DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 50-819

Dow Pharmaceutical Sciences
Attention: Barry M. Calvarese, MS
Vice President, Regulatory & Clinical Affairs
1330 Redwood Way
Petaluma, CA 94954-2600

Dear Mr. Calvarese:

Please refer to your new drug application (NDA) dated December 21, 2007, received December 26, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for [redacted] Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide). b(4)

We also refer to your submissions dated February 7, February 11, February 19, and February 29, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 26, 2008.

During our filing review of your application, we identified the following potential review issue:

> The carcinogenicity data set you provided may require some modifications. Specific modifications to the carcinogenicity data set will be communicated to you after a thorough evaluation of the data set is complete.

We are providing the above comment to give you preliminary notice of the potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information: b(4)

A. Letters of authorization for DMFs [redacted]

B. Registration stability data table 538-G BPO [redacted], Lot 1135 40 g [redacted]

b(4)

C. Representative samples with rheograms ([redacted]) for Benzoyl peroxide [redacted] %, trade size admixture, and physician sample.

D. Supplier(s) of clindamycin phosphate drug substance for each clinical batch, and clinical study number.

b(4)

E. The age of clindamycin phosphate [redacted] and benzoyl peroxide [redacted] at time of dispensing to Phase 3 study subjects.

F. Clarification on whether Lot #1918-123B that was used in the in vitro percutaneous absorption study was ever used in a clinical trial or in the manufacturing of the stability batches.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We are reviewing the draft labeling, submitted in Physician's Labeling Rule (PLR) format, and have identified the following formatting issues:

Highlights of Prescribing Information

1. The trademark symbols in the HIGHLIGHTS OF PRESCRIBING INFORMATION should be removed because XML can not convert the symbol to Structured Product Labeling (SPL) format.

2. Major limitations of use should be briefly noted under the INDICATIONS AND USAGE heading [21 CFR 201.57 (a)(6); 21 CFR 201.57 (c)(2)].

3. 21 CFR 201.57(a)(6) requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

   "(Drug) is a (name of class) indicated for (indication(s))."

   You should propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or provide a rationale why pharmacologic class should be omitted from the Highlights.

4. The Initial U.S. Approval date should be revised to reflect the year in which FDA initially approved the new combination of active ingredients [21 CFR 201.57 (a)(3)].

Full Prescribing Information: Contents; Full Prescribing Information

5. The FULL PRESCRIBING INFORMATION section should begin on the next page.

6. Headings and subheadings must be named and numbered correctly as outlined under 21 CFR 201.56 (d)(1). Any required section, subsection, or specific information that is clearly inapplicable may be omitted from the Full Prescribing Information. However, the numbering should not change. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

   8.1 Pregnancy
   8.3 Nursing Mothers (not 8.2)
   8.4 Pediatric Use (not 8.3)
   8.5 Geriatric Use (not 8.4)

We request that revised draft labeling addressing these issues be submitted by March 28, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a partial waiver of pediatric studies for this application for pediatric patients 0 to 11 years of age. Once review of your partial waiver request is complete, we will notify you whether the requested waiver has been granted. We note that you have submitted pediatric studies with this application for pediatric patients 12 to 17 years of age. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this age group.

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

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy 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
3/5/2008 03:50:47 PM

MEMORANDUM OF TELECON

DATE: February 13, 2008 TIME: 12:00 p.m.

APPLICATION NUMBER: NDA 50-819

BETWEEN:

Name: Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs
Phone: (650) 517-5300
Representing: Dow Pharmaceutical Sciences, Inc.

AND

Name: Margo Owens, Acting Supervisory Project Manager
Tamika White, Regulatory Project Manger
Division of Dermatology and Dental Products (DDDP), HFD-540

SUBJECT: Information Needed Prior to Filing NDA 50-819

On February 13, 2008, the FDA informed the sponsor of two information requests that would be needed prior to filing the new drug application for [redacted] Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide) for the treatment of acne vulgaris. The two information requests were:

1. Provide the carcinogenicity data sets electronically.

2. Direct us to, or provide, the validation report for the analytical method used to measure clindamycin, benzoyl peroxide and benzoic acid in study #2104-047-051-053-056 entitled "In Vitro Percutaneous absorption of Clindamycin and Benzoyl peroxide from Benzaclin, Clindaben (1/2.5), [redacted] (1/5) and DUAC Topical Gel using Intact human skin from two healthy donors". b(4)

   Provide the lot numbers of the investigational products and reference products used in the study listed above (i.e. # 2104-047-051-053-056).

