

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-408

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

1.7 Patent Certification

Bertek Pharmaceuticals Inc. certifies that pursuant to 21 CFR 314.53 the following is an accurate account of all patents containing the listed drug substance, butenafine hydrochloride:

<u>Patent number</u>	<u>Patent Holder</u>	<u>Type of Patent</u>	<u>Exp.</u>
5,021,458	Kaken Pharmaceuticals	Composition	6/4/08
5,106,866	Kaken Pharmaceuticals	Composition	4/21/09

To the best of our knowledge, there are no patents on the formulation or method of use for the drug product, Mentax® -TC (butenafine HCl) Cream, 1% that is the subject of this NDA.

Signed:

Sherron P. Wiechert
Sherron P. Wiechert, RAC

Title:

Director of Regulatory Affairs

Date:

December 7, 2001

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

EXCLUSIVITY SUMMARY for NDA # 21-408 SUPPL #
Trade Name MENTAX®-TC Cream, 1% Generic Name butenafine HCl
Applicant Name Bertek Pharmaceuticals, Inc. HFD- 540
Approval Date

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 / X / NO / /
b) Is it an effectiveness supplement? YES / / NO / X /

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

- 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.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

- d) Did the applicant request exclusivity?

YES / / NO / X /

**APPEARS THIS WAY
ON ORIGINAL**

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

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

2

YES /___/ NO /___/

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 /X/ NO /___/

If yes, NDA # 20-524/SE1-005

Name Mentax (butenafine HCl) Cream, 1%

This new formulation of Mentax has the same active ingredient, butenafine HCl, but has additional inactive ingredients for which the Applicant is requesting 3 years exclusivity.

The clinical investigations submitted in the application that are essential to the approval are:

Investigation #1, Study # PDC 010-033

Investigation #2, Study # PDC 010-036

Both investigations were conducted under this Applicant's (Bertek's) own IND 60,471. Said investigations have not been relied on by the agency to demonstrate the effectiveness of a previously approved drug product.

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 /___/

**APPEARS THIS WAY
ON ORIGINAL**

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 /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

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 /___/

**APPEARS THIS WAY
ON ORIGINAL**

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____
NDA # _____
NDA # _____

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /___/ 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.

APPEARS THIS WAY
ON ORIGINAL

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 /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (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 /___/ 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 /___/

If yes, explain: _____

(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 /___/ NO /___/

If yes, explain: _____

(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, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (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?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

- (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"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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?

Investigation #1	!	
IND # _____ YES /___/	!	NO /___/ Explain: _____
	!	_____
	!	_____
	!	_____
Investigation #2	!	
IND # _____ YES /___/	!	NO /___/ Explain: _____
	!	_____
	!	_____
	!	_____

- (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?

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
	!	
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
	!	

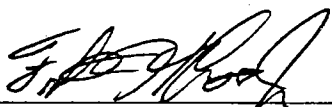
APPEARS THIS WAY
ON ORIGINAL

- (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_/

If yes, explain: _____



Signature of Preparer
Title: Project Manager

10/3/02
Date



Signature of ~~Office of~~ Division Director

10/9/02
Date

CC:

Archival NDA 21-408
HFD-540/Division File
HFD-540/Cross
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-408 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: December 17, 2002 Action Date: October 17, 2002

HFD -540 Trade and generic names/dosage form: MENTAX®-TC (butenafine HCl) Cream, 1%

Applicant: Bertek Pharmaceuticals, Inc. Therapeutic Class: Antifungal

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

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

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ☒ Partial Waiver ☐ Deferred ☒ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____

Max _____ kg _____ mo. _____ yr. 11 Tanner Stage _____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☒ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. Adult Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Frank Cross Jr.
Regulatory Project Manager

cc: NDA 21-408

HFD-950/ Terrie Crescenzi

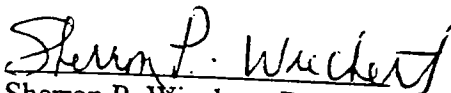
HFD-960/ Grace Carmouze

(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

1.4 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.


