CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-524/S-005

Administrative Documents

E. Debarment Certification Statement

Bertek Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Mary W. Treuhaft, PhD
Vice President Regulatory and Clinical Affairs

EXCLUSIVITY SUMMARY for NDA # 20-524 **SUPPL #** 005

Trade Name: Mentax® Cream, 1% **Generic Name:** butenafine HCl cream

Applicant Name Bertek Pharmaceuticals, Inc. **HFD-** 540

Approval Date 6/6/01

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /__/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /__/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   d) Did the applicant request exclusivity?

      YES /_X_/ NO /__/

      If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

      5 years

   e) Has pediatric exclusivity been granted for this Active Moiety?

      YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.) YES /___/ NO /___/ N/A

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_X_/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /_X__/ NO /__/

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, IND[ ] Study # PDC 010-031

Investigation #2, IND[ ] Study # PDC 010-032

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

IND [ ]

Investigation #1, Study # PDC 010-031 YES /__/ NO /_X_/

Investigation #2, Study # PDC 010-032 YES /__/ NO /_X_/

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

IND [ ]

Investigation #1, Study # PDC 010-031 YES /__/ NO /_X_/

Investigation #2, Study # PDC 010-032 YES /__/ NO /_X_/

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

IND [ ]

Investigation #1, Study # PDC 010-031

Investigation #2, Study # PDC 010-032

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor? YES /_X_/ NO /___/

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

YES /_X_/ NO /___/

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

/S/

Signature of Preparer — 6/1/01 Date

Title: Project Manager

/S/

Signature of ~~Office or~~ Division Director — 6/5/01 Date

cc:
Archival NDA
HFD-540/Division File HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi HFD-540/Cross

Form OGD-011347/Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	020524	**Trade Name:**	MENTAX (BUTENAFINE HCL CREAM 1% TOPICAL)
Supplement Number:	005	**Generic Name:**	BUTENAFINE HCL CREAM 1% TOPICAL
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TOPICAL APPLICATION IN THE TREATMENT OF INTERDIGITAL TINEA PEDIS
Action Date:	8/7/00		

Indication # 1 Topical treatment of tinea (pityriasis) versicolor due to Malassezia furfur (formerly Pityrosporum orbiculare).

Label Adequacy: Adequate for SOME pediatric age groups

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): Tinea versicolor is a disease entity that rarely occurs in pediatric patients below the age of 12 years.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
17 years	Adult	Completed	1/6/01
12 years	16 years	Completed	6/1/01

Comments: Use of Mentax Cream, 1%, in pediatric patients 12 to 16 years of age is supported by evidence from adequate and well-controlled studies of Mentax Cream, 1%, in adults.

0 years	11 years	Waived	6/4/01

Comments: Pediatric studies are not needed because the approved indication, Tinea versicolor, is a disease entity that rarely occurs in pediatric patients below the age of 12 years.

This page was last ~~edited~~ on 6/4/0. S 6/04/01

S

Signature

6/4/01

Date

(1SI -6/5/01

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
Clinical Study PDC 010-031	See attached
Clinical Study PDC 010-032	See attached

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mary W. Treuhaft, PhD	Vice President, Regulatory and Clinical Affairs
FIRM/ORGANIZATION: Bertek Pharmaceuticals Inc.	
SIGNATURE: Mary W. Treuhaft	DATE: August 4, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

Team Leader Addendum for NDA 20-524/SE1-005

This NDA Supplement is an efficacy supplement for Mentax (butenafine HCl cream) Cream 1%. The Sponsor has conducted two adequate and well-controlled trials in support of this new indication for its topical antifungal drug product.

As the primary clinical reviewer and the primary statistical reviewer indicate, the efficacy of this product for the proposed indication, as demonstrated in the submitted trials, is significantly better than the vehicle in one study (PDC 101-32) and only numerically better than vehicle in the other study (PDC 101-31). The rates of cure for this product when compared to vehicle should be published in labeling.

The primary clinical reviewer has suggested an alternative evaluation of efficacy whereby subjects who have any post-treatment positive mycology leading up to the agreed upon point of cure be excluded. Such an evaluation would not be appropriate due to the prior commitments made by Agency regarding this drug. Thus, the final analysis for efficacy does not take this alternative evaluation into account.

No new safety concerns are raised for this currently marketed drug product regarding this new indication, from the conducted Phase 3 studies.

Team Leader is in agreement with the decision of the primary clinical reviewer regarding a recommendation for approval of this efficacy supplement for NDA 20-524.

