



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  
Vice President, Regulatory and Clinical Affairs  
350 Corporate Boulevard  
Robbinsville, NJ 08691

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 September 18, 2006. The purpose of the meeting was to obtain input on the development plan 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 Walker, M.D.  
Division Director  
Division of Dermatologic and Dental  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES**



**Meeting Date:** September 18, 2006      **Time:** 9:00 A.M.  
**Location:** WO 1417      **Meeting ID:** 19663  
**Topic:** IND 41,733 Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel for treatment of acne vulgaris  
**Subject:** End of Phase 2 meeting  
**Sponsor:** Dow Pharmaceutical Sciences, Inc.  
**Meeting Chair:** Susan Walker, M.D./Division Director, DDDP  
**Meeting Recorder:** Margo Owens/Regulatory Project Manager, DDDP

**FDA Attendees:**

Susan Walker, M.D./Division Director, DDDP  
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDP, HFD-540  
Jiaqin Yao, M.D., Ph.D./Pharmacology Reviewer, DDDP, HFD-540  
Jane Chang, Ph.D./ Chemistry Reviewer, ONDQA  
Abimola Adebowale, Ph.D./ Pharmacokinetics Reviewer, DPEIII, HFD-880  
Tien-Mein Chen, Ph.D./ Pharmacokinetics Reviewer, DPEIII, HFD-880  
Markham Luke, M.D., Ph.D./Team Leader, Clinical, DDDP, HFD-540  
David Kettl, M.D./Clinical Reviewer, DDDP, HFD-540  
Kathleen Fritsch, Ph.D./Biostatistician, DBIII, HFD-725  
Clara Kim, Ph.D./Biostatistician, DBIII, HFD-725  
Fred Marsik, Ph.D./Microbiologist, DAIDP, HFD-520  
Margo Owens/Regulatory Project Manager, DDDP, HFD-540

**Sponsor Attendees:**

**Dow Pharmaceutical Sciences, Inc.**  
Gordon J. Dow, Pharm.D./Founder and Chief Technical Officer  
Barry M. Calvarese, M.S./Vice President, Regulatory and Clinical Affairs

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David Osborne, Ph.D./Vice President, Product Development (via teleconference)  
Karen Yu, Ph.D./Project Manager (via teleconference)  
A.J. Acker, RAC, Manager, Regulatory Affairs (via teleconference)  
Robert N. Decker, MS, Associate Manager, Clinical Affairs (via teleconference)  
Charles Chavdarian, Ph.D., Senior Director, Analytical Sciences (via teleconference)  
Simon Yeh, Ph.D. Manager, Methods Development, Analytical Sciences (via teleconference)

**Purpose:**

The sponsor requests input from the Agency on their proposed CMC and clinical development plans for Clindaben (clindamycin, 1% - benzoyl peroxide, 2.5%) Gel. The pre-meeting briefing document (submitted July 24, 2006) provides background and questions (pg. 10) for discussion.

The sponsor is reminded to refer to and address any pending issues conveyed during the November 13, 2003, March 7, 2005, and June 27, 2006, Guidance meetings.

**Chemistry, Manufacturing and Controls (CMC):**

From the FDA draft reviewer's comments dated June 21, 2006, the FDA stated that "a more comprehensive in-use admixture stability study should be performed on three registration batches to support an NDA filing". In response to this comment DPSI has generated a stability protocol for two upcoming registration batches of Clindaben (1/2.5) Gel. In addition, one registration batch of Clindaben (1/2.5) Gel is currently on stability.

**Sponsor's CMC Question 1:**

Does the Agency agree that the stability protocol as included in this Briefing Book will support an NDA filing?

**Agency's Response:**

No, the stability protocol provided in the Briefing Book is not adequate to support the NDA. The following issues should be addressed:

- 1) Add testing on the individual components \_\_\_\_\_ admixing for admixture stability. This is to ensure the quality, potency, and purity of each component is acceptable prior to admixing.

Sponsor: Agree. Testing of the individual components is done under a separate protocol.