Sherron P. Wiechert, RAC
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Authorization

Field Copy Certification

Patent Certification

FDA Financial Disclosure
Forms - FDA 3454

Pediatric Patients -
Request for Waiver

BEST POSSIBLE COPY



OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

AN NDA 21-408 Drug: MENTAX®-TC (butenafine HCl) Cream, 1% Applicant: Bertek Pharmaceuticals Inc. Type: 3
PM: Cross Phone: 827-2020 HFD- 540
USER FEE GOAL DATE: 10/17/02 DATE CHECKLIST COMPLETED: 10/17/02

Arrange package in the following order (include a completed copy of this CHECKLIST): Check or Comment

1. ACTION LETTER with supervisory signatures
Are there any Phase 4 commitments? AP X AE
Yes No
2. Have all disciplines completed their reviews?
If no, what review(s) is/are still in draft? Yes X No
3. LABELING (package insert and carton and container labels).
(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.) Draft
Revised Draft
Final X
4. PATENT INFORMATION X
5. EXCLUSIVITY CHECKLIST X
6. PEDIATRIC PAGE (all NDAs) X
7. DEBARMENT CERTIFICATION
(Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). X
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
If no audits were requested, include a memo explaining why. X
9. REVIEWS & MEMORANDA:
DIVISION DIRECTOR'S MEMO | If more than 1 review for any
GROUP LEADER'S MEMO | 1 discipline, separate reviews
MEDICAL REVIEW | with a sheet of colored paper. 10/10/02 (2)
SAFETY UPDATE REVIEW | Any conflicts between reviews
STATISTICAL REVIEW | must have resolution documented 7/24/02
BIOPHARMACEUTICS REVIEW 7/3/02
PHARMACOLOGY REVIEW (Include pertinent IND reviews)
Statistical Review of Carcinogenicity Study(ies) 7/21/02, (Primary) 7/21/02 (TL), 10/17/02
CAC Report/Minutes N/A
CHEMISTRY REVIEW N/A
ODS Review Memorandum 10/15/02, 10/15/02 (T/L)
Date EER completed 10/10/02
FUR needed N/A FUR requested
Have the methods been validated? Yes (attach) No X
Environmental Assessment Review /FONSI 10/15/02
CMC MICROBIOLOGY REVIEW 8/12/02
CLINICAL MICROBIOLOGY REVIEW 6/10/02
What is the status of the monograph? N/A
10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes X
11. MINUTES OF MEETINGS
Date of End-of-Phase 2 Meeting: None
Date of pre-NDA Meeting: 5/21/02
12. ADVISORY COMMITTEE MEETING MINUTES
or, if not available, 48-Hour Info Alert or pertinent section of transcript. Minutes Info Alert
Transcript No mtg X

APPEARS THIS WAY
ON ORIGINAL

15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)

_____X_____

16. INTEGRATED SUMMARY OF SAFETY (from NDA)

_____X_____

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 17, 2002 Number of Pages (including cover sheet) - 4

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: Please find attached to this facsimile transmission our minutes of our October 10, 2002, Pharmacology/Toxicology teleconference for your NDA 21-408, MENTAX®-TC (butenafine HCl) Cream, 1%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Teleconference Date: October 10, 2002
Meeting ID#

Time: 1730

Location: N212

NDA 21-408, TRADEMARK® (butenafine HCl) Cream, 1%

Indication: Tinea versicolor

Applicant: Bertek Pharmaceuticals, Inc.

Pharmacology/Toxicology Discussion of Proposed Phase 4 Commitment

Meeting Chair: Abby Jacobs, Ph.D.,

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

FDA Attendees, titles and offices:

Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540

Paul Brown, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540

Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Jim Sherry, M.D., Ph.D., Vice President, Clinical Research, Mylan Pharmaceutical, Inc.

Bruce Bottini, Ph.D., Clinical Research, Mylan Pharmaceuticals, Inc.

Jeffrey Smith, Ph.D., Pharmacologist/Toxicologist, Bertek Pharmaceuticals, Inc.

Andrea B. Miller, R.Ph., Esq., Director, Regulatory Affairs, Bertek Pharmaceuticals, Inc

Sherron Weichert, R.A.C., Director, Regulatory Affairs, Bertek Pharmaceuticals, Inc

Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs

Background:

The purpose of this teleconference was to discuss Agency's proposed Non-Clinical Toxicology Phase 4 Commitment for this NDA.

Agency:

After much discussion, the following Phase 4 Non-Clinical Toxicology Commitment was verbally conveyed to the Applicant to be followed up by a facsimile transmission of the same.

