DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 41,733

Dow Pharmaceutical Sciences
Attention: Barry M. Calvarese, MS
Vice President, Regulatory & Clinical Affairs
1330A Redwood Way
Petaluma, CA 94954-1169

Dear Mr. Calvarese:

Please refer to your Investigational New Drug Application (IND) file for Clindaben Gel (1% clindamycin phosphate, 2.5% benzoyl peroxide).

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2005. The purpose of the meeting was to discuss your drug development plans.

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, please call Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

*{See appended electronic signature page}*

Jonathan K. Wilkin, M.D.
Division Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel
Guidance Meeting

Meeting Date: March 7, 2005 Time: 10:30 a.m. Location: N225
Meeting ID# 14738

IND 41,733, Clindaben™ (1% clindamycin, 2.5% benzoyl peroxide) Gel

Indication: Treatment of Acne vulgaris

Sponsor: Dow Pharmaceutical Sciences

Guidance Meeting

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Jonca Bull, M.D., Office Director, ODEV, HFD-105
Shaw T. Chen, M.D., Ph.D., Associate Director for Special Product Review-Botanical Drug Products, HFD-105
Ramesh Sood, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Saleh Turujman, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Paul Brown, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Abi Adebowale, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer, DPEIII, HFD-880
Fred Marsik, Ph.D., Clinical Microbiology Team Leader, DAIDP, HFD-520
Markham Luke, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540
Phyllis Huene, M.D., Medical Officer, DDDDP, HFD-540
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DBEIII, HFD-725
Steve Thomson, Biostatistics Reviewer, DBEIII, HFD-725
James Morton, Pharmacist Intern, FDA Experiential Program
Frank H. Cross, M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Barry M. Calvarese, Vice President, Regulatory Affairs and Clinical Affairs **b(4)**
David Osborne, Ph.D., Vice President, Product Development
Gordon Dow, Ph.D., Founder and Chief Technical Officer
Karl Beutner, MD, Ph.D., Vice President and Chief Medical Officer

A.J. Acker, RAC, Associate Manager, Regulatory Affairs
Karen Yu, Ph.D., Senior Product Manager

With reference to the February 4, 2005, briefing package, the following discussion took place:

**Chemistry, Manufacturing and Controls:**

Sponsor's CMC Question 1 of February 4, 2005, Briefing Package: "DPS has updated the CMC section with new information taking into account previous questions by the Agency from the December 12, 2003 (*sic*) guidance meeting. The new information contains updated specifications and directions to the pharmacist for preparing the combination product. Does the Agency agree with the proposed CMC plan?"

Agency:

No. The sponsor did not adequately address the CMC issues raised at the Guidance Meeting of November 12, 2003. The sponsor is requested to respond to all the issues raised by the chemistry reviewer during the guidance meeting of November 12, 2003. If some of these issues were addressed in a previous IND amendment, the sponsor is requested to please cite the number and date. The deficiencies in the current briefing package are listed below.

The sponsor was requested at the guidance meeting of November 12, 2003, to provide a compilation table of the batches/lots used in the studies to date, clearly indicating in addition to the site and date of manufacture, the batch/lot size, the formulation (with or without preservatives, ——— , etc.), which batches were used in which studies i.e., clinical, toxicology, stability, studies (including protocol number), etc. The information provided in Table 2.3 in the current briefing package is inadequate. For example, it does not provide information on the site and date of manufacture of the batches listed, and how the batches were used (clinical, toxicological, biopharmaceutical, etc.?). b(4)

1. Quantitative Composition

   b(4)

   In Table 2.4, the ——— of benzoyl peroxide should be justified. The ——— of clindamycin phosphate in Table 2.5 should be justified.

   The amount of water in the combination product (Table 2.6) should be specified. Qs. is not acceptable as the sole entry for such a large amount. Minor adjustments to the specified amount may be made to take into account the variation in the amount of potassium hydroxide added to

   b(4)

2. Specifications

   a. The sponsor is reminded that according to the ICH Q6A, a specification is defined as a list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described. In the tables of proposed specifications for the drug products, the column heading entry should be "acceptance criterion", instead of the current "regulatory specifications".

   b. The identification test for benzoyl peroxide and for clindamycin phosphate should be specific. Simple matching of sample and standard retention times alone is not considered to be specific. However, HPLC coupled with UV or MS is considered specific.

