligible for a priority review based on the following:

1. There are presently no generic approvals for (b) (4) 1% - Benzoyl Peroxide 5% Gel.
2. There are no Orange Book-listed patents or exclusivities for the Reference Listed Drug, BenzaClin[®] Topical Gel.

DPSI conducted Clinical Study DPS-07-07-2005-001, A Phase III Multi-Center, Randomized, Evaluator-Blind, Vehicle Controlled, Three-Arm Clinical Trial to Evaluate the Bioequivalence of (b) (4) (1/5.0) Gel to BenzaClin Gel, and Superiority to (b) (4) Gel Vehicle, in the Treatment of Acne Vulgaris. The study report is contained in this submission.

DPSI acknowledges that all establishments referenced in this application must be in compliance with CGMP at the time of approval. Additionally, DPSI acknowledges that FDA's district Laboratory will perform analytical method validation work on the proposed product since it is not presently the subject of a current compendial (USP) monograph. In the event that DPSI's application is eligible for approval before method validation work is completed, DPSI hereby commits to fully cooperating with the District Laboratory to resolve any issues that may be identified in respect to the analytical methods after the application is approved.

This original ANDA is being submitted in eCTD format on 1CD-ROMs, with a total file size of approximately 210 MB. In addition, hard copy versions and original signatures are provided for the following documents:

- Cover letter
- Form FDA 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use
- Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators
- Field Copy Certification
- Debarment Certification and List of Convictions

The submission is virus free. All files have been scanned using Symantec's Antivirus Corporate Edition, Version 8.1.0.825.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

Gary J. Buehler
Page 3

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 x588 or ajacker@dowpharmsci.com. For questions concerning the electronic components of the submission, please contact Katie Ditton at x540 or kditton@dowpharmsci.com.

Sincerely,

A handwritten signature in black ink, appearing to read 'AJ Acker', written in a cursive style.

AJ Acker, RAC
Manager, Regulatory Affairs

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

| | |
|---|--|
| NAME OF APPLICANT Dow Pharmaceutical Sciences, Inc. | DATE OF SUBMISSION 02/07/2007 |
| TELEPHONE NO. (Include Area Code) 707-793-2600 | FACSIMILE (FAX) Number (include Area Code) 707-793-0145 |
| APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Dow Pharmaceutical Sciences, Inc. 1330 Redwood Way Petaluma, CA 94954 | AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE |

CDER/CDR
FEB 08 2007
RECEIVED

PRODUCT DESCRIPTION

| | | |
|---|--|-------------------------------------|
| NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) | | |
| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Clindamycin-Benzoyl Peroxide Gel | PROPRIETARY NAME (trade name) IF ANY | |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) | CODE NAME (If any) | |
| DOSAGE FORM: Gel | STRENGTHS: Clindamycin (1.0%) Ben.Perox. (5.0%) | ROUTE OF ADMINISTRATION: Topical |
| (PROPOSED) INDICATION(S) FOR USE: | | |

APPLICATION DESCRIPTION

| | | |
|---|--|--|
| APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input checked="" type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601) | | |
| IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2) | | |
| IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>BenzaClin Topical Gel</u> Holder of Approved Application <u>Sanofi Aventis U.S.</u> | | |
| TYPE OF SUBMISSION (check one) <input checked="" type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER | | |
| IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____ | | |
| IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA) | | |
| REASON FOR SUBMISSION <u>Abbreviated New Drug Application</u> | | |
| PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC) | | |
| NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC | | |
| ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. | | |
| <u>See Attached</u> | | |

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF (b)(4); DMF (b)(4)

FEB 09 2007 **FEB 09 2007**
CGD / CDER **CGD / CDER**

This application contains the following items: (Check all that apply)

| | |
|-------------------------------------|--|
| <input checked="" type="checkbox"/> | 1. Index |
| <input checked="" type="checkbox"/> | 2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling |
| <input checked="" type="checkbox"/> | 3. Summary (21 CFR 314.50 (c)) |
| <input checked="" type="checkbox"/> | 4. Chemistry section |
| <input checked="" type="checkbox"/> | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| <input type="checkbox"/> | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| <input checked="" type="checkbox"/> | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| <input type="checkbox"/> | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| <input checked="" type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| <input checked="" type="checkbox"/> | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| <input checked="" type="checkbox"/> | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| <input type="checkbox"/> | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| <input type="checkbox"/> | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| <input checked="" type="checkbox"/> | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| <input checked="" type="checkbox"/> | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| <input checked="" type="checkbox"/> | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| <input checked="" type="checkbox"/> | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| <input type="checkbox"/> | 15. Establishment description (21 CFR Part 600, if applicable) |
| <input checked="" type="checkbox"/> | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| <input checked="" type="checkbox"/> | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| <input type="checkbox"/> | 18. User Fee Cover Sheet (Form FDA 3397) |
| <input checked="" type="checkbox"/> | 19. Financial Information (21 CFR Part 54) |
| <input type="checkbox"/> | 20. OTHER (Specify) |

CERTIFICATION

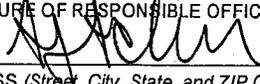
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| | | |
|---|--|--------------------------------------|
| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT  | TYPED NAME AND TITLE AJ Acker, RAC, Magager, Regulatory Affairs | DATE: 02/07/2007 |
| ADDRESS (Street, City, State, and ZIP Code) 1330 Redwood Way, Petaluma, CA 94954 | | Telephone Number (707) 793-2600 |

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : March 5, 2007

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 65-443 for Clindamycin Phosphate and Benzoyl Peroxide Gel, 1% and 5% to determine if the application is substantially complete for filing.

Dow Pharmaceuticals Sciences, Inc. has submitted ANDA 65-443 for Clindamycin Phosphate and Benzoyl Peroxide Gel, 1% and 5%. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Dow Pharmaceuticals Sciences, Inc. on February 7, 2007 for its Clindamycin Phosphate and Benzoyl Peroxide product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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

/s/

Eda Howard
3/5/2007 03:56:01 PM
APPLICATIONS EXA



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

RE

MAR

CL

02 March 2007

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MAR 05 2007

CDER CDR

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RE: **Abbreviated New Drug Application No. 065443, SN0001**
Product: Clindamycin-Benzoyl Peroxide Gel
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. DPSI respectfully submits Amendment 0001 to ANDA 065443.

This submission contains an authorization letter regarding Ms. Joan Janulis of Lachman Consultant Services Inc., providing permission for her to make status inquiries and discuss any technical and/or regulatory issues related to the referenced Abbreviated New Drug Application with members of the Office of Generic Drugs on our behalf.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 x588 or ajacker@dowpharmsci.com. For questions concerning the electronic components of the submission, please contact Katie Ditton at x540 or kditton@dowpharmsci.com.

Sincerely,

AJ Acker, RAC
Senior Manager, Regulatory Affairs

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MAR 06 2007

CDER

cc: Mr. Martin Shimer, Branch Chief, Regulatory Support Branch (by Facsimile)

**CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS**

ANDA# 65-443 _____ **FIRM NAME** Dow Pharmaceutical Sciences, Inc. _____

DRUG NAME Clindamycin-benzoyl peroxide gel, 1% _____

DOSAGE FORM topical gel _____

Requested by: Howard Eda _____ Date: 3/5/07 _____
Chief, Regulatory Support Team, (HFD-615)

| Summary of Findings by Clinical Review Team | |
|--|--|
| X | Study meets statutory requirements |
| | Study does NOT meet statutory requirements |
| | Reason: |
| | Waiver meets statutory requirements |
| | Waiver does NOT meet statutory requirements |
| | Reason: |

RECOMMENDATION: X COMPLETE INCOMPLETE

Reviewed by:

Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

Date: _____

Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Date: _____

| Item Verified: | YES | NO | Required Amount | Amount Sent | Comments |
|--|------------|-----------|------------------------|--------------------|------------------------------|
| Protocol | X | | | | This is an E-CTD submission. |
| Summary of Study | X | | | | |
| Clinical Site (s) | X | | | | |
| Study Investigator (s) | X | | | | |
| List of subjects included in PP/ (M)ITT populations per treatments | X | | | | |
| List of subjects excluded/ from PP/ (M)ITT per treatments | X | | | | |
| Reasons for discontinuation from the study if discontinued | X | | | | |
| Adverse Events | X | | | | |
| Concomitant Medications | X | | | | |
| Individual subject's scores/data per visit | X | | | | |
| Pre-screening of Patients | X | | | | |
| IRB Approval | X | | | | |
| Consent Forms | X | | | | |
| Randomization Schedule | X | | | | |
| Protocol Deviations | X | | | | |
| Case Report Forms | X | | | | |
| PD Data Disk (or Elec Subm) | X | | | | Located in M5 folder |
| Study Results | X | | | | |
| Clinical Raw Data/ Medical Records | X | | | | |
| Composition | X | | | | |

| | | | | | |
|---|---|---|--|--|--|
| BioStudy Lot Numbers | X | | | | |
| Date of Manufacture | | X | | | Expiration date (8/07) and stability data submitted. |
| Exp. Date of RLD | X | | | | |
| Statistical Reports | X | | | | |
| Defined BE endpoints | X | | | | |
| Summary results provided by the firm indicate studies pass BE criteria | X | | | | See comments below |
| Summary results provided by the firm indicate superiority of the active treatments over the vehicle/placebo | X | | | | |
| Waiver requests for other strengths / supporting data | | X | | | N/A |

Additional Comments regarding the ANDA:

1. The sponsor's proposed statistical analysis for establishing bioequivalence of this product is different from what we currently recommend. However, the sponsor presented sufficient data to show that their product may be bioequivalent to the RLD.
2. According to the sponsor, the 90% CI of the ratio of test/reference product for the absolute mean change from baseline in inflammatory and non-inflammatory lesions at week 10 in the per protocol population is (0.89 to 1.06 for inflammatory lesions and 0.92 to 1.15 for non-inflammatory lesions), which is within the bioequivalence limits of 0.80 to 1.25. However, the primary analysis of BE was computed from estimates derived by an analysis of covariance, with factors of treatment, baseline evaluator's global severity score and corresponding baseline lesion count as covariate.

Both the test and reference products demonstrated superiority over placebo at week 10 using analysis of covariance.

3. The sponsor's secondary analyses are summarized as follows:

| | Test | Reference | 90% CI for treatment difference | Test for superiority in ITT population for both test and reference products |
|---|--------------|--------------|---------------------------------|---|
| Mean percent change in inflamed lesion count (PP) | Ls mean=60.4 | Ls mean=61.3 | 0.91 to 1.07* | P<0.001* |

| | | | | |
|---|--------------|--------------|---------------|----------|
| Mean percent change in non-inflamed lesion count (PP) | Ls mean=51.4 | Ls mean=50.6 | 0.93 to 1.11* | P<0.001* |
| **success (PP) | 39% | 38.9% | -0.06-0.06 | P<0.001 |
| ^FDA success (PP) | 46% | 48% | - | - |

*Analysis of covariance used

** defined by the sponsor as global severity score at week 10 at least 2 grades less than baseline

^defined as global severity score of zero (clear) and 1 (almost clear) per table 14.2.4.1.

4. The preferred definition of success for this product based on physician global assessment is clear or almost clear at week 10. According to table 14.2.4.1, 46% in the test, 48% in the reference and 18% in the vehicle groups met this preferred definition of success at week 10.

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

/s/

Dena Hixon
3/9/2007 12:15:56 PM



ANDA 65-443

Dow Pharmaceutical Sciences, Inc.
Attention: A.J. Acker
1330 Redwood Way
Petaluma, CA 94954

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated March 2, 2007, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

Please submit an exclusivity statement per 21 CFR 314.94(a)(3)(ii)

Please submit chromatograms for the Benzoyl Peroxide drug substance and reference standard

Please submit an acceptance certificate of analysis for the drug substance Benzoyl Peroxide from Dow Pharmaceutical Sciences, Inc. (DPSI) or the contract manufacturer for the drug product

Please submit an IR spectra for Clindamycin Phosphate drug substance and reference standard

Please submit an acceptance certificate of analysis for the drug substance Clindamycin Phosphate from DPSI or the contract manufacturer for the drug product

Please submit cGMP/GLP statements for [REDACTED] (b)(4), and DPSI

Please submit a reprocessing statement for the drug product

Please submit a summary page for all of the suppliers and their addresses for the inactive ingredients

Please submit validation of non-USP/NF analytical procedures for the inactive ingredients

Please submit a sample statement to include the batch/lot numbers for the drug substances and drug product used for the exhibit batches

Please submit analytical procedures for the test methods used in the testing for the container closure systems.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition to the deficiencies listed above, please submit your Module 2, Quality Overall Summary, in an MS Word file.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Peter Chen
Project Manager
(301) 827-5837

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
3/16/2007 07:28:28 AM
Signing for Wm Peter Rickman



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

3!

CDER/CDER

MAR 30 2007

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Via Federal Express

28 March 2007

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

N/Ac

Subject: **Abbreviated New Drug Application No. 065443**
SN0002 Response to FDA Letter Dated 16 March 2007 and
Draft Labeling in SPL Format
Product: Clindamycin-Benzoyl Peroxide Gel
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc.

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 22 March 2007, DPSI received a letter from the Agency dated 16 March 2007 which included a list of deficiencies that precluded acceptance of the application. The letter also granted DPSI permission to correct the listed deficiencies by amending the application. To that end, DPSI respectfully submits Amendment 0002 to ANDA 065443.

Please refer to Table 1.2.1 DPSI Response to FDA Letter Dated 16 Mar 2007 included in this letter for a detailed response to each of the 11 aforementioned deficiencies as described in the above-referenced Agency letter.

Please note that this submission does not contain unamended or unmodified items previously submitted in the original application.

This submission also includes:

- MS Word versions of the Module 2 Quality Overall Summary Sections, as requested in the above-referenced Agency letter
- Draft Labeling in SPL format
- FDA Form 356h

RECEIVED

MAR 30 2007

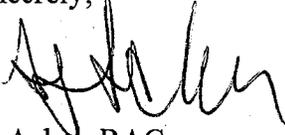
ODD/ODD

Gary J. Buehler
Page 2

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 x588 or ajacker@dowpharmsci.com. For questions concerning the electronic components of the submission, please contact Katie Ditton at x540 or kditton@dowpharmsci.com.

Sincerely,



AJ Acker, RAC
Senior Manager, Regulatory Affairs

cc Mr. Martin Shimer, Branch Chief, Regulatory Support Branch (by Facsimile)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 65-443

Dow Pharmaceutical Sciences, Inc.
Attention: A.J. Acker
1330 Redwood Way
Petaluma, CA 94954

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our "Refuse to Receive" letter dated March 16, 2007 and your amendment dated March 28, 2007. Reference is also made to your correspondence dated March 2, 2007.

NAME OF DRUG: Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%

DATE OF APPLICATION: February 7, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 30, 2007

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Rosalyn Adigun
Project Manager
301-827-5754

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
4/23/2007 01:17:22 PM
Signing for Wm Peter Rickman

RECORD OF TELEPHONE CONVERSATION

| | |
|---|--|
| <p>On this date, I contacted Dow Pharmaceutical Sciences, Inc. (DPSI) to request the following information regarding their clinical endpoint study:</p> <ol style="list-style-type: none">1. Please provide packaging information regarding the Placebo product used in the clinical endpoint study.2. Please provide the areas where the topical steroids were applied for Patients 105-67, 107-83 and 109-175. <p>I instructed Mr. Acker to submit DPSI's response as a Clinical Bioequivalence Amendment, with a courtesy copy faxed to 240-276-8966.</p> <p>Mr. Acker agreed to do so.</p> | DATE: 9/12/07 |
| | ANDA NUMBER 65-443 |
| | TELECON INITIATED BY AGENCY |
| | PRODUCT NAME: Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% |
| | FIRM NAME: Dow Pharmaceutical Sciences, Inc. |
| | FIRM REPRESENTATIVES: AJ Acker, RAC, Manager, Regulatory Affairs |
| | TELEPHONE NUMBER: 707-793-2600 ext. 588 |
| | FDA REPRESENTATIVES Sarah Ho |
| | SIGNATURES: S.Ho |

Orig: ANDA 65-443

Cc: Division File

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/s/

Sarah H. Ho
9/12/2007 03:46:37 PM



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

ORIG AMENDMENT

N000/MC

Via Federal Express

14 September 2007

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

RECEIVED

SEP 17 2007

CDER CDR

Subject: **Abbreviated New Drug Application No. 065443**
SN0003: Response to FDA Request for Information
Product: Clindamycin-Benzoyl Peroxide Gel
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc.(DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 13 September 2007, Ms. Sarah Ho of the FDA telephoned DPSI to request the following information:

- **What packaging was used for the placebo in clinical study Protocol No. DPS-07-07-2005-001?**
- **What area of the body was the topical steroid used by patients 105-67, 107-83, and 109-175 applied to?**

Please refer to DPSI Response to FDA Request for Additional Information included in this amendment for responses to these questions.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 x588 or by e-mail at: ajacker@dowpharmsci.com.