- 2) The stability protocol for the current stability batch should be amended to include testing for benzoyl peroxide particle size distribution and homogeneity for all remaining time points if DPSI choose to pursue the proposed plan of \_\_\_\_\_ stability batch plus \_\_\_\_\_ registration batches of Clindaben (1/2.5) Gel. This approach is not a filing issue. However, it may carry some risk pending on the outcome of the stability data as particle size data at the early time points will not be available for the current stability batch.

Sponsor: Agree. The stability protocol of the current stability batch will be amended to include testing for benzoyl peroxide particle size distribution and homogeneity for all remaining time points starting at \_\_\_\_\_

- 3) Samples for admixture stability study should be prepared using validated admixing procedure. That is, each admixture sample should be individually prepared in the to-be-marketed container closure system following the validated admixing procedure. The procedure proposed on page 39 of the Briefing Book, \_\_\_\_\_, is not acceptable as it is not the procedure intended to be used by pharmacists.

Agency: Type of mixing, i.e. hand mixing vs. \_\_\_\_\_, used for preparation of admixture could affect the physical stability of the admixture. Admixture samples prepared by the proposed \_\_\_\_\_ mixer do not represent actual samples dispensed

by pharmacists. Therefore, the physical stability is not monitored adequately with the proposed protocol.

Sponsor: The sponsor acknowledged that they had not thought about the impact of mixing on the physical stability of the admixture. The sponsor stated that variability in the assays was observed with admixture prepared by hand mixing procedure. b(4)

The sponsor will submit a clarifying statement on this issue for the Agency's review.

- 4) The organisms tested in the microbial limit test (Table 3.1.1) should be described and their acceptance criteria should be provided.

Sponsor: Agee. Information will be provided.

- 5) We reiterate the recommendation made in the November 12, 2003 and June 27, 2006 Guidance Meetings for the necessity of a photostability study on the admixture. The Briefing Book does not include this study.

Sponsor: Agee. Information will be provided.

- 6) Numerical limits for clindamycin phosphate, clindamycin, and clindamycin phosphate degradation products should be proposed in the tentative regulatory specification of Clindaben (1/2.5) Gel (Table 3.1.1). Similar comment, i.e. numerical limits for clindamycin phosphate and clindamycin, was conveyed to you in the June 27, 2006 Guidance Meeting.

Sponsor: Agee. Information will be provided.

DPSI has developed a protocol to validate the admixing instructions (e.g. mixing time) for Clindaben (1/2.5) Gel to ascertain that sufficient mixing is achieved.

**Sponsor's CMC Question 2:**

Does the Agency agree that this protocol as included in this Briefing Book is sufficient to validate the mixing time for Clindaben (1/2.5) Gel?

**Agency's Response:**

No, it is not adequate to validate the mixing time. The criteria for selecting the mixing time should include a total clindamycin content of \_\_\_\_\_ of label claim. Validated regulatory analytical methods should be used for the assay. The clindamycin phosphate analytical method (STM-04-91) described on page 27 of the Briefing Book is not consistent with the methods (STM 04-95 for clindamycin phosphate and STM 04-113 for clindamycin) listed in the Clindaben (1/2.5) Gel Regulatory Specification (Table 3.1.1). Please clarify. b(4)

Sponsor: Agree. An error in the analytical method was in the Briefing book. The correct information will be provided.

**Pending Issues from Previous Guidance Meetings**

The following items were conveyed to you in the November 12, 2003 and June 27, 2006 Guidance Meetings and have not yet been addressed:

- Please discuss the issue of clindamycin precipitation referred to in the November 20, 1995, amendment. Also, justify the absence of a test for precipitate formation with either clindamycin solution or the combination product. (A verbal response was given in the June 27, 2006 Guidance Meeting. But a written response has not been given.)
- Perform photostability studies on clindamycin phosphate concentrate, benzoyl peroxide gel, and the combination product \_\_\_\_\_ gel.