The sponsor is requested to clarify what is meant by the entry "positive for" in the identification test for benzoyl peroxide and for clindamycin phosphate in the tentative specification tables.

c. The proposed impurity levels are too high. Have batches with this level of impurities been qualified? Each acceptance criterion should be set no higher than the qualified level of the given degradation product. Furthermore, the acceptance criteria for specified impurities and for total impurities should be based on the actual results of stability studies of manufactured batches (clinical and registration). While it is understood that the impurity profiles for the two drug substances will be defined as a result of the stability study, and that the impurities will be evaluated as required by the Phase 3 stability protocol, the following deficiencies are noted in the proposed specifications of the intermediate and final drug products.

3. Tentative Specification for Benzoyl Peroxide Gel

There are several deficiencies in the proposed tentative regulatory specification of Benzoyl Peroxide Gel (Table 2.7).

**Table 2.7 Tentative Product Specifications of Benzoyl Peroxide Gel**

| Test | Regulatory Specification |
|---|---|
| Appearance | Opaque white to off-white smooth gel |
| Identification Test | Positive for Benzoyl Peroxide |
| pH | |
| Benzoyl Peroxide Content | |
| Degradation Products: | |
| | |
| | |
| Homogeneity | |
| Viscosity | |
| Microscopic Examination | |
| Microbial Limit Test | |

NMT = Not More Than

b(4)

a. Although the appropriateness of the proposed values for acceptance criteria are review issues, the proposed acceptance criteria of the degradation products seem too high. For example, the acceptance criterion of [redacted] for [redacted] is too high without adequate justification. As stated above, justification should be provided for all the proposed acceptance criteria. b(4)

b. The sponsor states on page 11 in the CMC section of the briefing jacket (CMC Tab) that no [redacted] was detected in early stability studies (7%, benzoyl peroxide formulation), yet an acceptance criterion of [redacted] is set for [redacted] The sponsor also states that " b(4)

If oxidation were to occur, the final oxidation products are likely to be the natural products ——————, yet no acceptance criterion is set for either "likely" decomposition product. If no acceptance criterion is set for either of these compounds, the sponsor has to demonstrate that these "likely" compounds are absent from the drug product through its shelf life. b(4)

c. "Report", as shown in the above table, is not an acceptable entry for an acceptance criterion. The homogeneity and microscopic examination attributes should be specified.

d. The proposed limit of ', for unknown degradation impurities is too high. The sponsor is referred to the recommended values under ICH Q3B, and to the additional comments below. b(4)

e. The sponsor is requested to justify the upper limit of the benzoyl peroxide content (——). b(4)

4. Tentative Specification for Clindamycin Phosphate Concentrate

There are several deficiencies in the proposed tentative regulatory specification of Clindamycin Phosphate Concentrate (Table 2.8).

**Table 2.8 Tentative Product Specifications of Clindamycin Phosphate Concentrate**

| Test | Regulatory Specification |
|---|---|
| Appearance | Colorless to pale yellow clear solution with a distinctive odor |
| Identification Test (HPLC) | Positive for Clindamycin Phosphate |
| pH | |
| Clindamycin Content (Clindamycin Phosphate and Clindamycin) | |
| Degradation products | |
| Sterility | |

NMT = Not More Than

b(4)

a. The sponsor is asked to explain the source of the "pale yellow" color and the "distinctive odor". An odor test is not recommended.

b. An acceptance criterion is not provided for "free" clindamycin. Instead, clindamycin is listed together with the parent drug substance, clindamycin phosphate. This is not acceptable. The sponsor is requested to list clindamycin separately from the parent drug substance, clindamycin phosphate, and to provide an acceptance criterion for "free" clindamycin. The sponsor should also be requested to provide properly labeled HPLC chromatograms (LCs) where the two compounds are resolved (separated).

c. The sponsor is requested to justify the upper limit of the clindamycin content (——). The sponsor is reminded that ———— are not permitted. b(4)

d. The only specified degradation product of clindamycin is ' ———— for which an acceptance criterion of —is proposed. b(4)