Sincerely,

AJ Acker, RAC
Senior Manager, Regulatory Affairs
Enclosures

RECEIVED

SEP 18 2007

OGD

Telephone Fax

ANDA 65-443

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8987



TO: Dow Pharmaceutical Sciences, Inc

TEL: 707-793-2600 x 588

ATTN: A.J. ACKER

FAX: 707-793-0145

FROM: ADOLPH VEZZA

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Clindamycin/Benzoyl Peroxide Gel, 1%/5%.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **65-443** Dates of Submission: **February 7 and March 28, 2007**

Applicant's Name: **Dow Pharmaceutical Sciences, Inc.**

Established Name: **Clindamycin/Benzoyl Peroxide Gel, 1%/5%**

Labeling Deficiencies:

1. GENERAL COMMENT

The established name for this drug product is "Clindamycin/Benzoyl Peroxide Gel, 1%/5%". Please revise your labels and labeling accordingly.

2. CLINDAMYCIN PHOSPHATE SOLUTION CONTAINER

We note that you have indicated the name of the manufacturer on every piece of labeling save for this one. Please comment.

3. BENZOYL PEROXIDE [FINAL PRODUCT] JAR

"One 50 gram Jar"
"after admixing"

4. CARTON

- a. See comment under (2) above.
- b. Increase the prominence of the established name.
- c. Increase the prominence of "Rx ONLY".

5. INSERT

a. TITLE

Place "Rx Only" in conjunction with the established name.

b. DESCRIPTION

- i. Structural formula – Improve the depiction of the subscripts.
- ii. Third paragraph – "... has a molecular ..." [add "a"]

c. PRECAUTIONS

- i. General – Place a blank line-space immediately beneath "Avoid contact with eyes and mucous membranes".

- ii. Carcinogenesis, Mutagenesis, Impairment of Fertility, Fourth paragraph, last sentence - Place "2.5" and "grams" on the same line of text [note "grams" rather than "g"]
- d. HOW SUPPLIED
 - i. "40 grams" and "10 grams" rather than "40g" and "10g"
 - ii. We note that you have represented Dow Pharmaceutical Sciences, Inc. as the manufacturer of this drug product yet your application states that CPL-Niagara is the manufacturer. What is the relationship between these two entities?

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA". The immediate container labels may be submitted either electronically or in hard copy. However, for ease of review, we ask that you submit electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lillie Golson
10/12/2007 03:56:33 PM
Lillie Golson for Wm. Peter Rickman

MINOR AMENDMENT

ANDA 65-443

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Dow Pharmaceutical Sciences, Inc.

TEL: 609-495-2737

ATTN: Joan Janulis

FAX: 609-495-2709

FROM: Rosalyn Adigun

PROJECT MANAGER: (301)-827-5754

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 7, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Clindamycin-Benzoyl Peroxide Gel (Clindamycin 1% and Benzoyl Peroxide 5%).

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

See Chemistry comments provided

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

Following this page, 3 pages withheld in full - (b)(4)

34. Please include a commitment [REDACTED] (b) (4)

35. We note that you did not request a categorical exclusion from the requirement of an environmental assessment or state if you are in compliance with all federal, state and local environmental regulations. Please provide this information.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available drug product room temperature stability data.
2. The Labeling and bioequivalence information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you separately.
3. All facilities referenced in your ANDA should be in compliance with CGMP at the time of approval.

Sincerely yours,

{See appended signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

James Fan
11/5/2007 10:22:57 AM
James M. Fan for Rashmikant Patel



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

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DEC 19 2007

CDER CDR

N/AM

18 December 2007

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

Subject: **Abbreviated New Drug Application No. 065443**
SN0004: **MINOR AMENDMENT to ANDA No. 065443**
Product: Clindamycin-Benzoyl Peroxide Gel
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc.(DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 5 November 2007 a facsimile message was received from Rashmikant M. Patel, PhD, Director, Division of Chemistry I of the Office of Generic Drugs, informing DPSI that ANDA No. 065443 was deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in a 4-page attachment appended to Dr. Patel's letter.

Under the provisions of 21 CFR §314.120, DPSI herewith submits this MINOR AMENDMENT to ANDA No.065443 to address the MINOR deficiencies noted in Dr. Patel's aforementioned letter of 5 November 2007. The deficiencies listed in the letter are comments provided by the Agency's Chemistry reviewer(s). In addition to responding to the list of deficiencies, DPSI was asked to note and acknowledge the following comments:

1. Please provide all available drug product room temperature stability data.
2. The Labeling and bioequivalence information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you separately.

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DEC 20 2007

OGD

Gary J. Buehler
Page 2

3. All facilities referenced in your ANDA should be in compliance with CGMP at the time of approval.

DPSI has taken note of these comments and duly acknowledges, by submission of this cover letter, the comments in the Agency's 5 November 2007 letter.

DPSI respectfully requests that the Office of Generic Drugs review our response to the deficiencies listed in the 5 November 2007 letter according to current OGD policies and procedures. We look forward to your response.

Please note that, as requested, the DPSI response to the list of deficiencies will be submitted in electronic PDF format, with a signed cover letter and 356h form.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 x588 or by e-mail at: ajacker@dowpharmsci.com.

Sincerely,



AJ Acker, RAC
Senior Manager, Regulatory Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

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19 December 2007

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DEC 21 2007

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Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/A F

*No labeling
in this submission
Allyson 1/28/08*

Subject: Abbreviated New Drug Application No. 065443
SN0005: MINOR AMENDMENT to SN0004 for ANDA No. 065443
Product: Clindamycin-Benzoyl Peroxide Gel
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc.(DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 5 November 2007 a facsimile message was received from Rashmikant M. Patel, PhD, Director, Division of Chemistry I of the Office of Generic Drugs, informing DPSI that ANDA No. 065443 was deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in a 4-page attachment appended to Dr. Patel's letter.

Under the provisions of 21 CFR §314.120, DPSI submitted a MINOR AMENDMENT to ANDA No.065443 on 18 December 2007 to address the MINOR deficiencies noted in Dr. Patel's letter of 5 November 2007. DPSI has corrected Section 3.2.P.8.1.8.6 of submission number 0004 dated 18 December 2007. DPSI is respectfully providing the correct Section 3.2.P.8.1.8.6 in submission number 0005.

DPSI respectfully requests that the Office of Generic Drugs review this MINOR AMENDMENT in addition to SN0004, our response to the deficiencies listed in the 5 November 2007 letter according to current OGD policies and procedures. We look forward to your response.

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Gary J. Buehler
Page 2

Please note that the DPSI response is being submitted in electronic PDF format, with a signed cover letter and 356h form.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 x588 or by e-mail at: ajacker@dowpharmsci.com.

Sincerely,

A handwritten signature in black ink, appearing to read 'AJ Acker', with a stylized flourish at the end.

AJ Acker, RAC
Senior Manager, Regulatory Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

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Via Federal Express

20 December 2007

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

N/AF

Subject: Abbreviated New Drug Application No. 065443
SN0006: Response to FDA Labeling Comments
Product: Clindamycin-Benzoyl Peroxide Gel
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. DPSI received a facsimile from the Agency on 12 October 2007 which included a list of labeling deficiencies. The letter granted DPSI permission to correct the listed deficiencies by amending the application. To that end, DPSI respectfully submits Amendment 0006 to ANDA 065443. In addition to the labeling deficiencies, DPSI would like to inform OGD that Mylan Pharmaceuticals Inc. will be the marketing partner for Clindamycin/Benzoyl Peroxide Gel, 1%/5%.

Please refer to Table 1.2.1 DPSI Response to FDA Facsimile Dated 12 Oct 2007 included in this letter for a detailed response to each of the aforementioned deficiencies as described in the above-referenced Agency fax.