"A Phase 4 study should be conducted to address the concern of whether the drug product can alter the production of UV-induced skin tumors. To satisfy this need, you may propose and conduct either a photocarcinogenicity study in hairless mice or a short-term study that evaluates markers of UV-induced skin damage. Either animal or human models may be acceptable. Markers of UV induced damage that may be appropriate endpoints could include, but are not limited to, MED, thymine dimers or p53 levels. A protocol should be submitted to the relevant IND for review and concurrence prior to study initiation.

This recommendation is consistent with Division and CDER practice for a topical drug product used on sun exposed skin for a chronic intermittent indication. Please

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

refer to the Pharmacology/ Toxicology draft guidance on Photosafety Testing on the CDER website (<http://www.fda.gov/cder/guidance/index.htm>).

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of
the approval of the protocol

Final Report
Submission: Within 12 months after the study
completion."

Agency:

The Agency informed the Applicant that any findings (from the proposed Phase 4 Non-Clinical Toxicology study) indicative of UV damage would be a matter of labeling and would not result in Agency's request for the Applicant to conduct a photocarcinogenicity study

Applicant:

The Applicant agreed to respond to the Agency's proposed Phase 4 Commitment by October 15, 2002.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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

/s/

Abby Jacobs

10/16/02 12:15:58 PM

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 17, 2002 Number of Pages (including cover sheet) - 3

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: Please find attached to this facsimile transmission our minutes of our September 20, 2002, CMC teleconference for your NDA 21-408, MENTAX®-TC (butenafine HCl) Cream, 1%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE

Teleconference Date: September 20, 2002
Meeting ID# 9285

Time: 1320

Location: N225

NDA 21-408, MENTAX®-TC (butenafine HCl) Cream, 1%

Indication: Tinea versicolor

Applicant: Bertek Pharmaceuticals, Inc.

CMC Discussion

Meeting Chair: Wilson DeCamp, Ph.D.

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

FDA Attendees, titles and offices:

Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830

Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs

Agency:

1. The Agency requested that revised carton/container labeling be submitted with the approved trademark, Mentax®-TC.
2. In addition, the Agency requested that the established name only appear in the parentheses on the all labeling, *i.e.*, the dosage form, "cream" should be deleted. The rationale for this request is that only established names (*e.g.*, USAN, USP monograph titles) should appear in the parentheses.
3. As previously requested during the July 19, 2002, teleconference, please submit UV-visible absorption spectra (— nm) for the — new degradation products.

Applicant:

The Applicant agreed and will make the requested submissions in the near future.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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

/s/

Frank Cross
9/20/02 04:10:16 PM
CSO

Wilson H. DeCamp
9/20/02 04:47:50 PM
CHEMIST
concur

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 17, 2002 Number of Pages (including cover sheet) - 4

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: Please find attached to this facsimile transmission our minutes of our July 19, 2002, teleconference for your NDA 21-408, MENTAX®-TC (butenafine HCl) Cream, 1%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Teleconference Date: July 19, 2002
Meeting ID# 9415

Time: 1115

Location: N225

NDA 21-408, TRADEMARK® (butenafine HCl) Cream, 1%

Indication: Tinea versicolor

Applicant: Bertek Pharmaceuticals, Inc.

CMC, Pharmacology/Toxicology Discussion

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
Wilson 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
Kumar Mainigi, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Brenda Carr, M.D., Medical Reviewer, DDDDP, HFD-540
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Walter Owens, Director, Product Development, Mylan Pharmaceuticals, Inc.
Sherron Weichert, R.A.C., Director, Regulatory Affairs
Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs

Agency:

Chemistry, Manufacturing and Controls:

1. Please submit UV-visible absorption spectra (— , nm) for the — new degradation products.
2. The TRADEMARK® (butenafine HCl) Cream, 1%, specifications contained — new degradation products than those reported for Mentax Cream. They are —
Acceptance criteria for the individual degradation products were proposed at — of butenafine HCl, respectively. In this regard, the Applicant is advised to qualify these impurities as per ICH guidance titled "Guidance for Industry -Q3B Impurities in New Drug Products (1996)."
3. It is recommended that — expiration date be proposed for the drug product instead of the — expiration date as proposed in the NDA. The reason for this request is because the stability studies (Lot # PEGF-2) revealed these degradation products at levels of — of butenafine HCl after —
By lowering the expiration to — , the Agency could approve the NDA without qualification data at this time. However, if a higher expiration date is required than —
— an approvable action would be granted with a Phase 4 commitment to submit supporting data to qualify these impurities.
4. In addition, the following CMC deficiencies were noted in the NDA:
 - a. The TRADEMARK® (butenafine HCl) Cream, 1%, specifications failed to include —
Please submit — , when available.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