Justification for such a high acceptance criterion should be provided. No other known degradation products of clindamycin phosphate, such as [redacted], are listed in the proposed regulatory specification. The sponsor is requested to provide justification (evidence) that these related degradation products do not increase on storage or are absent over the requested shelf life of the product. (Representative chromatograms recorded under analytical conditions which can detect these degradation products at the expected ICH levels in the drug product should be provided in the NDA.) b(4)

e. The proposed limit of [redacted] for unknown degradation impurities is too high. The proposed acceptance limit for individual degradation products should be justified based on the actual accrued data. Although ICH Q3B guidance does not apply to products containing fermentation and semi-synthetic drug substances, the sponsor can use the general principles described in this guidance to set appropriate acceptance criteria for impurities. The recurring impurities should be classified as specified unknown impurities with their individual acceptance criteria. More restrictive acceptance criteria should be proposed for unspecified unknown individual impurities. b(4)

5. Tentative Specification for Clindaben (clindamycin phosphate 1%, benzoyl peroxide 2.5%) Gel

There are several deficiencies in the proposed tentative regulatory specification of Clindaben (clindamycin phosphate 1%, benzoyl peroxide 2.5%) Gel (Table 2.9).

**Table 2.9 Tentative Regulatory Specifications of Clindaben (1/2.5) (clindamycin/benzoyl peroxide) Gel to Access Shelf Life of Admixed Product**

| Test | Regulatory Specification |
|---|---|
| Appearance | Opaque white to off-white smooth gel |
| Microbial Limit Test* | Pass |
| pH | [redacted] |
| Benzoyl Peroxide Content | [redacted] % label claim |
| Degradation Products** [redacted] | Report as % of label claim |
| Clindamycin Content (Clindamycin Phosphate and Clindamycin) | [redacted] % label claim |
| Degradation Products*** [redacted] | Report as % of label claim |

b(4)

* On initial
** Expressed as percentage of benzoyl peroxide label claim.
*** Expressed as percentage of Clindamycin label claim.
NMT – Not More Than

a. An acceptance criterion is not provided for "free" clindamycin. Instead, clindamycin is listed together with the parent drug substance, clindamycin phosphate. This is not acceptable. The sponsor is requested to list clindamycin separately from the parent drug substance, clindamycin phosphate, and to provide an acceptance criterion for "free" clindamycin. The sponsor should also provide properly labeled HPLC chromatograms (LCs) where the two compounds are resolved (separated).

b. The sponsor is requested to provide justification for the upper limit of the clindamycin content ( —— similarly, for the upper limit of the benzoyl peroxide content —— b(4)

c. The above (deficiency) comments concerning the known degradation products of benzoyl peroxide in the Benzoyl Peroxide Gel and the known degradation products of clindamycin phosphate in the Clindamycin Phosphate Concentrate apply also to the Clindaben Gel.

d. The proposed limits for unknown degradation impurities related to benzoyl peroxide exceed the recommended values under ICH Q3B. The limits under ICH Q3B are calculated on the basis of the maximum daily use of the drug product. According to the absorption evaluation of Clindaben (Maximum topical exposures in Appendix 2 of the briefing jacket), 4 g of the drug product was applied to the face, back, neck and chest. The ICH Q3B limits are calculated below on the basis of a 4 gm daily dose. Please see our comment 5 above under clindamycin phosphate concentrate regarding setting acceptance criterion for individual impurities related to clindamycin phosphate.

e. According to ICH Q3B (Attachment 1), when the maximum daily dose of a drug substance is >100 mg but less than 2 g, as it is for benzoyl peroxide (1.2 g) in this drug product, the respective identification and qualification thresholds for impurities would be 0.2% or 2 mg TDI and 0.2% or 3 mg total daily dose, whichever is lower. The proposed acceptance criterion for each unknown related degradant of benzoyl peroxide is also ' — which is — times the ICH Q3B threshold. b(4)

The sponsor is requested to provide a justification for the acceptance criteria of NMT — for any unknown substances related to benzoyl peroxide in the regulatory specification of the benzoyl peroxide gel drug product (Table 2.7). b(4)

6. Manufacturing, Controls

a. Although a general step-by-step description of the manufacturing method for Benzoyl Peroxide Gel is provided (on page 14), the in-process controls required to monitor the step in question are not provided. For example, in one of the ————, the instructions call for the ———— without stating how the operator determines the proper ———— Similarly, —— calls for the [benzoyl peroxide] ———— without providing how proper —— and even —— is ascertained. b(4)

b. Similar deficiencies are found in the manufacturing controls provided in the general step-by-step description of the manufacturing method of the Clindamycin Phosphate Solution.

c. A brief description of the packaging and labeling process for clinical supplies should be also provided. Reprocessing procedures and pertinent controls should be described, if applicable.