This submission also includes:

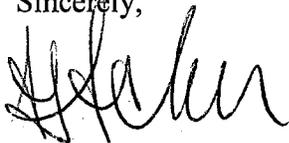
- Final Printed Labeling in SPL format
- Final Printed Labeling in Microsoft Word
- Carton Container Label Text
- 1.14.1.2 Annotated Draft Labeling Text:
 - A side-by-side comparison of proposed container labeling against reference listed drug labeling with all differences annotated and explained, in accordance with 21 CFR 314.94(a)(8)(iv). Please refer to Table 1.14.1.2.1 Carton Labels Side-by-Side-Comparison, Table 1.14.1.2.2 Jar Container Labels Side-by-Side Comparison, and Table 1.14.1.2.3 Bottle Container Labels Side-by-Side-Comparison
- 1.14.3.1.1 Statement of Proposed Labeling including:
 - A side-by-side comparison of proposed labeling against reference listed drug labeling with all differences annotated and explained, in accordance with 21 CFR 314.94(a)(8)(iv). Please refer to Table 1.14.3.1.1.1 Package Insert Side-by-Side Comparison
- Artwork for Clindamycin Phosphate Solution Container Label, Benzoyl Peroxide [Final Product] Jar Label, and Carton Container Label
- FDA Form 356h

As requested by the Agency in their 12 October 2007 comments, DPSI is submitting Final Printed Labeling.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 x588 or by e-mail at: ajacker@dowpharmasci.com.

Sincerely,



AJ Acker, RAC
Senior Manager, Regulatory Affairs

Enclosures

Telephone Fax

ANDA 65-443

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8987



TO: Dow Pharmaceutical Sciences, Inc.

TEL: 707-793-2600 EXT. 588

ATTN: A.J. ACKER

FAX: 707-793-0145

FROM: ADOLPH VEZZA

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Clindamycin/Benzoyl Peroxide Gel, 1%/5%.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **65-443** Date of Submission: **December 20, 2007**

Applicant's Name: **Dow Pharmaceutical Sciences, Inc.**

Established Name: **Clindamycin/Benzoyl Peroxide Gel, 1%/5%**

Labeling Deficiencies:

1. CARTON
 - a. Improve the legibility of "Rx only".
 - b. It appears that the established name is presented in two different fonts. Please revise accordingly.
 - c. Right panel (package right side) – The font size does not look consistent. Please revise accordingly.
 - d. Back panel (package back) – See comment under (c) above.

2. INSERT

We remind you that the package insert labeling must be submitted in final print as it will appear in the marketplace.

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA".

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Chan Park
1/25/2008 03:04:46 PM
Chan Park for Wm Peter Rickman



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

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*Labeling review
drafted 3/11/08
A. Vazza*

Via Federal Express

27 February 2008

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

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FEB 29 2008

CDER CDR

Subject: **Abbreviated New Drug Application No. 065443**
SN0007: Response to FDA Labeling Comments
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin/Benzoyl Peroxide Gel, 1%/5% was submitted to the Agency on 07 February 2007. On 25 January 2008 DPSI received a facsimile from the Agency which included both a list of labeling deficiencies and a request for a final package insert. In order to address these items, DPSI respectfully submits Amendment 0007 to ANDA 065443.

Please refer to Table 1.2.1 DPSI Response to FDA Facsimile Dated 25 January 2008 included in this letter for a response to each of the above-mentioned deficiencies.

In addition, this submission includes updated container labels. The changes are listed below.

10g Clindamycin Phosphate Solution Container Label

A change was made to the label size in order to accommodate the automated labeling equipment. This resulted in the following:

- Vertical dimension was reduced slightly
- The Rx was moved down
- The Mylan logo was removed
- The online verification code "XG" was added (it is in the smallest font allowed by the automated labeling equipment)

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MAR 03 2008

OGD

50g Clindamycin/Benzoyl Peroxide Gel, 1%/5% Container Label

- Consistent with the changes suggested by the Agency for the carton, "Rx only" was changed to be more legible.
- The product code 033819 was added to the left of the bar code
- The number 8688 was removed from underneath the bar code

In addition to the hardcopy version of the final carton container label, this submission includes hardcopy versions of the final 10g Clindamycin Phosphate Solution Container Label and the final 50g Clindamycin/Benzoyl Peroxide Gel, 1%/5% Container Label.

This submission also includes FDA Form 356h.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at: ajacker@dowpharmasci.com.

Sincerely,



AJ Acker, RAC
Senior Manager, Regulatory Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

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JUN 23 2008

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Via Federal Express

20 June 2008

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

ME

Re: Abbreviated New Drug Application No. 065443
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)
Submission: 0008 - Response to FDA Request for CMC Information — "Telephone Amendment"

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 12 June 2008, DPSI received a facsimile from the Agency which requested that DPSI respond to two MINOR deficiencies as well as acknowledge the Agency's comments regarding specifications for (b) (4) and commit to (b) (4)

DPSI was instructed to respond to the above-mentioned items with a "Telephone Amendment" within ten working days. To address these items, and in lieu of scheduling a teleconference with ODG, DPSI respectfully submits Amendment 0008 to ANDA 065443 concurrent with providing a facsimile copy of the response to the Project Manger, Rosalyn Adigun.

DPSI's response to the Agency's request can be found in the following document:

DPSI Response to FDA Telephone Conference Fax Received June 12, 2008.

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JUN 24 2008

ODG

Gary J. Buehler
Page 2

This submission also includes:

- Cover Letter
- Form FDA 356h

This submission is in eCTD format. Hard copies of the cover letter and form FDA 356h are included with this submission.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at: ajacker@dowpharmasci.com.

Sincerely,



AJ Acker, RAC
Senior Manager, Regulatory Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

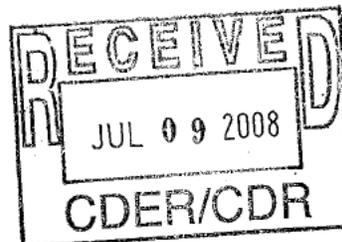


Via Federal Express

08 July 2008

ORIG AMENDMENT

N/A/M



Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Re: Abbreviated New Drug Application No. 065443
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)
Submission: 0009 - Response to FDA Request for CMC Information

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 02 July 2008, DPSI received a telephone call from James Fan, PhD, Chemistry Team Leader, Office of Generic Drugs, requesting the following information be submitted to the Agency as soon as possible:

- Stability specs for [redacted] ^{(b) (4)}. It was also requested that room temperature data for these formulations be provided, if possible.
- Provide Certificates of Analyses, or statement(s) from the vendor(s) indicating that the excipients comply with USP <467> or ICHQ3C.
- Provide the release specs for the Drug Product with regard to USP <467>.

DPSI's response to the Agency's request can be found in the following document:

DPSI response to 02 July 2008 FDA Telephone Request for CMC Information

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JUL 10 2008

Gary J. Buehler
Page 2

This submission also includes:

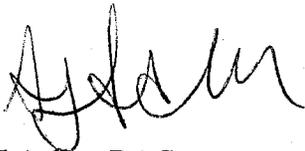
- Cover Letter
- Form FDA 356h

This submission is in eCTD format. Hard copies of the cover letter and form FDA 356h are included with this submission.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at: ajacker@dowpharmasci.com.

Sincerely,



AJ Acker, RAC
Senior Manager, Regulatory Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

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Via Federal Express

28 July 2008

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CDER CDR

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Re: Abbreviated New Drug Application No. 065443
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)
Submission: 0010 – Change Contact Agent
(Change Notification Re Official Correspondent for the Application)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel for the treatment of acne vulgaris, which was submitted to the Agency on 07 February 2007.

Please note that the Official Correspondent for ANDA No. 065443 has changed. Please refer to:

Section 1.3.1.2 Change Contact Agent

This submission is presented entirely electronically on one CD. In addition, hard copy versions and original signatures are provided for in the following documents:

- Cover letter
- Form FDA 356h

RECEIVED

JUL 31 2008

OGD

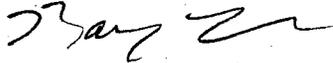
Susan J. Walker, MD

Page 2

The material and data contained in this amendment and cover letter are considered to be proprietary and confidential. The legal protection of such confidential material is claimed under the applicable provisions of 18 USC, §1905 and/or 21 CFR 331j.

If you have any questions regarding the content of the submission, please contact me at 707-793-2600 or by e-mail at bcalvarese@dowpharmsci.com.