- b. The specifications were found to be higher for — impurities — than those reported in the specifications for Mentax Cream (NDA 20-524), please justify.
- c. Please give the reason for the — new degradation products appearing at — of storage.
- d. Please indicate if the TRADEMARK® (butenafine HCl) Cream, 1%, specifications are your regulatory specifications for both the release and stability of the finished dosage product.
- e. The NDA failed to include a typical C.O.A., for the drug product.
- f. The NDA failed to include the vendors' COAs for the inactive ingredients.

Pharmacology/Toxicology:

1. The degradants that were present in earlier formulations are considered to be qualified per ICH Q3B.
2. — should be qualified before a shelf life of greater than — is approved.
3. For a shelf life of greater than —, the Sponsor should propose how it will qualify the degradants —.
4. Toxicities of interest for — include genotoxicity, contact sensitization, and general and dermal toxicity after repeated dose application (e.g., 28 days). Results of these studies will determine the need for further studies.

Agency:

The Applicant has three options:

1. Receive an Approvable letter for NDA 21-408 as it stands, with the deficiency being the Pharmacology/Toxicology data qualifying the — degradation products, and thus allowing the Agency to set the acceptance criteria for the Applicant.
2. Accept a reduction in expiry to — for NDA 21-408 to receive an Approval Letter, with a Pharmacology/Toxicology commitment (phase 4?) to submit the qualification data for —. The Applicant may then submit a prior approval SCE supplement to extend the expiration date.
2. The Applicant agrees to amend its product release and stability specification for NDA 21-408 to state the acceptance criteria for — as —. The Applicant receives an Approval Letter with the current expiration of —. The Agency can make the Pharmacology/Toxicology qualification data an information request, but not a Phase 4 commitment. However, until the Agency receives the data, the Applicant will not be able to change the product specification for NDA 21-408.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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

/s/

Jonathan Wilkin
10/17/02 11:12:46 AM

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 17, 2002 Number of Pages (including cover sheet) – 1

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs

COMPANY: Bertek Pharmaceuticals, Inc.

FAX #: 919-993-5910

MESSAGE: From our Biopharmaceutics review of your NDA 21-408, Mentax-TC (butenafine HCl) Cream, 1%, we have the following Biopharmaceutics Information Request:

“The sponsor is encouraged to develop an *in vitro* drug release test method and test specification for the Mentax®-TC cream.”

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR

TITLE: Senior Regulatory Management Officer

PHONE #: 301-827-2063

FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 17, 2002 Number of Pages (including cover sheet) - 17

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: Please find attached to this facsimile transmission a copy of our Action Letter for your NDA 21-408, MENTAX®-TC (butenafine HCl) Cream, 1%:

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Tuesday, October 15, 2002 11:36 AM
To: Jacobs, Abigail (Abby) C
Subject: RE: NDA 21-408, MENTAX - TC Pharm/Tox Phase 4 Commitment

Thanks, Abby.

Frank

-----Original Message-----

From: Jacobs, Abigail (Abby) C
Sent: Tuesday, October 15, 2002 11:34 AM
To: Cross Jr, Frank H
Subject: RE: NDA 21-408, MENTAX - TC Pharm/Tox Phase 4 Commitment

I concur with the final wording.

Abby

-----Original Message-----

From: Cross Jr, Frank H
Sent: Tuesday, October 15, 2002 11:33 AM
To: Jacobs, Abigail (Abby) C
Subject: NDA 21-408, MENTAX - TC Pharm/Tox Phase 4 Commitment

Hi Abby,

Here is the final wording that we discussed late last week for the proposed Phase 4 Commitment for this NDA.

Please let me know your concurrence.