/S/ 5/18/01

Markham C. Luke, M.D., Ph.D.
Acting Clinical Team Leader, Dermatology

Cc:
NDA 20-524 6/5/01
HFD-540/DD/Wilkin
HFD-540/Clinical/Vaughan
HFD-540/Biostat/Friedlin
HFD-540/Biostat TL/Alosh
HFD-540/Pharm/Mainigi
HFD-880/Biopharm/Adebowale

Teleconference Date: October 24, 2000 Time: 0915 Location: N250

SAS Dataset Discussion for Mentax® (butenafine hydrochloride cream) Cream, 1%,

Sponsor: Bertek Pharmaceuticals, Inc.

Meeting Chair: Valeria Freidlin, Ph.D., Biostatistics Reviewer

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

FDA Attendees, titles and offices:

Valeria Freidlin, Ph.D., Biostatistics Reviewer DOBIV, HFD-725
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Bertek Pharmaceuticals, Inc.:

Mary Treuhaft, Ph.D., Vice President, Regulatory and Clinical Affairs

The following discussion took place:

Agency:

The Applicant is requested to provide the following:

1. For Study PDC 010-031:

   a. Tables similar to Tables 9, 11, and 12 on pages 2-128, 2-132, and 2-133 of Volume 2. The only difference is that the regression model should control for only one covariate: site.

   b. In addition, a table similar to Table 12 on page 2-133 with the logistic model before removal of site, i.e., the logistic model controlling for all baseline covariates: site, tinea versicolor duration, age, gender, race, and the baseline TSS score.

   c. In Table 10 on page 2-130, we need p-values in the primary efficacy analysis separately for the following subgroups: males, females, Caucasians, and non-Caucasians.

2. For Study PDC 010-032:

a. Tables similar to Tables 9, 11, and 12 on pages 5-093, 5-096, and 5-099 of Volume 5. The only difference is that regression model should control for only one covariate: site.

b. In addition, a table similar to Table 11 on page 5-096 with the logistic model before removal of site, i.e., the logistic model controlling for all baseline covariates: site, tinea versicolor duration, age, gender, race, and the baseline TSS score.

c. In Table 10 on page 5-095, we need p-values in the primary efficacy analysis separately for the following subgroups: males, females, Caucasians, and non-Caucasians.

3. The data could not be extracted from the SAS Datasets provided, please provide the appropriate methodology needed for extraction of the data.

Applicant:

On behalf of the Applicant, will provide the SAS Data via SAS for Windows, v. 6.12.

Agency:

4. Please provide a description of the SAS Dataset files content, i.e., which file contains the efficacy data, etc.

Applicant:

The Applicant agreed to provide the requested information in the near future.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

Teleconference Date: July 10, 2000 Time: 1130 Location: N225
Meeting ID # 5929

Follow-up to Pre-sNDA Meeting – Biostatistics Discussion - NDA 20-524, Mentax (butenafine hydrochloride) Cream, 1%

Indication: Tinea versicolor

Applicant: Bertek Pharmaceuticals, Inc.

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

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

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Mohamed Al-Osh, Ph.D., Acting Biostatistics Team Leader, DOBIV, HFD-725
Shiowjen Lee, Ph.D., Biostatistician, DOBIV, HFD-725
Joseph Porres, M.D., Ph.D., Medical Officer, DDDDP, HFD-540
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Mary Treuhaft, Ph.D., Vice President, Regulatory and Clinical Affairs
Barbara Brennan, B.S., Executive Director, Clinical Operations
Kathy Schmidt, Associate Director, Clinical Operations

Discussion:

With reference to the briefing package of March 17, 2000, the additional briefing material of March 23, 2000, and to the minutes of the April 17, 2000, teleconference, the Agency offered the following advice/recommendations concerning Action Item 1 from the aforementioned April 17, 2000, teleconference:

"Action Item:

A follow-up teleconference will be scheduled to discuss the multiplicity issues, which may arise as a result of having six secondary efficacy variables."

Agency:

1. The Agency is primarily interested in the following three endpoints:

   a. Proportion of subjects with complete cure for all lesions, where complete cure is defined as negative mycology plus total signs/symptoms score equal to 0.

   b. Proportion of subjects with negative mycology for all lesions.

c. Effective Treatment, defined as negative mycology plus total signs and symptoms ≤ 1 at day 56 which is that proportion of subjects with Investigator's Overall Assessment of Treatment Efficacy.

2. With reference to the Sponsor's previously proposed secondary endpoints, numbers 3, 4 and 5, i.e.,:

Agency:

These statements are not appropriate secondary endpoints since they are not relevant to the clinical setting or to the proposed labeling for this proposed supplemental NDA.

Sponsor:

The Sponsor proposed deleting the Clinical Studies Section of the proposed labeling for this supplemental NDA.

Agency:

The Agency suggested that the Sponsor propose a Clinical Studies Section for the labeling for this supplemental NDA.

Sponsor:

The Sponsor anticipates submitting this supplemental NDA in late July, 2000.