Sincerely,

A handwritten signature in black ink, appearing to read "Barry M. Calvarese". The signature is fluid and cursive, with a prominent initial "B" and a long, sweeping underline.

Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs

RECORD OF TELEPHONE CONVERSATION

Office of Generic Drugs

Division of Chemistry 1

Team 3

FROM: Mahnaz Farahani

DATE: August 18, 2008

ANDA: 65443

NAME/TITLE OF INDIVIDUAL(S) from FDA: Mahnaz Farahani, chemist

FIRM: Dow Pharmaceutical Sciences, Inc.

PRODUCT NAME: Clindamycin 1% and Benzoyl Peroxide 5%

TEL #: (707) 793-2600

Notes of Conversation:

Deficiency:

The firm should submit the revised DP release specification to include (b) (4)
(b) (4) test with specification as (b) (4).

SIGNATURE OF OGD REPRESENTATIVES:

Mahnaz Farahani, Ph.D., chemist

Location of Electronic Copy:

V:\Division I\Team3\T-CON\65443.TCON

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

/s/

Mahnaz Farahani
11/7/2008 10:34:04 AM
CHEMIST



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

ORIG AMENDMENT

U/am

Via Federal Express

19 August 2008

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AUG 20 2008

CDER CDR

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Re: Abbreviated New Drug Application No. 065443

Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%

Indication: Acne Vulgaris

Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)

Submission: 0011 - Response to FDA Request for CMC
Information – “Telephone Amendment”

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 18 August 2008, DPSI received a telephone call from Mahnaz Farahani, PhD, Chemistry Reviewer, Office of Generic Drugs, requesting the following information be submitted to the Agency as soon as possible:

- Add the (b) (4) test (b) (4) and specifications to the drug product table.

A facsimile response was sent to Mahnaz Farahani, PhD, Chemistry Reviewer, on 18 August 2008.

DPSI’s response to the Agency’s request can be found in the following document:

3.2.P.5.1 Specifications

This submission also includes:

- Cover Letter
- Form FDA 356h

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AUG 21 2008

OGD

Gary J. Buehler
Page 2

This submission is in eCTD format. Hard copies of the cover letter and form FDA 356h are included with this submission.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at: bcalvarese@dowpharmsci.com

Sincerely,



Barry M. Calvarese, MS
Vice President, Regulatory and
Clinical Affairs

Enclosures



Dow Pharmaceutical Sciences

The D in Topicals R&D

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Via Federal Express

06 November 2008

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMEN

N/A m

Re: Abbreviated New Drug Application No. 065443
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)
Submission: 0012 - Response to FDA Request for CMC
Information – “Telephone Amendment”

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 07 October 2008, DPSI received a telephone call from Chemistry Reviewers, Mahnaz Farahani, PhD, and James Fan, PhD, Office of Generic Drugs, requesting additional CMC information be submitted to the Agency as soon as possible.

A facsimile response was sent to the attention of Mahnaz Farahani, PhD, Chemistry Reviewer, on 05 November 2008 (fax number (240) 276-8504).

DPSI's response to the Agency's request can be found in the following document:

DPSI Response to FDA Request for CMC Information Received October 7, 2008

This submission also includes:

- Cover Letter
- Form FDA 356h

This submission is in eCTD format. Hard copies of the cover letter and form FDA 356h are included with this submission.

NOV 12 2008

Gary J. Buehler
Page 2

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j. If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at: bcalvarese@dowpharmsci.com

Sincerely,

A handwritten signature in black ink, appearing to read "Barry" followed by a stylized flourish.

Barry M. Calvarese, MS
Vice President, Regulatory and
Clinical Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

Via Federal Express

11 December 2008

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

REC

DEC 15 2008

CLR

ORIG AMENDMENT

N-000-AA

Re: Abbreviated New Drug Application No. 065443
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)
Submission: 0013 - Response to FDA Request for CMC Information:
Additional Stability Data – “Gratuitous Amendment”

Dear Mr. Buehler:

Abbreviated New Drug Application (ANDA) No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 07 October 2008, DPSI received a telephone call from Chemistry Reviewers, Mahnaz Farahani, PhD, and James Fan, PhD, Office of Generic Drugs, requesting additional CMC information, included stability data for the Clindamycin Phosphate Solution stored in the horizontal or inverted position.

A facsimile response was sent to the attention of Mahnaz Farahani, PhD, Chemistry Reviewer, as a Telephone Amendment on 06 November 2008 (fax number (240) 276-8504). The eCTD was also updated to include this Amendment on 06 November 2008 (SN0012). In response to the Agency's request for stability data in the horizontal or inverted storage container storage position for Clindamycin Phosphate Solution, (b) (4), DPSI provided a commitment and draft stability protocol for Clindamycin Phosphate Solution, (b) (4) in bottles stored in the horizontal orientation, under accelerated, intermediate and long term storage conditions. These studies were initiated on 12 November 2008. As stated in the Telephone Amendment, stability data for the bottle in the horizontal orientation will be provided to the Office of Generic Drugs as it becomes available. Please refer to “2.0 FDA COMMENT 2: STABILITY DATA” and “2.1 DPSI RESPONSE 2: STABILITY DATA” in SN0012.

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DEC 16 2008

OGD

Gary J. Buehler
Page 2

The purpose of this Gratuitous Amendment (SN0013) is to provide one month stability data for a research and development study for bottles of Clindamycin Phosphate Solution, (b) (4) in the horizontal orientation at 30 °C/65%RH and 40 °C/75%RH for two lots. The study was initiated on 30 October 2008. This amendment provides stability data to evaluate potential for extractables from the bottle cap/liner and/or other interactions related to Clindamycin Phosphate Solution, (b) (4)

The stability data from the one-month study demonstrates that horizontal orientation is similar to vertical orientation, showing comparable levels of clindamycin phosphate, total clindamycin content, and impurities/degradation products. For the horizontal samples, it is important to note that no new chromatographic peaks were observed in the HPLC chromatograms, as compared with the analytical results from the vertical orientation stability study.

The Gratuitous Amendment can be found in the following document:

Supplementary Information for DPSI Response to FDA Request for CMC Information: Stability Data – Received October 7, 2008

As stated in SN0012, the Division of Dermatological and Dental Products, Office of Drug Evaluation III approved the same Clindamycin Phosphate Solution, (b) (4) in the identical container and on the basis of stability data for bottles stored in the vertical orientation only, as part of FDA approval of NDA 050819 for Acanya™ (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%) Gel (approved 23 October 2008).

This submission also includes:

- Cover Letter
- Form FDA 356h

This submission is in eCTD format. Hard copies of the cover letter and form FDA 356h are included with this submission.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j. If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at bcalvarese@dowpharmsci.com.

Sincerely,



Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

Via Federal Express

12 January 2009

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

N-AA

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JAN 14 2009

CDR

RECEIVED

JAN 15 2009

OGD

Re: Abbreviated New Drug Application No. 065443
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)
Submission: 0014 - Response to FDA Request for CMC Information:
Additional Stability Data – "Gratuitous Amendment"

Dear Mr. Buehler:

Abbreviated New Drug Application (ANDA) No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 07 October 2008, DPSI received a telephone call from Chemistry Reviewers, Mahnaz Farahani, PhD, and James Fan, PhD, Office of Generic Drugs, requesting additional CMC information, included stability data for the Clindamycin Phosphate Solution stored in the horizontal or inverted position.

A facsimile response was sent to the attention of Mahnaz Farahani, PhD, Chemistry Reviewer, as a Telephone Amendment on 06 November 2008 (fax number (240) 276-8504). The eCTD was also updated to include this Amendment on 06 November 2008 (SN0012). In response to the Agency's request for stability data in the horizontal or inverted storage container storage position for Clindamycin Phosphate Solution, (b) (4), DPSI provided a commitment and draft stability protocol for Clindamycin Phosphate Solution, (b) (4), in bottles stored in the horizontal orientation, under accelerated, intermediate and long term storage conditions. These studies were initiated on 12 November 2008.

As stated in the Telephone Amendment, stability data for the bottle in the horizontal orientation will be provided to the Office of Generic Drugs as it becomes available. Please refer to "2.0 FDA COMMENT 2: STABILITY DATA" and "2.1 DPSI RESPONSE 2: STABILITY DATA" in SN0012.