**Clindamycin \_\_\_\_\_ Specification:**

- Numerical limits for clindamycin phosphate and clindamycin should be proposed. "Report", as shown in Table 3.5.2 (SN:068) is not an acceptable entry.
- Add "total clindamycin content" and its acceptance criterion
- The organisms tested in the microbial limit test should be described and their acceptance criteria should be provided.

**Benzoyl Peroxide \_\_\_\_\_ Specification:**

- Add particle size test and its proposed acceptance criterion
- Add homogeneity and its acceptance criterion
- The organisms tested in the microbial limit test should be described and their acceptance criteria should be provided.

**Pharmacology/Toxicology:**

The Agency understands that the sponsor is establishing a clinical bridge to Benzaclin by conducting a bioequivalence study with the 1/5 \_\_\_\_\_ formulation and Benzaclin. If, after review of this study, the Agency determines that this bridge is adequate then the existing nonclinical information and an in vitro chromosome aberration study with clindamycin phosphate appear to be adequate in principal to support a 505(b)(2) NDA. Please include copies of all references and English translations if necessary.

b(4)

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)] including a chronic topical toxicity study in a nonrodent model, three genotoxicity studies for clindamycin phosphate, besides the literature information outlined by the sponsor previously. Information from the labeling of an approved drug product can not be referred to unless a sufficient clinical bridge has been established to the approved drug product.

It is recommended that the sponsor provide information on the levels of the degradation products in the drug product/substances used in the nonclinical and clinical studies so that it can be determined if they are adequately qualified or the sponsor otherwise qualify the levels of the degradation products.

It should be emphasized that because complete data are not currently available, the perceived nonclinical data requirement may change during review of the IND/NDA.

**Clinical Pharmacology/Biopharmaceutics:**

There were no clinical pharmacology or biopharmaceutics questions identified in this briefing package. We summarize the previous discussions in the meetings and have a comment for the sponsor:

- In the 11/12/03 meeting, the Agency indicated that pharmacokinetic studies to assess the degree of and/or potential for systemic absorption would be needed.
- In the 03/07/05 meeting, you indicated that a Phase 2 systemic absorption study would be proposed to be conducted and submitted in the NDA. However, the Agency did not agree with the overall design of the protocol.
- In the 06/27/06 meeting package, you indicated "In the sponsor's opinion, the presence of a large safety data base for the two actives (BPO and clindamycin), the establishment of a safety bridge via the comparison of (1/5) gel to Benzacilin and the ability to cross-reference the Clindagel absorption study support the rationale not to conduct an absorption study on Clindaben (1/2.5) Gel. The supporting information and rationale is provided in Sections 4, 5, and 6 of this briefing package. DPSI proposes not to conduct a phase 2 absorption study at this time."

b(4)

The Agency responded in the meeting "the information provided in the briefing document appears insufficient for a waiver of phase 2 absorption studies to be granted. The Clindagel data is not sufficient to satisfy the recommended elements of the phase 2 maximal use study which would use a formulation identical to the clinically studied/to-be-marketed formulation. Clindamycin gel product absorption data in place of the combination product would require justification, since there might be differences in absorption due to a vehicle effect. Please submit your rationale to demonstrate why data from the clindamycin only product is sufficient."

However, you reiterated in the meeting that adequate safety data would be presented to justify the decision not to perform the absorption study. You would present bioequivalence data and supporting safety data (including use of their product under maximal use conditions) to the reference listed drug, Benzacilin, in a written waiver request.

To date, we are still awaiting your written waiver request with your rationale to demonstrate why an in vivo bioavailability study of your product under maximal use conditions will not be conducted at this time.

The sponsor stated they will submit the waiver request within the next 2-3 weeks.

**Clinical and Biostatistics:**

**Sponsor's Clinical Question 1:**

The sponsor seeks approval for moderate to severe inflammatory acne. Is this labeling indication agreeable to the Agency?

b(4)

**Agency's Response:**

Labeling is a review issue and depends on the information submitted to the NDA. Acne vulgaris is an evolving indication and the contributions of inflammatory versus non-inflammatory lesions

are the focus of ongoing discussions. Labeling decision for specific acne lesions may be referred to an advisory committee for resolution. In general, patients seek treatment for, and clinicians treat, "acne vulgaris" and sponsors are encouraged to consider this broader indication.