Thanks,

Frank

"A Phase 4 study should be conducted to address the concern of whether the drug product can alter the production of UV-induced skin tumors. To satisfy this need, you may propose and conduct either a photocarcinogenicity study in hairless mice or a short-term study that evaluates markers of UV-induced skin damage. Either animal or human models may be acceptable.

Markers of UV induced damage that may be appropriate endpoints could include, but are not limited to, MED, thymine dimers or p53 levels. A protocol should be submitted to the relevant IND for review and concurrence prior to study initiation.

This recommendation is consistent with Division and CDER practice for a topical drug product used on sun exposed skin for a chronic intermittent indication. Please refer to the Pharmacology/ Toxicology draft guidance on Photosafety Testing on the CDER website (<http://www.fda.gov/cder/guidance/index.htm>).

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval

Cross Jr, Frank H

To: Jacobs, Abigail (Abby) C
Cc: Kozma-Fornaro, Mary J; Wilkin, Jonathan K
Subject: RE: NDA 21-408, Phase 4 Commitment - Applicant's Acceptance Letter

Thanks, Abby.

Frank

-----Original Message-----

From: Jacobs, Abigail (Abby) C
Sent: Wednesday, October 16, 2002 7:13 AM
To: Cross Jr, Frank H
Subject: RE: NDA 21-408, Phase 4 Commitment - Applicant's Acceptance Letter

Their qualification is what we told them. Furthermore, it is true that we will not ask for them to conduct a photocarcinogenicity study if they conduct an adequate alternative study.

-----Original Message-----

From: Cross Jr, Frank H
Sent: Tuesday, October 15, 2002 6:01 PM
To: Jacobs, Abigail (Abby) C
Subject: NDA 21-408, Phase 4 Commitment - Applicant's Acceptance Letter

Hi Abby,

In the last sentence, paragraph 2, page 2 of the attached letter the Applicant has qualified their acceptance of our proposed Phase 4 Commitment.

Is this qualification acceptable?

I do not believe that we can qualify Phase 4 Commitments.

Please let me know.

Thanks,

Frank



Untitled.pdf

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 15, 2002

TO: Jonathan K. Wilkin, M.D.

FROM: Wilson H. DeCamp, Ph.D.

SUBJECT: Team Leader's Addendum to Chemistry Review #1
NDA 21-408, Mentax TC (butenafine HCl) Cream

At our DNDCIII team leaders meeting last Thursday, Chi-Wan asked that I assure that a few additional issues with regard to the impurities are adequately discussed in this review. This memorandum covers these three issues, as follows:

1. Did the new impurities (which prompted our 7/19 telecon with Bertek that resulted in their reduction of the expiration dating) require qualification and/or identification per Q3B?

The labeling (package insert) contains no express limitation on the amount of Mentax TC to be used per day; however, there is a statement that "Efficacy at greater than 12 g/day has not been established." If we take that as the maximum daily exposure, then 12 gms of a 1% cream implies a daily exposure of 120 mg. At this level of exposure to the drug, the reporting threshold for degradation products is —, the identification threshold is —, and the qualification threshold is —. The latter two levels correspond to a total daily exposure of —.

2. Were there other issues about these impurities that prompted the pharm/tox concerns?

The following issues were raised by the Supervisory Pharmacologist for the telecon of July 19:

1. The degradants that were present in earlier formulations are considered to be qualified per ICH Q3B.
2. — should be qualified before a shelf life of greater than — is approved.
3. For a shelf life of greater than — the sponsor should propose how it will qualify the degradants —.
4. Toxicities of interest for these aldehydes include genotoxicity, contact sensitization, and general and dermal toxicity after repeated dose application (e.g., 28 days). Results of these studies will determine the need for further studies.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

3. Were the impurities of known structure?

The impurities _____ were known as potential degradants.

Therefore, it appears that the recommendation that the expiration dating be reduced to _____ until the impurities was technically sound and supported by applicable guidances.

In addition, Review #1, as entered into DFS, shows (pg. 49) that the CGMP inspections are incomplete. An overall evaluation of "Acceptable" has been received (SFerguson, 10/10/02). The application may be approved.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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

/s/

Wilson H. DeCamp
10/15/02 06:20:48 PM
CHEMIST
TL addendum per request

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



Bertek Pharmaceuticals Inc.