The purpose of this Gratuitous Amendment (SN0014) is to provide horizontal stability information from DPSI for Protocol 635-G (Lot 1396) at the 1 month interval, 40 °C/75%RH. Protocol 635-G (Lot 1396) was submitted in the 06 November 2008 Telephone Amendment (SN0012); please refer to "2.1.2 Stability Study Commitment and Draft Protocol" in Amendment SN0012.

The horizontal orientation data at the 1 month pull point compares well with vertical orientation data for total degradation products and the degradation profile. No new chromatographic peaks were observed.

The Gratuitous Amendment can be found in the following document:

SECOND SET OF SUPPLEMENTARY INFORMATION FOR DPSI RESPONSE TO
FDA REQUEST FOR CMC INFORMATION - STABILITY DATA - RECEIVED
OCTOBER 7, 2008

This submission also includes:

- Cover Letter
- Form FDA 356h

This submission is in eCTD format. Hard copies of the cover letter and form FDA 356h are included with this submission.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j. If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at bcalvarese@dowpharmsci.com.

Sincerely,



Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

Via Federal Express

29 January 2009

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

RECEIVED

~~DEC 30 2008~~
JAN 30 2009
CDER GDR

N-000-AA

Re: Abbreviated New Drug Application No. 065443
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)
Submission: 0015 - Response to FDA Request for CMC Information:
Additional Stability Data – “Gratuitous Amendment”

Dear Mr. Buehler:

Abbreviated New Drug Application (ANDA) No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 07 October 2008, DPSI received a telephone call from Chemistry Reviewers, Mahnaz Farahani, PhD, and James Fan, PhD, Office of Generic Drugs, requesting additional CMC information, included stability data for the Clindamycin Phosphate Solution stored in the horizontal or inverted position.

A facsimile response was sent to the attention of Mahnaz Farahani, PhD, Chemistry Reviewer, as a Telephone Amendment on 06 November 2008 (fax number (240) 276-8504). The eCTD was also updated to include this Amendment on 06 November 2008 (SN0012). In response to the Agency’s request for stability data in the horizontal or inverted storage container storage position for Clindamycin Phosphate Solution, (b) (4), DPSI provided a commitment and draft stability protocol for Clindamycin Phosphate Solution, (b) (4) in bottles stored in the horizontal orientation, under accelerated, intermediate and long term storage conditions. These studies were initiated on 12 November 2008.

As stated in the Telephone Amendment, stability data for the bottle in the horizontal orientation will be provided to the Office of Generic Drugs as it becomes available. Please refer to “2.0 FDA COMMENT 2: STABILITY DATA” and “2.1 DPSI RESPONSE 2: STABILITY DATA” in SN0012.

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The purpose of this Gratuitous Amendment (SN0015) is to provide horizontal stability information from DPSI for Protocol 635-G (Lot 1396) at the 2 month interval, including 30 °C/65%RH and 40 °C/75%RH. Protocol 635-G (Lot 1396) was submitted in the 06 November 2008 Telephone Amendment (SN0012); please refer to "2.1.2 Stability Study Commitment and Draft Protocol" in Amendment SN0012.

The horizontal orientation data at the 2 month pull point compares well with vertical orientation data for total degradation products and the degradation profile, with no new chromatographic peaks observed.

The Gratuitous Amendment can be found in the following document:

THIRD SET OF SUPPLEMENTARY INFORMATION FOR DPSI RESPONSE TO
FDA REQUEST FOR CMC INFORMATION - STABILITY DATA - RECEIVED
OCTOBER 7, 2008

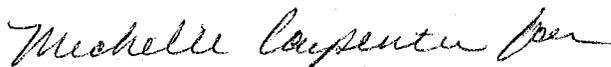
This submission also includes:

- Cover Letter
- Form FDA 356h

This submission is in eCTD format. Hard copies of the cover letter and form FDA 356h are included with this submission.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j. If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at bcalvarese@dowpharmsci.com.

Sincerely,



Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

Via Federal Express

11 February 2009

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

RECEIVED

FEB 12 2009

CDER CDR

N-000-AA

RECEIVED

FEB 13 2009

Re: Abbreviated New Drug Application No. 065443
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)
Submission: 0016 – Response to FDA Request for Information in Support
of Propylene Glycol in ^{(b) (4)} – “Gratuitous Amendment”

OGD

Dear Mr. Buehler:

Abbreviated New Drug Application (ANDA) No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007 and has been under OGD review since that time.

In January 2009, Lachman Consultant Services, Inc., a consultant for DPSI, called OGD to request status of the Agency’s review of the bioequivalence study submitted in the NDA in February 2007. In response, Lachman’s representative, Joan Janulis, received a voicemail message from Debbie Catterson of OGD’s Medical Affairs Division, stating that the OGD has a specific safety concern due to the fact that DPSI’s formulation contained a “significantly greater” concentration of propylene glycol than the Reference Listed Drug (RLD), BenzaClin®. Ms. Catterson further explained that because propylene glycol may act as a penetration enhancer, the relatively high concentration of this ingredient in our formulation (as compared to BenzaClin) may lead to increased blood level concentrations of clindamycin, which can cause *c. difficile* diarrhea.

Ms. Catterson encouraged the voluntary submission of any available information that may assist OGD in resolving this concern, as this is the rate-limiting factor in OGD’s completion of the Bioequivalence review of our pending application.

To that end, DPSI submits this Amendment, providing information on the absorption of clindamycin from topical preparations containing propylene glycol as a Gratuitous Amendment in support of the concentration of propylene glycol in (b) (4)

The information being submitted is provided in:

2.7.2 Summary of Clinical Pharmacology Studies

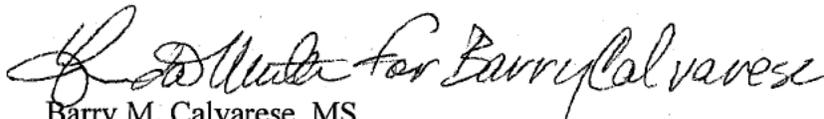
This submission also includes:

- Cover Letter
- Form FDA 356h

This submission is in eCTD format. Hard copies of the cover letter and form FDA 356h are included with this submission.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j. If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at bcalvarese@dowpharmsci.com.

Sincerely,



Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

Via Federal Express

18 February 2009

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

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FEB 19 2009

CDR

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FEB 20 2009

OGD

Re: Abbreviated New Drug Application No. 065443
Product: Clindamycin/Benzoyl Peroxide Gel, 1%/5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)
Submission: 0017 - Response to FDA Request for CMC Information:
Additional Stability Data – “Gratuitous Amendment”

Dear Mr. Buehler:

Abbreviated New Drug Application (ANDA) No. 065443 for Clindamycin-Benzoyl Peroxide Gel was submitted to the Agency on 07 February 2007. On 07 October 2008, DPSI received a telephone call from Chemistry Reviewers, Mahnaz Farahani, PhD, and James Fan, PhD, Office of Generic Drugs, requesting additional CMC information, included stability data for the Clindamycin Phosphate Solution stored in the horizontal or inverted position. Three months of stability data for the horizontal or inverted storage position was to be submitted to the ANDA in one or more Gratuitous Amendment(s).

Gratuitous Amendments containing one month and 2 month comparative accelerated stability data for the horizontal and vertical storage positions were submitted on January 12, 2009 and January 29, 2009. The purpose of this Gratuitous Amendment (SN0017) is to provide long-term, intermediate and accelerated horizontal stability information for the three month test station. The stability protocols included in this submission are 488-G (Lot 166WX3) and 635-G (Lot 1396).

The horizontal orientation data at the 3 month test station compares well with vertical orientation data for total degradation products and the degradation profile, with no new chromatographic peaks observed. DPSI expects that the data contained in this Gratuitous Amendment will satisfy the Agency's requirement for submission of stability data in the horizontal or inverted storage position, and will enable the advancement of ANDA

approval. We submit additional stability data from the ongoing, long term stability study for the horizontal storage position in our Annual Report following ANDA approval.

The Gratuitous Amendment can be found in the following document:

FOURTH SET OF SUPPLEMENTARY INFORMATION FOR DPSI RESPONSE TO
FDA REQUEST FOR CMC INFORMATION - STABILITY DATA - RECEIVED
OCTOBER 7, 2008

This submission also includes:

- Cover Letter
- Form FDA 356h

This submission is in eCTD format. Hard copies of the cover letter and form FDA 356h are included with this submission.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j. If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at bcalvarese@dowpharmsci.com.