However, an indication for "~~\_\_\_\_\_~~" has precedent, given demonstrable efficacy and safety in at least two adequate and well-controlled studies.

b(4)

Patients with acne characterized as "severe" are likely to have significant non-facial acne, and this is not addressed in the protocol. Please clarify how this issue will be addressed.

**Sponsor's Clinical Question 2:**

Is the phase 3 protocol in Appendix 5.3 acceptable?

**Agency's Response:**

Review of the phase 3 protocols submitted in serial number 71 is ongoing and comments regarding the protocol will be conveyed to the sponsor when complete. The sponsor is encouraged to submit the phase 3 protocol as a Special Protocol Assessment.

The sponsor stated that they plan to begin the study in two weeks and will not submit an SPA to the Agency for review.

In brief, the primary endpoints of absolute change in inflammatory lesion counts, and percent of subjects who achieve a two point reduction at week 12 in the Evaluator's Global Severity Score seem acceptable for an indication for inflammatory lesions of acne. As previously recommended at the June 27, 2006 guidance meeting, efficacy would be demonstrated if:

1. The sponsor's combination product is superior to vehicle in inflammatory and non-inflammatory lesions and the global severity score, and
2. The sponsor's combination product is superior to both monads in two of three lesion counts (inflammatory, non-inflammatory, and total) and the global severity score.

The Agency stated that while approval of subsets of acne has some regulatory precedent, clinicians do not generally evaluate patients as "inflammatory", or "non-inflammatory". It was recommended that the indication sought should be acne vulgaris, as opposed to "~~\_\_\_\_\_~~". This is especially true given that this is a combination product.

b(5)

The sponsor pointed out that the proposed indication was developed because of the language of the draft guidance for acne. The Agency responded that as long as all the appropriate endpoints were measured, this would be a review issue to determine approval for the treatment of acne vulgaris indication.

After extensive discussion regarding proposed endpoints and review of the sponsor's phase 2 study results, agreement was reached on the following endpoints:

Success would be demonstrated if:

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.

For phase 3 protocols, the Agency does not recommend the use of a visual analog scale (VAS). Rather, the static, global integer scale is recommended to be used. The VAS can be measured as an exploratory secondary endpoint but would have little regulatory utility.

Please refer to additional endpoints from biostatistics concerning the proposed evaluation criteria.

**Sponsor's Clinical Question 3:**

Dow Pharmaceutical Sciences, Inc. (DPSI) is proposing a nested statistical analysis approach that would allow for an initial labeling claim of ' \_\_\_\_\_ ' followed by analysis of the noninflammatory lesions which, if successful, would allow for an acne vulgaris claim. Is the attached Statistical Analysis Plan (SAP) in Appendix 5.4 acceptable to the Agency? (Note: this approach was suggested prior to the agreement on the above success criteria)

b(4)

**Agency's Response:**

The sponsor's proposed nested approach is novel and the Agency cannot agree to it at this time. The SAP does not clearly state how the set of hypothesis test results would be collated into claims. In addition, especially for combination products, the Agency is interested in evaluating overall acne and not limiting to a subset of acne lesion types. The Agency's thinking on the most appropriate way to evaluate combination products for acne continues to evolve as new information becomes available. It may be possible to reduce the number of comparisons needed to establish efficacy for the full indication and fulfill the combination policy. The Agency is open to further discussion on this issue.

