



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: August 13, 2008

To: Barry M. Calvarese, MS, Vice President, Regulatory and Clinical Affairs	From: Tamika White, Regulatory Project Manager
Company: Dow Pharmaceutical Sciences, Inc.	Division of Dermatology and Dental Products
Fax number: 707-793-0145	Fax number: 301-796-9895
Phone number: 707-793-2600 x601	Phone number: 301-796-2110
Subject: NDA 50-819 Information Requests	

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond as soon as possible but no later than 3:00 p.m. on August 20, 2008.

Document to be mailed: YES NO

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NDA 50-819

Please refer to your December 21, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME ~~_____~~, Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide).

b(4)

We are reviewing your submission and have the following CMC information requests.

1. The validation reports for methods STM 4-88 and 4-91 can not be located in your submission. Provide validation summaries for methods STM 4-88 and 4-91 per ICH Q2A and 2B. Validation information related to ~~_____~~ is not provided in Method STM 4-91; please provide.
2. Revise the expiration date instructions on the "Clindamycin Vial Label" from / months to 2 months (for post dispensed admixed drug product).
3. Per CFR 21 CFR 201.25, provide the bar code on all container/carton labels.
4. Include "Lot number and expiration date" on all container/carton labels.
5. Submit color mock-ups of all container/carton labels with the recommended changes.
6. All manufacturing sites should be included when the NDA is submitted. The new site identified in your submission dated July 23, 2008 is considered to be too late for consideration in this review cycle and should be submitted as a post-approval supplement.

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We request receipt of your written response no later than 3:00 p.m. on August 20, 2008.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-0310.

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/s/

Tamika White
8/13/2008 10:14:59 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 20, 2008

TO: Tamika White, Regulatory Project Manager
Brenda Vaughan, M.D., Medical Officer
Division of Dermatologic and Dental Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch 1
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 50-819

APPLICANT: Dow Pharmaceutical Sciences, Inc. **b(4)**

DRUG: _____

NME: No

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATION: Treatment of moderate to severe acne vulgaris

CONSULTATION
REQUEST DATE: April 8, 2008

DIVISION ACTION
GOAL DATE: August 22, 2008

PDUFA DATE: October 26, 2008

b(4)

I. BACKGROUND:

_____ is proposed for the treatment of acne vulgaris. _____ is a combination of clindamycin and benzoyl peroxide. The study was designed to determine the safety and efficacy of this combination of drugs as compared to the individual components and the drug vehicle.

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Dr. Mraz's site was selected for inspection because her financial disclosure form indicates a potential conflict of interest (she is an Associate Medical Director for Dow Pharmaceutical Sciences _____). Sites 40 and 72 had larger sample sizes and relatively large treatment effects.

b(6)

The protocols inspected included protocols # DPSI-06-22-2006-012 and DPSI-06-22-2006-017, both entitled "A Phase III, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 4-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of Clindabene (1/2.5) Gel, _____ Vehicle, Clindamycin (1%), and Benzoyl Peroxide (2.5%) Gels in the Treatment of Moderate to Severe Acne Vulgaris".

b(4)

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects	Inspection Date	Final Classification
Serena Mraz, M.D. Solano Clinical Research 127 Hospital Drive, #202 Vallejo, CA 94589	DPSI-06-22-2006-012: 65	30 Jun-6 Jul 08	Pending. (Interim classification is NAI)
Leonard Swinyer, M.D. Dermatology Research Center 3920 South 110 East, Suite 210 Salt Lake City, UT 84124	DPSI-06-22-2006-012: 79	23-26 Jun 08	NAI
Ronald Savin, M.D. The Savin Center, PC 134 Park Street New Haven, CT 06511	DPSI-06-22-2006-017: 47	18-27 Jun 08	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

b(4)

1. Serena Mraz, M.D.
Solano Clinical Research
127 Hospital Drive, #202
Vallejo, CA 94589

- a. **What was inspected:** Receipt and review of the endorsed inspection report is pending. Review of the preliminary report indicated that 72 subjects were screened, 67 subjects were randomized, and 54 subjects completed the study. Consent forms were reviewed for all 72 subjects. The records for 27 of the 54 subjects completing the study were reviewed, including, but not limited to, source documents, case report forms, medical records, inclusion/exclusion criteria, primary endpoint data, safety data, concomitant medications, adverse events, and drug accountability.
- b. **General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