Sincerely,



Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs

Enclosures

Telephone Fax

ANDA 65-443

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8987



TO: Dow Pharmaceutical Sciences, Inc.

TEL: 707-793-2600 EXT. 588

ATTN: A.J. ACKER

FAX: 707-793-0145

FROM: ADOLPH VEZZA

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Clindamycin/Benzoyl Peroxide Gel, 1%/5%.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **65-443**

Date of Submission: **February 27, 2008**

Applicant's Name: **Dow Pharmaceutical Sciences, Inc.**

Established Name: **Clindamycin/Benzoyl Peroxide Gel, 1%/5%**

Labeling Deficiencies:

GENERAL COMMENT

Upon further consideration, the established name for this drug product should be as shown below:

“Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%”

Please revise your labels and labeling accordingly.

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA".

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lillie Golson
5/6/2009 01:26:02 PM
Lillie Golson for Wm. Peter Rickman

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-443

APPLICANT: Dow Pharmaceutical Sciences, Inc.

DRUG PRODUCT: Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 65-443, using the primary endpoint of mean percent reduction in inflammatory and non-inflammatory lesion counts from baseline to Week 10, are adequate to demonstrate bioequivalence of Dow Pharmaceutical Sciences, Inc.'s Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% with the reference listed drug, Benzaclin[®].

You have submitted sufficient data to ensure that your formulation, containing (b)₍₄₎% propylene glycol, will not increase the risk of systemic clindamycin exposure and associated adverse events, compared to the RLD.

A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow verification of the treatment identity for each patient.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are patient to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Dale Conner

5/18/2009 01:19:08 PM



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

ORIG AMENDMENT

NIAF

Via Federal Express

1 July 2009

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Subject: **Abbreviated New Drug Application No. 065443**
SN0018: Labeling Telephone Amendment – Update in Accordance with RLD Labeling
Product: Clindamycin and Benzoyl Peroxide Gel, 1%/5%
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin and Benzoyl Peroxide Gel, 1%/5% was submitted to the Agency on 07 February 2007. On 06 May 2009 DPSI received a facsimile from the Agency which included a general comment about labeling deficiencies and a request that labels and labeling be revised accordingly. DPSI also participated in a phone conversation with Mr. Adolph Vezza on 08 May 2009 who requested that an asterisk be added to the established name to indicate, where appropriate, that the clindamycin percentage refers to the clindamycin as phosphate. In a follow-up conversation on 11 June 2009, Mr Vezza specified that the established name for the Clindamycin Phosphate Solution Label could be modified to indicate that the clindamycin was in the base form rather than use an asterisk. Further contact from Mr. Vezza on 23 June 2009 indicated that the Reference Listed Drug, BenzaClin, updated their product labeling and requested that DPSI update their product package insert accordingly. In order to address these items, DPSI respectfully submits Amendment 0018 to ANDA 065443.

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JUL 06 2009

OGD

Table 1.2.1 DPSI Response to FDA

| No. | Deficiency Items and Follow-on FDA Requests | Response | Location |
|-----|--|---|--|
| 1. | <p>GENERAL COMMENT: Upon further consideration, the established name for this drug product should be as shown below:</p> <p>“Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%:</p> <p>Please revise your labels and labeling accordingly</p> | <p>This submission includes the carton and container labels as they will appear in the marketplace in electronic form.</p> <p>An electronic copy of the final print of the package insert as it will appear in the marketplace has been included.</p> | <p>Updated Final 10g Clindamycin Phosphate Solution Container Label</p> <p>Updated Final 50g Clindamycin and Benzoyl Peroxide Gel, 1%/5% Container Label</p> <p>Updated Final Carton Label</p> |
| 2. | <p>Add asterisk to established name, when appropriate, to indicate clindamycin as phosphate:</p> <p>“Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%*/5%</p> | | <p>Final Clindamycin and Benzoyl Peroxide Gel, 1%/5% Package Insert</p> |
| 3. | <p>Refer to clindamycin base on the Clindamycin Phosphate Solution container label:</p> <p>Clindamycin Phosphate and Benzoyl Peroxide Gel, 1% (Base)/5%</p> | | |
| 4. | <p>Update Package Insert to match recent changes to the Precautions and Adverse Reactions sections of the BenzaClin (RLD) package insert</p> | | |

As requested, this submission includes updated container labels in final print, as well as a side-by-side comparison of the proposed labeling with the reference listed drug labeling with all the differences annotated and explained. The container label changes are listed below.

10g Clindamycin Phosphate Solution Container Label

The established name for the drug product was changed to “Clindamycin Phosphate and Benzoyl Peroxide Gel, 1% (Base)/5%.”

50g Clindamycin and Benzoyl Peroxide Gel, 1%/5% Container Label

The established name for the drug product was changed to “Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%*/5%” and an asterisk was added to “*clindamycin as phosphate.”

In addition to the electronic versions of the final 10g Clindamycin Phosphate Solution Container Label and the final 50g Clindamycin and Benzoyl Peroxide Gel, 1%/5%

Container Label, this submission includes electronic versions of the final carton container label and the package insert.

As proposed and agreed upon with Mr Vezza on 08 May 2009, DPSI will implement the new labeling change when the next commercial package printing is initiated. Mr Vezza indicated that it would be acceptable for DPSI to utilize their current inventory with the original established name provided by the Agency on 12 October 2007.

In accordance with 21 CFR 314.94(a)(8)(iv) and to facilitate review of this submission, a side-by-side comparison of proposed labeling with the reference listed drug labeling, with all differences annotated and explained, as requested by the Agency, is included in the submission.

Hard copies of the following documents are included:

- Cover Letter
- Form FDA 356h

This submission is in eCTD format and is being submitted entirely on one (1) CD-ROM, with a total file size of approximately 5 MB. The submission files passed inspection for viruses using Trend MICRO OfficeScan software, version 7.3, engine version 8.950.1052.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at: bcalvarese@dowpharmasci.com.

Sincerely,



Barry M. Calvarese, MS
Vice President Regulatory and Clinical Affairs

Enclosures

T-conference

Participant:

Radhika Rajagopalan, Ph.D./FDA

With

AJ Acker\Dow Pharmaceutical Sciences Inc.

707-793-2600

ANDA: 65-443

Clindamycin Phosphate, Benzoyl peroxide gel, 1% (base)/5%

Dow PSI

7/15/09

1. Requested Dow to reconsider expiration dating on the concentrate from (b) (4) months to 18 months based on the fact that we do not have admixture data on aged product; OGD approves tentative expiration date only to 24 months.
2. As requested in their ANDA, we can not grant (b) (4) months (concentrate) + 90 days = (b) (4) months for drug product; briefly touched upon Dow's experience with RLD and NDA products, and that they may be able to extend concentrate expiration to 21 months after conducting stability studies on actual aged (to 21 months) samples after admixing.
3. Requested Dow re-consider total impurities down from the proposed (b) (4) to actual number they see on the admixture product.
4. Dow to resubmit release and stability specifications based on revised total impurities and decrease expiration dating of the concentrates. They will submit this information as a T-deficiency and fax information to R. Adigun's attention.

Radhika Rajagopalan

7/15/09

V:\Division I\Team 3\FIRMSAM\DOW\LTRS&REV\65443Tcon.71509.doc

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

/s/

Radhika Rajagopalan
7/15/2009 04:07:15 PM
CHEMIST



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

ORIG AMENDMENT

U/AM

Via Federal Express

22 July 2009

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Subject: **Abbreviated New Drug Application No. 065443**
SN0019: Telephone Amendment to Pending Application
Product: Clindamycin and Benzoyl Peroxide Gel, 1%/5%
Dosage Strength: Clindamycin 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin and Benzoyl Peroxide Gel, 1%/5% was submitted to the Agency on 07 February 2007. On July 15, 2009, DPSI received a telephone call from Ms. Radhika Rajagopalan of the Office of Generic Drugs, who stated that the telephone call served as a telephone deficiency notice and that DPSI needed to address the following two deficiencies:

1. The expiration date on the product should be reduced from ^{(b) (4)} months for the components + 3 months with the admixture to 18 months for the components + 3 months with the admixture.
2. The Total Impurities specification for clindamycin phosphate should be reduced from ^{(b) (4)} % to a lower level based on the 18 + 3 month data.