7. Container Closure System

The sponsor is reminded that any changes in the container closure system (also referred to as the packaging system) should be reported. The sponsor is also reminded to ascertain that their vehicle does not cause extractables to contaminate the drug product, by including qualitative and quantitative extraction profiles of the container closure using the particular vehicle or an appropriate solvent. Please refer to Attachment C of the CDER Guidance for Industry "*Container Closure Systems for Packaging Human Drugs and Biologics*", which is available on the CDER website.

8. Stability

a. The sponsor states that they plan to manufacture additional batches at the commercial site, and that the batches will be used in the proposed clinical studies. The sponsor also states that stability studies will be performed on these batches, and the data will be provided to the Agency. However, a stability protocol was not provided.

b. The sponsor is reminded of the following:

i. To provide the stability protocol that will be used in the primary stability studies. The stability protocol should include a description of the drug product under investigation in the stability program, a description of the packaging, a list of the tests, sampling time points for each of the tests, temperature and humidity conditions to be studied, expected duration of the stability program, and the proposed bracketing/matrixing protocol, if applicable.

ii. The following information should be included in an NDA (needed information to bear in mind for an NDA submission)\

- A detailed data table that includes the lot number, manufacturing site, the date of manufacture of the drug product, and the drug substance used to manufacture the lot should be provided. Each table should contain data from only one storage condition. Individual data points for each test should be reported. Representative chromatograms should be provided, if applicable.

- A short description should be provided for each of the parameters being investigated in the stability program (i.e., stress, long-term, and accelerated) demonstrating that the appropriate controls and storage conditions are in place to ensure the quality of the product used in clinical trials. Tests unique to the stability program should be adequately defined.

- The shelf life (expiration date) that will be granted will be based on a review of stability data provided under ICH conditions. For planning purposes, it is recommended that the stability protocol be extended through the proposed expiration data. It is recommended that the NDA submission contain stability information from accelerated and long-term testing on three batches of the same formulation of the dosage form in the container closure proposed for marketing. Two of the three batches should be at least pilot scale. The third batch may be smaller.

**Pharmacology/Toxicology:**

Sponsor's question 2 of February 4, 2005, Briefing Package: "DPS believes that the nonclinical studies completed for [redacted] (1/5) Gel fully supports Clindaben (1/2.5) Gel. In addition to the studies already completed, DPS will complete genotoxicity studies prior to filing of the NDA. Does the Agency agree?"

Agency:

1. As previously noted, the nonclinical studies already conducted for Clindaben appear to be adequate in principal to support a 505(b)(2) NDA provided that the sponsor establishes a sufficient clinical bridge to an approved clindamycin/benzoyl peroxide product. If the sponsor does not establish a clinical bridge to an approved clindamycin/benzoyl peroxide product (whether 505(b)(1) or 505(b)(2)) then additional nonclinical information would be needed to support an NDA including a chronic topical toxicity study in a nonrodent model, genotoxicity and developmental and reproductive toxicity. Studies conducted with the 1/5 formulation would likely be adequate to support the 1/2.5 formulation. Note that other changes such as increased levels of active or inactive ingredients may not be supported by the existing studies.

2. It is noted that the sponsor plans to complete genotoxicity studies to support the NDA. It is recommended that this information be consistent with the appropriate ICH guidances (S2A, S2B). In general, genotoxicity studies are conducted with individual compounds. Reproductive and developmental toxicity information for each active ingredient was also previously noted as absent. It is recommended that reproductive and developmental toxicity studies consistent with ICH guidances be included in an NDA (See ICH M3, S5A, S5B).

3. It is also noted that the tentative product specifications have relatively high levels of degradation products. The sponsor should provide information on the levels of these degradation products in the materials used in the nonclinical and clinical studies so that it can be determined if they are adequately qualified or the sponsor should otherwise qualify these levels.

**Clinical Microbiology:**

1. In the Phase 3 study protocol (#7002-EIHP-01-05), please include a provision to collect specimens from inflammatory and non-inflammatory lesions of subjects who do not respond to treatment with Clindaben for culture of *Propionibacterium acnes*. All isolates of *P. acnes* need to be tested against clindamycin and benzoyl peroxide to determine the concentrations of these antimicrobials individually and combined required to inhibit the growth of the P. acnes isolates.