2. Leonard Swinyer, M.D.
Dermatology Research Center
3920 South 110 East, Suite 210
Salt Lake City, UT 84124

- a. **What was inspected:** 79 subjects were enrolled in the study. The records for 34 subjects were reviewed including, but not limited to, source documents, case report forms, inclusion/exclusion criteria, concomitant medications, adverse event reporting, and drug accountability.
- b. **General observations/commentary:** Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

3. Ronald Savin, M.D.
The Savin Center, PC
134 Park Street
New Haven, CT 06511

- a. **What was inspected:** 47 subjects were enrolled in the study. Consent forms for all subjects were reviewed. Source documents and case report forms were compared for 27 subjects. Primary efficacy endpoints were verified for inflammatory and non-inflammatory lesions. Inclusion/exclusion criteria, concomitant medications, adverse event reporting, and test article accountability were also reviewed.

- b. General observations/commentary:** The protocol required that the same qualified individual assess the same subject at each visit to maintain consistency of evaluation. Review of source documents and case report forms revealed that lesion assessments for certain subjects (e.g., #s 008, 011, and 026) were done by two different evaluators at different visits. The case report forms stated that every effort should be made to use the same assessor. This discrepancy in evaluation procedures between the protocol and the CRF was noted in the letter to the investigator. The study coordinator (SC), who was not a trained and validated evaluator signed the "Evaluator Signature" line on the Tolerability Evaluation form for 12 subjects (#s 002, 006, 008, 009, 011, 021, 025, 026, 037, 041, 047, and 048). The SC's function to transcribe results was explained during the inspection and these evaluations were later countersigned by the investigator. Both observations in the letter to the investigator were noted as examples of lack of adherence to the investigational plan.
- c. Assessment of data integrity:** Data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Receipt of the endorsed inspection report for Dr. Mraz is pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR(s).

The data generated by the sites of Drs. Mraz, Swinyer, and Savin appear acceptable in support of the respective application.

{See appended electronic signature page}

Roy Blay, Ph.D.
GCP Reviewer
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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/s/

Roy Blay
8/21/2008 12:37:57 PM
CSO

Constance Lewin
8/21/2008 12:44:50 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-819

Dow Pharmaceutical Sciences, Inc.
Attention: Barry M. Calvarese, M.S.
Vice President, Regulatory & Clinical Affairs
1330 Redwood Way
Petaluma, CA 94954-7121

Dear Mr. Calvarese:

b(4)

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME _____, Gel (clindamycin phosphate 1.2%, benzoyl peroxide 2.5%).

We are in the process of reviewing your original NDA submission and have the following comments and recommendations.

1. Based on our review of the submitted information in your NDA 50-819, we have determined that you have not established a clinical bridge to an approved-listed drug. You have submitted a study report DPS 07-07-2005-001 to support a clinical bridge, however a clinical bridge cannot be established to an unapproved product / _____ (1% clindamycin, 5% benzoyl peroxide) gel (ANDA # 065443).

b(4)

You have submitted the in vitro percutaneous absorption data as an attempt to link this product to the currently unapproved ANDA product. In diseases where there is a disruption of the skin, in vitro studies are not accepted as a surrogate for in vivo bioavailability for the following reasons:

- a. The use of non-viable skin can alter the permeation properties of the skin (e.g. storage conditions).
- b. The use of normal skin instead of diseased skin, which due to the disrupted stratum corneum in diseased skin, can markedly affect drug penetration.
- c. The preparation of the skin samples usually requires the microtoming of the skin to a uniform layer, a situation that is neither physiologic nor relevant to diseased skin.
- d. In addition, there is no in vitro based clinical pharmacology class-labeling regarding topical benzoyl peroxide/clindamycin combination drug products as you have suggested.

2. If a sufficient clinical bridge is not established to an approved clindamycin/benzoyl peroxide product, additional nonclinical information would be needed to support an NDA [505(b)(2)] for the TRADENAME _____, Gel. The information needed would include an Ames test and an in vivo micronucleus assay for clindamycin phosphate. The information could be from the literature, but not referring to any marketed pharmaceutical.

b(4)

As soon as possible, please submit any additional information you may have relevant to these issues.

If you have any questions, call Tamika White, Regulatory Project Manager, at 301-796-2110.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Division Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Stanka Kukich
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