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/

Attachment/Handouts:
Briefing Package, dated March 17, 2000
Additional Briefing Material, dated March 23, 2000
Minutes of April 17, 2000, Teleconference

Teleconference Date: April 17, 2000 Time: 1300 Location: N225
Meeting ID # 5514

Pre-sNDA Meeting for NDA 20-524, Mentax (butenafine hydrochloride) Cream, 1%

Indication: Tinea versicolor

Applicant: Bertek Pharmaceuticals, Inc.

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

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

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Tony DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Ernie Pappas, Chemistry Reviewer, DNDCIII, HFD-830
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader DDDDP, HFD-540
Abi Adebowale, Ph.D., Biopharmaceutist, DPEIII, HFD-880
Sousan Altaie, Ph.D., Clinical Microbiology Reviewer, DAIDP, HFD-520
Susan Walker, M.D., Dermatology Team Leader, DDDDP, HFD-540
Brenda Vaughan, M.D., Medical Officer, DDDDP, HFD-540
Mohamed Al-Osh, Ph.D., Acting Biostatistics Team Leader, DOBIV, HFD-725
Shiowjen Lee, Ph.D., Biostatistician, DOBIV, HFD-725
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Mary Treuhaft, Ph.D., Vice President, Regulatory and Clinical Affairs
Barbara Brennan, B.S., Executive Director, Clinical Operations
Bhaskar Chaudhuri, Ph.D., Vice President and General Manager

Discussion:

With reference to the briefing package of March 17, 2000, and to the additional briefing material of March 23, 2000, the Agency offered the following advice/recommendations:

Chemistry, Manufacturing and Controls:

1. The formulation in the proposed NDA supplement should be the same as that currently approved (i.e., no changes are proposed).
2. The CMC in the proposed NDA supplement should be the same as that currently approved (i.e., no changes are proposed).
3. The technical sections of the package insert should be the same as those currently approved (i.e., no changes are proposed).

4. Due to the likelihood of an increased patient population and/or an increase in production, new Environmental Assessment calculations should be provided, which may support a claim for categorical exclusion.

Sponsor:

The Sponsor said that no changes are proposed to the CMC Sections of the currently marketed product.

Pharmacology/Toxicology:

No comments to convey at this time.

Biopharmaceutics:

No comments to convey at this time.

Clinical Microbiology:

Did the sponsor sample the lesions for microscopic examination using Wood's lamp directed search for areas of involvement? The Sponsor "yes". If so what is the reason for the variation observed in the KOH results in the example of line listing provided on page 145 of this submission. The Sponsor also recognized this variation.

Clinical:

1. Question 1 from Sponsor's March 17, 2000, Meeting Briefing Package: "Does the Agency agree that the results from the Phase 3 clinical studies, PDC 010-031 and PDC 010-032 constitute strong support for approval of the supplemental efficacy application (SNDA) for once daily, two-week treatment of tinea versicolor?"

Agency:

Adequacy of results of clinical trials in support of an NDA approval is a review issue. The Agency recommends that safety and efficacy be demonstrated with two independent, multicenter, randomized, double-blind, parallel group, vehicle controlled clinical studies, for a new indication of an approved drug product. It appears that the Sponsor has planned accordingly.

2. Question 2 from Sponsor's March 17, 2000, Meeting Briefing Package: "Are there any particular review issues identified at this time?"

Agency:

Pooled data are useful for evaluation of safety. Efficacy data from the two pivotal Phase 3 studies are not pooled to demonstrate statistical significance in support of approval. Confirmation of statistical superiority for efficacy from independent trials is generally sought.

3. Question 3 from Sponsor's March 17, 2000, Meeting Briefing Package: "Are the contents of the SNDA as detailed in the Draft Index to the Application acceptable?"

Agency:

a. Sponsor's March 17, 2000, Meeting Briefing Package, pg.14 and pg. 160, Section 4, Analysis Population, 4.2 and 4.3: The sponsor makes a distinction between Regulatory MITT and Labeling MITT populations. The label of drug products should reflect the conduct of the clinical trials and analyses used to demonstrate safety and efficacy that supported approval; thus, the same populations used for approval would be described in the label of the approved drug product. There is no known Regulatory MITT Population.

b. The Intent-to-Treat Population (ITT) and the MITT Population for this application are the same populations. since a positive KOH was required prior to randomization and there were no pending positive culture results needed for study continuation.

4. Question 4 from Sponsor's March 17, 2000, Meeting Briefing Package: "Are there any comments or requests regarding the proposed tables or line listings for the clinical study reports for the pivotal Phase 3 studies, PDC 010-031 and PDC 010-032?"

Agency:

a. Please add "outcome" group data for each visit, especially the final visit, (e.g., complete cure, effectively treated, dropout) for both all treated lesions and all target lesions.

b. Also provide a sort by "effectively treated" (as defined on pg. 60 of the Sponsor's March 17, 2000, Meeting Briefing Package) listing by patients, treatment, and site.