The FDA advised the sponsor to submit this information no later than February 20, 2008 because the lack of these data affects the completeness of the application and could affect our ability to file the application.

The sponsor indicated that the request for clinical pharmacology information should be able to be submitted by the February 20, 2008 deadline. The sponsor expressed concern about submitting the carcinogenicity data electronically by February 20, 2008 since the studies were over ten years old.

The sponsor indicated that if the lack of electronic data sets for carcinogenicity data was used as a reason for refusing to file the application, they would not accept that and would take the decision to a higher level.

The FDA reminded the sponsor that the discussion of these data was a topic at the Pre-NDA meeting held on November 27, 2007 where we advised them to submit these data with the NDA.

The call ended with a confirmation from FDA that the information requests would be sent via fax on February 13, 2008.

Tamika White
Regulatory Project Manager

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/s/

Tamika White
3/4/2008 04:28:54 PM
CSO

Margo Owens
3/5/2008 03:53:59 PM
CSO

Tamika White
3/5/2008 03:56:06 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 28, 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:** 301-796-9894/9895
Phone number: 707-793-2600 x601	**Phone number:** 301-796-2110

Subject: NDA 50-819 Clinical Pharmacology Information Request

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 3:00 p.m. on March 4, 2008.

Document to be mailed: ☐ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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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 ——— Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide). b(4)

We also refer to your submissions dated February 7, 2008, February 11, 2008 and February 19, 2008.

We have reviewed your February 19, 2008, submission responding to our information request dated February 13, 2008. Based on the information you submitted, we have the following information request:

> It appears that the Lot Number 1918-123B for Clindaben (1/2.5) Gel that was used in the in vitro skin permeation study No. 2104-047-051-053-056 is not in agreement with the Lot numbers (i.e. those used in the clinical studies or stability studies) currently provided in this NDA . Provide information on how Lot Number 1918-123B relates to the to-be-marketed formulation (e.g. provide a copy of the manufacturing batch record which contains a batch formula for this lot).

We request receipt of your written response no later than 3:00 p.m. on March 4, 2008.

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

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/s/

Tamika White
2/28/2008 12:57:40 PM
CSO

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Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: February 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:** 301-796-9894/9895
Phone number: 707-793-2600 x601	**Phone number:** 301-796-2110

Subject: NDA 50-819 Clinical Pharmacology/Nonclinical Information Request

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 3:00 p.m. on February 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 . ——— Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide). b(4)

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

1. Submit the data for the carcinogenicity studies in the appropriate format to permit statistical analysis.

2. Direct us to, or provide the validation report for the analytical method used to measure clindamycin, benzoyl peroxide and benzoic acid in study #2104-047-051-053-056 entitled "In Vitro Percutaneous absorption of Clindamycin and Benzoyl peroxide from Benzaclin, Clindaben (1/2.5), ——— (1/5) and DUAC Topical Gel using Intact human skin from two healthy donors". b(4)

   Provide the lot numbers of the investigational products and reference products used in the study listed above (i.e. # 2104-047-051-053-056).

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

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

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/s/

Tamika White
2/13/2008 04:15:11 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 7, 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:** 301-796-9894/9895
Phone number: 707-793-2600 x601	**Phone number:** 301-796-2110

Subject: NDA 50-819 Statistical Information Request

Total no. of pages including cover: 3

Comments:

Review the attached request for information and respond no later than 1:00 p.m. on February 12, 2008.

Document to be mailed: ☐ YES ☑ NO

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NDA 50-819

b(4)

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 ——————, Gel (1.2% clindamycin phosphate, 2.5% benzoyl peroxide).

We are reviewing the Statistical section of your submission and have the following comments and information requests.

> You submitted dataset titled "Analysis Dataset Subject Level" (ADSL.xpt) for both studies: DPSI-06-22-2006-012 and DPSI-06-22-2006-017. However, these datasets do not include a unique subjects ID number for each subject. It appears that the last digit in Variable USUBJID is missing. This is shown in the following example of the identification numbers that were included in ADSP.xpt (Study DPSI-06-22-2006-012).

Obs	INVID	SUBJID	USUBJID
1	11	2	01100
2	11	3	01100
3	11	5	01100
4	11	7	01100
5	11	11	01101
6	11	15	01101
7	11	16	01101
8	11	18	01101
9	11	19	01101
10	11	21	01102
11	11	22	01102

> The Division requests that you provide datasets that include the full USUBJID variable.

We request a prompt written response no later than 1:00 p.m. on February 12, 2008 in order to continue our evaluation of your NDA.

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

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/s/

Tamika White
2/7/2008 02:36:47 PM
CSO