NDA 21-408

Mentax®-TC (butenafine HCl) Cream, 1%

**Amendment 023: Response to FDA Facsimile Transmission
Dated 10/11/02 – Post-Marketing Commitment
for the Drug Product**

P.O. Box 14149 ♦ Research Triangle Park, NC 27709

Submitted October 15, 2002

FDA Archive Copy

October 15, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

**RECEIVED
OCT 16 2002
MEGA/CDER**

**RE: Mentax® - TC (butenafine HCl) Cream, 1%
NDA #21-408, Amendment 023
Response to FDA Facsimile Transmission Dated 10/11/02
Post Marketing Commitment for the Drug Product**

Dear Dr. Wilkin:

Reference is made to NDA 21-408 for Mentax®-TC (butenafine HCl) Cream, 1% submitted to FDA on December 14, 2001. Reference is also made to the FDA facsimile transmission received October 9, 2002, the two FDA facsimile transmissions received October 10, 2002, the FDA-Sponsor teleconferences on October 10 and the FDA facsimile transmission dated October 11, 2002, which pertained to the FDA's request for a non-clinical toxicology post marketing commitment.

The purpose of this amendment is to notify FDA that the Sponsor agrees to accept the requested post marketing commitment for Mentax®-TC (butenafine HCl) Cream, 1%. It is the Sponsor's understanding that this post marketing commitment may be satisfied by conducting a short-term human or animal study (i.e., one to two weeks) that evaluates markers of UV-induced skin tumors (i.e., MED, thymine dimers or p53 levels). The Sponsor acknowledges that the protocol for such a study will need to be submitted within four months of the approval date of the NDA and subsequently reviewed and approved by the Division. Once the Division approves the protocol, the study must commence within six months of the protocol approval date. In addition, it is the Sponsor's understanding that any findings indicative of UV damage would be a matter of labeling and would not be a precursor to a photocarcinogenicity study.

It is the Sponsor's belief that this amendment completes the Sponsor response to all outstanding issues related to the approval of this NDA and we look forward to receiving an "approval" letter from FDA in the near future.

**APPEARS THIS WAY
ON ORIGINAL**

Jonathan Wilkin, MD
Page 2 of 2

This amendment is being submitted in duplicate with a completed Form FDA 356h. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5913.

Sincerely,

Charity M. Schuller

Charity Metz Schuller, Pharm.D.
Senior Associate
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 11, 2002 Number of Pages (including cover sheet) – 31

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs

COMPANY: Bertek Pharmaceuticals, Inc.

FAX #: 919-993-5910

MESSAGE: For your review and comments, please find attached to this facsimile transmission our labeling for your NDA 21-408, MENTAX®-TC (butenafine HCl) Cream, 1%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR

TITLE: Senior Regulatory Management Officer

PHONE #: 301-827-2063

FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



BEST POSSIBLE COPY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 11, 2002 Number of Pages (including cover sheet) - 2

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: "Please commit to the following Post Marketing Commitment for your NDA 21-408, MENTAX®-TC (butenafine HCl) Cream, 1%:

A Phase 4 study should be conducted to address the concern of whether the drug product can alter the production of UV-induced skin tumors. To satisfy this need, you may propose and conduct either a photocarcinogenicity study in hairless mice or a short-term study that evaluates markers of UV-induced skin damage. Either animal or human models may be acceptable. Markers of UV induced damage that may be appropriate endpoints could include, but are not limited to, MED, thymine dimers or p53 levels. A protocol should be submitted to the relevant IND for review and concurrence prior to study initiation.

This recommendation is consistent with Division and CDER practice for a topical drug product used on sun exposed skin for a chronic intermittent indication. Please refer to the Pharmacology/ Toxicology draft guidance on Photosafety Testing on the CDER website (<http://www.fda.gov/cder/guidance/index.htm>).

