



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-819

NDA ACKNOWLEDGMENT

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

Dear Mr. Calvarese:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: _____ Gel (1% clindamycin phosphate – 2.5% benzoyl peroxide) **b(4)**

Date of Application: December 21, 2007

Date of Receipt: December 26, 2007

Our Reference Number: NDA 50-819

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 22, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(I)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above must be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

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

Sincerely,

{See appended electronic signature page}

Margo Owens
Acting Chief, Project Management Staff
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
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/

Margo Owens
1/29/2008 04:52:59 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 41,733

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

Dear Mr. Calvarese:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5 %) Gel.

We also refer to the meeting between representatives of your firm and the FDA on November 27, 2007. The purpose of the meeting was to obtain input on the content and format of the planned NDA submission for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: November 27, 2007 **Time:** 1:00 P.M.
Location: WO 22 Room 1313 **Meeting ID:** 22665
Topic: IND 41,733 Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel for treatment of acne vulgaris
Subject: Pre-NDA meeting
Sponsor: Dow Pharmaceutical Sciences, Inc.
Meeting Chair: Susan J. Walker, M.D./Division Director, DDDP
Meeting Recorder: Margo Owens/Regulatory Project Manager, DDDP

FDA Attendees:

Susan J. Walker, M.D./Division Director, DDDP
Markham Luke, M.D., Ph.D./Team Leader, Clinical, DDDP
David Kettl, M.D./Clinical Reviewer, DDDP
Jane Liedtka, M.D./Clinical Reviewer, DDDP
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDP
Jiaqin Yao, M.D., Ph.D./Pharmacology Reviewer, DDDP
Rajiv Agarwal, Ph.D./ Chemistry Reviewer, ONDQA
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDQA
Abimola Adebowale, Ph.D./ Clinical Pharmacology/Biopharmaceutics Reviewer, DPEIII
Mohamed Alesh, Ph.D./Biostatistics Team Leader, DBIII
Clara Kim, Ph.D./Biostatistician, DBIII
Don Hare/Special Assistant to the Director, OGD
Nam Kim/Regulatory Counsel, ORP
Margo Owens/Regulatory Project Manager, DDDP

Sponsor Attendees:

Gordon J. Dow, Pharm.D./Founder and Chief Technical Officer, Dow
Barry M. Calvarese, M.S./Vice President, Regulatory and Clinical Affairs, Dow
A.J. Acker, RAC, Manager, Regulatory Affairs

b(4)

David Osborne, Ph.D./Vice President, Product Development
Diana Chen/Medical Affairs
Bhaskar Chaudhuri, Ph.D./President and CEO
Pramod Sarpotdar, Sr./Director, Formulation Product Development
Karen Yu, Ph.D./Project Manager (via teleconference)
Linda Mutter, Ph.D., DABT/Director, Preclinical, Regulatory Affairs (via teleconference)

Purpose:

The sponsor requests input from the Agency on the content and format of their planned NDA submission for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel. The pre-meeting briefing document (submitted October 22, 2007) provides background and questions for discussion.

Introductory Comments:

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Chemistry, Manufacturing and Controls:

Summary: IDP-110Gel (Clindaben Gel) is a combination product, containing 1% clindamycin (1.2 % clindamycin phosphate) and 2.5% benzoyl peroxide. IDP -110 Gel will be distributed as a kit containing two separate components that are to be mixed by the pharmacist prior to dispensing to the patient. _____ the physician samples. b(4)

Question:

IDP -110 Gel will be distributed as a kit containing two separate components that are to be mixed by the pharmacist prior to dispensing to the patient. _____ the physician samples. The _____ results in a product that conforms to the exact same specifications as the product produced when separate component formulations are admixed by the pharmacist. Provided the stability data is compelling, _____ physician samples concurrent with launch of the commercial kit using data submitted during the NDA review process. Is this acceptable to the agency? b(4)

Response:

This is a review issue. _____ physician samples are acceptable if the mechanically mixed (pre-mixed samples) are equivalent to the manually mixed product. To assess the equivalence, we will need to review and compare the following data: in-vitro drug release profile, impurity profile, homogeneity, batch analysis, and stability. We may raise other questions during the NDA review. b(4)

Additional comments:

1. _____

- _____ . Any method must be able to detect potential degradation products of both the active pharmaceutical ingredients.
2. Detailed information on the container/closure system and the manufacturing process, including in-process tests on _____ drug product for physician sample, must be provided in the submission.
 3. An expiration date will be established for the physician samples based on the real time stability data on three batches of the _____ drug product.
 4. Please clarify if the _____ is the only configuration proposed for the physician sample.
 5. Please address how the expiry dating of the physician sample package will be addressed, since no pharmacy controls would apply to this sample product once distributed. Given the typical use of office samples in a clinical setting, expired product could easily be administered to patients, presenting theoretical safety or lack of efficacy concerns. Labeling for the sample size product will also need to be addressed.
 6. We remind you that all issues from the previous Guidance meetings must be addressed in your submission.

b(4)

Pharmacology/Toxicology:

Question:

At the End of Phase 2 meeting with the Agency, DPSI proposed to support the 505(b)(2) NDA for IDP-110 Gel with clindamycin and BPO literature, nonclinical studies conducted with _____ (1/5) Gel, and a chromosome aberration study with clindamycin phosphate. FDA agreed that this strategy appeared to be acceptable if a clinical bridge to BenzaClin was established in the bioequivalence study with _____ (1/5) Gel and BenzaClin. The bioequivalence study has clearly established bioequivalence of _____ (1/5) Gel to the reference listed drug BenzaClin and a relatively better tolerability profile of IDP-110 Gel. The Clindamycin-Benzoyl Peroxide Gel ANDA is currently under review at the Office of Generic Drugs (ANDA #065443).

b(4)

Does the Agency agree that nonclinical commitments have been met for IDP-110?

Response:

The nonclinical database appears acceptable for the NDA filing. However, the final adequacy will be a review issue. Please provide the impurity profile of the _____ physician samples. If any new impurity exists at an unqualified level, sufficient nonclinical data on the new impurity should be submitted to support the safety of the drug product.

b(4)

In addition, the data for the carcinogenicity studies should be submitted in the appropriate format to permit statistical analysis. Information on providing electronic data can be found at <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>. The specific format (table) for submission of tumor data of two-year carcinogenicity studies can be found at <http://www.fda.gov/cder/regulatory/ersr/Studydata.pdf>. Guidance on statistical aspects of

carcinogenicity studies can be found in the draft guidance entitled Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals, which is available at <http://www.fda.gov/cder/guidance/815dft.htm>.

Clinical Pharmacology/Biopharmaceutics:

Question:

Does the Agency grant a waiver to Dow Pharmaceutical Sciences, Inc. for the absorption study?

Response:

No, we cannot grant the waiver for the absorption study at this time. Based on previous communications between the Agency and the sponsor, the following information would need to be provided for the waiver to be granted:

- Approval of ANDA # 065443 for _____ (1/5) Gel
- A full study report of the new in vitro skin permeation data conducted with IDP-110 Gel (Clindaben 1/2.5 Gel), _____ (1/5) Gel, Benzaclin, and Duac
- Comparative evaluation of the systemically related adverse events obtained with the Clindaben (1/2.5) Gel dosed QD, _____ (1/5) Gel dosed BID and Benzaclin® Topical Gel dosed BID obtained from clinical studies

b(4,

On August 2, 2007, the Agency sent a fax to the sponsor regarding their request for a waiver of the Phase 2 absorption study (submitted as SS 0079 and 0087 on 02/02/2007 and 05/16/2007). Please refer to those comments.

We acknowledge the inclusion of the summary of the bioequivalence study submitted in ANDA #065443, in this submission. However, we note that ANDA #065443 is still under review by the Office of Generic Drugs. In addition the comparative safety data with regards to the systemically related adverse events obtained with the Clindaben (1/2.5) Gel dosed QD, _____ (1/5) Gel dosed BID and Benzaclin® Topical Gel dosed BID obtained from the Phase 2 and 3 studies was not provided in this submission.

We acknowledge the inclusion of a summary of a recently completed in vitro skin absorption study with IDP-110 Gel (Clindaben 1/2.5 Gel), _____ (1/5) Gel, Benzaclin, and Duac provided in this submission. We note that this information was previously submitted in SN 0092: Response to FDA Facsimile of August 2nd, 2007 Regarding IND Serial Submissions 0079 and 0087 for _____[™] Gel IND 41733 and Request for Agency Reconsideration of absorption Waiver request Presented by Sponsor in SS0079. However, the sponsor did not provide the full study report that also includes the analytical method and validation report in both submissions. Therefore, we could not conduct a full review of the study report that would allow us to arrive at explicit conclusions.