After extensive discussion, the sponsor proposed to evaluate the following comparisons to achieve a successful clinical study:

- Combination product vs. vehicle
  - Evaluator's Global Severity Score (EGSS)
  - Inflammatory lesions count
  - Non-inflammatory lesion count
- Combination product vs. each monad
  - Inflammatory lesion count
  - EGSS

**Following comments are in response to the SAP.**

1. The Division reiterates previous comments from the March 7, 2005 meeting that the Evaluator's Global Severity Score should be on a 5-grade scale instead of a 6-grade scale.
2. The sponsor proposed to stratify subjects by Baseline Evaluator's Global Severity Score (EGSS) (moderate vs. severe) and by two skin phototype groups (I, II, III vs. IV, V, VI), therefore by 4 strata. The sponsor should provide the reasoning for using such stratification factors. Stratification should be limited to factors that are expected to be highly correlated to the efficacy results. Each stratum should have sufficient number of subjects to avoid empty cells and their impact on the analysis.
3. If the sponsor chooses to stratify subjects at randomization, the stratification factors should be included in the analysis model. This should be applied in both the lesion count and EGSS analyses.

The sponsor agreed to include the stratification factors in the analysis model for lesion counts. However, they stated that it would be infeasible to include the factors in the Cochran-Mantel-Haenszel (CMH) model to analyze EGSS. The sponsor suggested that they could use Generalized Linear Interactive Modeling (GLIM) instead of CMH. The Agency responded that GLIM could be used as a supportive analysis.

4. If the treatment by center interaction is significant, the protocol should pre-specify a sensitivity analysis to ensure that the efficacy results are not driven by extreme centers (e.g. evaluating efficacy after deleting extreme centers).
5. The sponsor proposed two sensitivity analyses to investigate the impact of data imputation on the EGSS. The protocol should include a sensitivity analysis to investigate the impact of the imputation method on lesion counts as well to ensure that the efficacy results are not driven by the imputation method.
6. The protocol states to use an ANOVA model with treatment, center, center by treatment interaction as factors, and baseline lesion count as covariate to analyze the lesion counts. The reviewer assumes that the sponsor plans to use an ANCOVA model, not an ANOVA model for the analysis.

**Clinical Microbiology:**

There were no clinical microbiology questions identified in this briefing package. We have the following comment for the sponsor:

**Agency:**

1. The Sponsor needs to be aware that because no microbiology data is being gathered during the Phase 3 clinical studies the "Microbiology" section of the package insert will be limited in what is said about Clindaben™ from a microbiology perspective.
2. Please provide information on the in vitro activity of clindamycin and benzoyl peroxide individually against *P. acnes*. Information on the in vitro activity of the combination of clindamycin and benzoyl peroxide required to inhibit the growth of *P. acnes* should also be submitted to the Agency. This information can be from recent laboratory studies (within the last 3 years) or from the recent literature (within the last 3 years).

The Sponsor asked for the number of bacterial isolates for which clindamycin, benzoyl peroxide, and the combination of benzoyl peroxide in vitro susceptibility data had to be provided. The Agency indicated that data for at least 100 isolates of *Propionibacterium acnes* needs to be provided. Included in the 100 isolates should be isolates with different mechanisms of antimicrobial resistance. The Sponsor indicated that they are in the process of obtaining the information and in the mean time they will submit the data they have to date to the IND for review and comment by the Agency. The Agency indicated that this is acceptable.

**Project Management:**

**Agency:**

1. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.
2. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or information requests.
3. Based on the repeal of section 507 of the Food, Drug and Cosmetic Act, the sponsor is advised that Clindaben Gel (clindamycin, 1% - benzoyl peroxide, 2.5%) 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. The sponsor 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. The sponsor is encouraged to submit its revised protocols as Special protocols through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review, comment and agreement, prior to study initiation.
5. The sponsor is encouraged to request a Pre-NDA Meeting at the appropriate time.
6. The sponsor is reminded that all new NDAs/BLAs and efficacy supplements submitted on or after June 30, 2006 must include content and format of prescribing information based on the new Physicians Labeling Rule at the time of submission (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

Minutes Preparer: \_\_\_\_\_  
Margo Owens/Regulatory Project Manager DDDP

Chair Concurrence: \_\_\_\_\_  
Susan Walker, M.D./Division Director, DDDP

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

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Susan Walker  
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