5. Question 5 from Sponsor's March 17, 2000, Meeting Briefing Package: "Are there any comments or requests regarding the proposed tables for the ISS and ISE?"

Agency:

a.

For example, (pg.237) Appendix B.7.4 and B.7.5 provides safety analysis for patients to age 56 and greater than age 56 respectively. We would like to see analyses for those subjects > 56 years of age and those subjects aged 65 and older.

a. Provide on-treatment summary of All Adverse Events by Treatment and Body System [Number (%) of Patients] Safety Population without respect to causality or severity.

6. Question 6 from Sponsor's March 17, 2000, Meeting Briefing Package: "Is the following plan for electronic components of the SNDA acceptable?"

Agency:

Acceptable.

7. Question 8 from Sponsor's March 17, 2000, Meeting Briefing Package: "No case report tabulations (line listings for efficacy data by subject) will be provided beyond those provided in the clinical study reports. See pg. 145, Appendix D.7.2, for an example. Is this acceptable?"

Agency:

Acceptable.

8. Question 9 from Sponsor's March 17, 2000, Meeting Briefing Package: "CRF for deaths, other serious adverse experiences and for discontinuations due to adverse experiences will be provided as appendices in the clinical study reports. No other case report forms will be provided. Is this acceptable."

Agency:

In addition to the above, please provide the following:

a. CRF for all drop-outs

b. A copy of a blank CRF

c. Include a copy of each protocol with all amendments in the study report section instead of as an appendix

d. Index the investigators, appendices, tables, etc. for ease of location during review

Agency:

9. Additional clinical comment:

Since recurrences can be expected, this drug product can be expected to be used chronically with repeat intermittent use for longer than six months.

The sponsor is referred to the ICH-E1A Guidance Document. The sponsor should follow ICH-E1A Guideline for Industry (The Extent of Population Exposure to Assess Clinical Safety: for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions) on sample size for patients on active drug in trials to demonstrate safety.

10. The Sponsor said that they would provide a copy of each finalized protocol, the final study reports and the proposed labeling in MS Word.

Biostatistics:

1. Question 2 from Sponsor's March 17, 2000, Meeting Briefing Package: "Are there any particular review issues identified at this time?

Agency:

a. According to the regulation, efficacy should be established from two independent, adequate and well-controlled multicenter trials. The use of the pooled study (combined two studies) is not recommended for efficacy assessment or does not constitute independent evidence to support efficacy claims.

b. An adjustment in the significance level for multiplicity might need to be considered.

2. Question 4 from Sponsor's March 17, 2000, Meeting Briefing Package: "Are there any comments or requests regarding the proposed tables or line listings for the clinical study reports for the pivotal Phase III studies, PDC010-031 and PDC010-032?

Agency:

Inferential statistics for subgroup data display (by center, age, gender and race) should be included.

3. Question 6, Bullet 1, from Sponsor's March 17, 2000, Meeting Briefing Package: "Is the following plan for electronic components of the SNDA acceptable?"

- "SAS data sets and efficacy analysis programs in SAS v.6.12 along with Data Management User Guides for the pivotal Phase III clinical studies PDC010-031 and PDC010-032 and for PDC010-031 and PDC010-032 combined."

Agency:

The listed components in the electronic form seem to be acceptable. The sponsor is also recommended to provide code description used in SAS data sets.

4. Question 8 from Sponsor's March 17, 2000, Meeting Briefing Package: "No case report tabulations (line listing of efficacy data by subject) will be provided beyond those provided in the clinical study reports. See Pg. 145, Appendix D.7.2, for an example. Is this acceptable?

Agency:

The line listing of efficacy data by subject shown in the example on pg. 145, Appendix D.7.2, seems to be acceptable.

Divisional Comments:

1. Pediatric Rule:

   The Applicant was reminded of the following:

   The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, effective April 1, 1999, requires the following:

   Per 21CFR 314.50(d)(7), NDA applications are required to contain "A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under Section 314.55."

2. Financial Disclosure:

   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.

   Sponsor:

   The Sponsor queried the Agency on the necessity of submitting a form for the Financial Disclosure requirements of an NDA Applicant.

3. Labeling:

   If the Applicant has an Information for Patients leaflet/labeling, please submit it with the proposed supplemental NDA. The Sponsor should also submit the Carton/Container labeling for the proposed supplemental NDA.

Action Items:

1. A follow-up teleconference will be scheduled to discuss the multiplicity issues, which may arise as a result of having six secondary efficacy variables.

2. The Project Manager will discuss the form to be used for financial disclosure with the Sponsor.

Signature, minutes preparer: /S/
Concurrence Chair (or designated signatory): /S/
Attachment/Handouts:
Briefing Package, dated March 17, 2000
Additional Briefing Material, dated March 23, 2000