Clinical/Biostatistics:

Question 1:

As discussed at the End of Phase 2 meeting with the Agency on September 18, 2006 (Appendix 4), the two phase 3 clinical studies will be successful if the following endpoints are demonstrated:

- 1) the sponsor's combination product is superior to vehicle in inflammatory and non-inflammatory lesion counts and the global severity score; and
- 2) the sponsor's combination product demonstrates superiority to both monads in global severity score and inflammatory lesion counts. Non-inflammatory lesion counts will be assessed for each of the arms, however, the dyad will not have to demonstrate superiority over the monads for this endpoint.

Does the Agency concur that if the above endpoints are demonstrated in the Phase 3 studies that an indication of Acne Vulgaris is achievable?

Response: As discussed at the End-of-Phase 2 meeting, the above endpoints will be considered as the primary endpoints for an indication for the treatment of acne vulgaris. However, whether the indication for the treatment of acne vulgaris will be achieved is a review issue.

Meeting Discussion:

The sponsor inquired whether formal analysis of non-inflammatory lesions including p-values should be conducted or whether descriptive analysis would be sufficient. In response, the Agency recommended that formal analysis of non-inflammatory and total lesion counts should be submitted in addition to the analysis of inflammatory lesion counts.

Question 2:

Is the Agency willing to reconsider this nested approach?

Response:

- 1) The proposed nested approach implies that the indication of this product may be for the treatment of inflammatory lesions of acne. Whether treatment of inflammatory lesions of acne can be considered as an indication is an issue to be discussed with the Division.
- 2) To control the type I error, the nested approach has to be pre-specified.
- 3) The endpoints agreed with the Agency were inflammatory and non-inflammatory lesion counts and not total lesion counts. The second stage of the proposed nested approach involves analyses of non-inflammatory and total lesion counts. The nested approach should evaluate the same efficacy variables as the method that does not include the nested approach.

Additional Clinical Comments:

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

All Case Report Forms (CRFs) should be submitted from the two phase 3 studies with electronic links for:

- a) all Serious AEs
- b) all Severe AEs
- c) all patients who discontinued for whatever the reason (not just because of adverse events).

Meeting Discussion:

The Agency requested that the sponsor submit all photographs taken during the conduct of these studies in an organized and reviewable manner.

A request for a waiver for pediatric studies with a suitable justification should be submitted with the NDA to ensure compliance with FDAAA of 2007.

A formal request for a waiver of further dermal safety studies for this product should be submitted with the application. This issue was previously reviewed in response to sponsor submission serial number 081 on February 9, 2007.

Additional Statistical Comments

The sponsor should provide the Agency with SAS transport files in electronic form. The data sets should include demographic and baseline data as well as efficacy and safety data. Data Sets should include:

- a. The database for the Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses.
- b. Each data set should include the treatment assignments. For each of the primary and secondary endpoints, an indicator variable that denotes whether measurements are actual or imputed should be included.
- c. The submission should include adequate documentation for the data sets including definitions of each variable in the data set, formulas for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation.
- d. In addition to the electronic data sets, the NDA submission should include the following items:
 - o Study protocols including the statistical analysis plan, protocol amendments and their dates, and a copy of the Case Report Form.
 - o The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

Project Management:

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. Based on the repeal of section 507 of the Food, Drug and Cosmetic Act, you are advised that clindamycin would not be eligible for marketing exclusivity. The Sponsor may refer to the guidance document issued by the Agency in May 1998, *Guidance for Industry and Reviewers Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. This guidance document defines the administrative actions required by the agency for reviewing and

approving antibiotic drug applications that were submitted after November 21, 1997. You may also refer to the *Federal Register* notice 99N-3088, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs* issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507.

4. We remind you of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain and assessment of the safety and effectiveness of the pediatric patients unless this requirement is waived or deferred.
5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
6. You are reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

ACTION ITEM:

The Agency will ask our Office of Biostatistics about whether carcinogenicity data sets are required from the older studies that the sponsor intends to submit in the NDA.

- A response to this issue was sent via facsimile to the sponsor on December 7, 2007.

Minutes Preparer: _____
Margo Owens/Regulatory Project Manager DDDP

Chair Concurrence: _____
Susan J. Walker, M.D./Division Director, DDDP

b(4)

Linked Applications

Sponsor Name

Drug Name

IND 41733

DOW
PHARMACEUTICAL
SCIENCES

BENZOYL PEROXIDE \leq /CLINDAMYCIN
PHOSPHAT

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

/s/

SUSAN J WALKER
12/19/2007