DPSI's response to the Agency's request can be found in the following document:

DPSI Response to FDA Request for CMC Information Received July 15, 2009

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JUL 23 2009

OGD

Hard copies of the following documents are included:

- Cover Letter
- Form FDA 356h

This submission is in eCTD format and is being submitted entirely on one (1) CD-ROM, with a total file size less than 5 MB. The submission files passed inspection for viruses using Trend MICRO OfficeScan software, version 7.3, engine version 8.950.1052.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at: bcalvarese@dowpharmasci.com.

Sincerely,

A handwritten signature in black ink, appearing to read "Barry M. Calvarese", with a stylized flourish at the end.

Barry M. Calvarese, MS
Vice President Regulatory and Clinical Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

Via Federal Express

24 July 2009

Labeling review done 8/6/09 Allza

SD-26 orig-1

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

RECEIVED

JUL 27 2009

CDR

Subject: **Abbreviated New Drug Application No. 065443**
SN0020: Telephone Amendment to Pending Application
Product: Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%
Dosage Strength: Clindamycin Phosphate 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin and Benzoyl Peroxide Gel, 1%/5% was submitted to the Agency on 07 February 2007. On 06 May 2009 DPSI received a facsimile from the Agency which included a general comment about labeling deficiencies and a request that labels and labeling be revised accordingly.

In order to address these labeling items, SN0018 was submitted to ANDA 065443 on 1 July 2009. However, subsequent to that submission, Mr. Adolph Vezza telephoned DPSI and informed the Sponsor that there were some errors in the labeling submitted in SN0018 and that DPSI should re-submit the labeling with the correct information.

DPSI respectfully submits Telephone Amendment SN0020 to ANDA 065443 which contains the electronic versions of the final 10g Clindamycin Phosphate Solution Container Label and the final 50g Clindamycin and Benzoyl Peroxide Gel, 1%/5% Container Label, and electronic versions of the final carton container label and the package insert.

Hard copies of the following documents are included in this submission:

- Cover Letter
- Form FDA 356h and Attachment

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JUL 28 2009

CGD

This submission is in eCTD format and is being submitted entirely on one (1) CD-ROM, with a total file size less than 5 MB. The submission files passed inspection for viruses using Trend MICRO OfficeScan software, version 7.3, engine version 8.950.1092.

DPSI considers all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, §1905 and/or 21 USC, §331j.

If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at: bcalvarese@dowpharmsci.com.

Sincerely,

A handwritten signature in cursive script, appearing to read "Barry M. Calvarese".

Barry M. Calvarese, MS
Vice President Regulatory and Clinical Affairs

Enclosures



Dow Pharmaceutical Sciences, Inc.

The D in Topicals R&D

Since 1977

Via Federal Express

30 July 2009

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Origl SD-27

*Labeling review
done 8/6/09
Allyson*

Subject: **Abbreviated New Drug Application No. 065443**
SN0021: Telephone Amendment to Pending Application
Product: Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%
Dosage Strength: Clindamycin Phosphate 1% and Benzoyl Peroxide 5%
Indication: Acne Vulgaris
Sponsor: Dow Pharmaceutical Sciences, Inc. (DPSI)

Dear Mr. Buehler:

Abbreviated New Drug Application No. 065443 for Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% was submitted to the Agency on 07 February 2007.

On 30 July 2009 DPSI received a telephone call from Mr. Adolph Vezza, Office of Generic Drugs, requesting that the package insert component of the labeling for Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%*/5% (Topical Gel: clindamycin (1%) *as clindamycin phosphate, benzoyl peroxide (5%)) be submitted as a pdf document to the ANDA as a Telephone Amendment. DPSI respectfully submits Telephone Amendment SN0021 to ANDA 065443 which contains the electronic version of the final package insert for Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%.

Hard copies of the following documents are included in this submission:

- Cover Letter
- Form FDA 356h and Attachment

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JUL 31 2009

OGD

This submission is in eCTD format and is being submitted entirely on one (1) CD-ROM, with a total file size less than 5 MB. The submission files passed inspection for viruses using Trend MICRO OfficeScan software, version 7.3, engine version 8.950.1094.

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If you have any questions regarding the content of the submission, please contact me at (707) 793-2600 or by e-mail at: bcalvarese@dowpharmsci.com.

Sincerely,

A handwritten signature in black ink, appearing to read "Barry M. Calvarese". The signature is written in a cursive style with a large initial "B" and "C".

Barry M. Calvarese, MS
Vice President Regulatory and Clinical Affairs

Enclosures

OGD APPROVAL ROUTING SUMMARY

ANDA # 65-443 Applicant DOW Pharmaceuticals Sciences
Drug Clindamycin/Benzoyl Peroxide Strength(s) 1%/5%

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. **Martin Shimer**
Chief, Reg. Support Branch
Date 2 OCT 2008 Date _____
Initials MHS Initials _____
Contains GDEA certification: Yes No Determ. of Involvement? Yes No
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes No Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted
Notify patent holder/NDA holder Yes No Written request issued
Was applicant sued w/in 45 days: Yes No Study Submitted
Has case been settled: Yes No Date settled: _____
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes No
Type of Letter: Full Approval.
Comments: ANDA submitted on 2/9/2007, BOS=BenzaClin Topical Gel NDA 50756. RTR issued 3/16/2007. Sponsor responded to RTR on 3/30/2007-ANDA ack for filing on 3/30/2007 (LO dated 4/23/2007). As the RLD that served as the BOS for this ANDA is a 50,000 series AB there are no patents or exclusivities which preclude approval of this ANDA. ANDA is eligible for Full Approval.

2. **Project Manager, Rosalyn Adigun Team 3** Date October 1, 2008 Date 8/11/2009
Review Support Branch Initials R.A Initials NP
Original Rec'd date February 7, 2007 EER Status Pending Acceptable OAI
Date Acceptable for Filing November 5, 2007 Date of EER Status April 15, 2008
Patent Certification (type) N/A Date of Office Bio Review May 13, 2009
Date Patent/Exclus. expires N/A Date of Labeling Approv. Sum August 7, 2009
Citizens' Petition/Legal Case Yes No Date of Sterility Assur. App. N/A
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes No
First Generic Yes No MV Commitment Rcd. from Firm Yes No
Priority Approval Yes No Modified-release dosage form: Yes No
(If yes, prepare Draft Press Release, Email Interim Dissol. Specs in AP Ltr: Yes
it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes No
Bio Review Filed in DFS: Yes No
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted Rejected Pending
Previously reviewed and tentatively approved Date _____
Previously reviewed and CGMP def. /NA Minor issued Date _____
Comments:

3. **Labeling Endorsement**
Reviewer: Labeling Team Leader:
Date _____ Date _____
Name/Initials _____ Name/Initials _____

Comments:
See labeling approval summary dated 8/7/09. np

4. **David Read (PP IVs Only)** Pre-MMA Language included Date _____
OGD Regulatory Counsel, Post-MMA Language Included Initials _____
Comments:

5. **Div. Dir./Deputy Dir.** Date 6/3/09
Chemistry Div. I Initials PS

Comments: CMC Ok
Concentrations refer to after the components are mixed

6. **Frank Holcombe** First Generics Only Date _____
Assoc. Dir. For Chemistry Initials _____
Comments: (First generic drug review)
CMC OK'd by Frank Holcombe on 8/6/09. np for FH

7. Vacant Date _____
Deputy Dir., DLPS Initials _____

8. **Peter Rickman** Date 8/10/09
Director, DLPS Initials swpr
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: BOS=BenzaClin Topical Gel NDA 50756. ANDA ack for filing on 3/30/2007.
The RLD that served as the BOS for this ANDA is a 50,000 series AB there are no patents or exclusivities which preclude approval of this ANDA. Labeling acceptable 8/7/2009 per AP Summary; Bio acceptable (clinical endpoint study) 5/13/2009; EER acceptable 4/15/2008; ANDA is eligible for Full Approval.

OR

8. **Robert L. West** Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Press Release Acceptable
Comments:

9. **Gary Buehler** Date _____
Director, OGD Initials _____
Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue
Press Release Acceptable

10. Project Manager, SELECT PM NAME Team TEAM # Date _____
Review Support Branch Initials _____
_____ Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
11:00am Time notified of approval by phone
11:10 am Time approval letter faxed

FDA Notification:
8/11/2009 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
8/11/2009 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---------------------|------------------------|--------------|--|
| ----- ANDA 65443 | ----- ORIG 1 | ----- | ----- CLINDAMYCIN BENZOYL PEROXIDE |

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

/s/

NITIN K PATEL
08/11/2009