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 12 months after the study completion.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-408
MENTAX®-TC (butenafine HCl) Cream, 1%:
Facsimile Transmission of Post Marketing Commitment
Page 2

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0338 Expiration Date: March 31, 2003 See OMB Statement on page 2.	
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE (Title 21, Code of Federal Regulations, 314 & 601)		FOR FDA USE ONLY	
		APPLICATION NUMBER	
APPLICANT INFORMATION			
NAME OF APPLICANT Bertek Pharmaceuticals Inc.		DATE OF SUBMISSION October 11, 2002	
TELEPHONE NO. (include Area Code) 919-981-9800		FACSIMILE (FAX) Number (include Area Code) 919-993-5913	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Post Office Box 14149 Research Triangle Park, NC 27709-4149		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A	
PRODUCT DESCRIPTION			
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-408			
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) butensine HCl cream, 1%		PROPRIETARY NAME (trade name) IF ANY Mentax® -TC Cream, 1%	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine hydrochloride		CODE NAME (if any) KP-363	
DOSAGE FORM Cream	STRENGTHS 1%	ROUTE OF ADMINISTRATION Topical	
(PROPOSED) INDICATION(S) FOR USE: Tinea versicolor			
APPLICATION INFORMATION			
APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.60) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.84) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 605 (b)(1) ☐ 505 (b)(2)			
IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____			
TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER			
IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)			
REASON FOR SUBMISSION Response to FDA request concerning carton and tube labels (Amendment 021)			
PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED		THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC	
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (construction sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/Testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.			
Cross References (list related License Applications, INDs, NDAs, PMAs, 610(k)s, IDEs, BMFs, and DMFs referenced in the current application)			
RM FDA 356h (4/00)			

APPEARS THIS WAY
ON ORIGINAL

RECEIVED

OCT 15 2002 PAGE 1

BEST POSSIBLE COPY

This application contains the following items: (Check all that apply)

- ☒ 1. Index
- ☒ 2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
- ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
- ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
- ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (f)(2)(A))
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(l)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER (Specify) Cover letter, diskette and Form FDA 356h

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 680 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

TYPED NAME AND TITLE

DATE

Sharon P. Wiechert, RAC
Director, Regulatory Affairs

October 11, 2002

ADDRESS (Street, City, State, and ZIP Code)

Post Office Box 14149

Research Triangle Park, NC 27709-4149

TELEPHONE NUMBER

919-991-9878

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services

Food and Drug Administration

OER, HFM-99

1 Rockville Pike

Rockville, MD 20852-1448

FORM FDA 356h (4/00)

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.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



P.O. Box 14149 • Research Triangle Park, NC 27709-4149 USA • (919) 991-9800 • (888) 5-BERTEK

October 11, 2002

RECEIVED
OCT 15 2002
CDR/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: Mentax[®] - TC (butenafine HCl) Cream, 1%
NDA #21-408, Amendment 021
Response to FDA Telephone Conversation on October 7, 2002

Dear Dr. Wilkin:

Reference is made to an October 7, 2002 telephone conversation between Commander Frank Cross and Sherron Wiechert, Bertek Pharmaceuticals Inc. Commander Cross requested that the Sponsor provide the Agency with electronic copies of the Sponsor's proposed trade dress for the immediate labels and unit cartons with the trade name "Mentax[®] - TC" as submitted on September 23, 2002 (Amendment #018). Enclosed in this submission is a diskette containing a true and exact copy of the Sponsor's proposed carton and tube labels for the _____ 15-g and 30-g packaging sizes as submitted in Amendment #018.

This amendment is being submitted in duplicate with a completed Form FDA 356h. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5913.

Sincerely,

A handwritten signature in cursive script, reading 'Charity Metz Schuller'.

Charity Metz Schuller, Pharm.D.
Senior Associate, Regulatory Affairs

Enclosure

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

BEST POSSIBLE COPY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 9, 2002 Number of Pages (including cover sheet) - 1

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: Please commit to the following Post Marketing Commitment for your NDA 21-408, MENTAX®-TC (butenafine HCl) Cream, 1%:

A Phase 4 study should be conducted to evaluate the
This would be consistent with Division and CDER practice and CDER guidance for a chronic intermittent indication.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 12 months after the study completion

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

APPEARS THIS WAY
ON ORIGINAL

Cross Jr, Frank H

From: Jacobs, Abigail (Abby) C
Sent: Wednesday, October 09, 2002 11:12 AM
To: Cross Jr, Frank H
Subject: N21408 bz of 9/9/02 butenafine cream

Frank,

In this submission, the sponsor agrees with the pharm/tox comments, to qualify the excipients _____ and to discuss the details with the FDA before seeking approval of a shelf-life of more than _____

Abby

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



DUPLICATE

P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

October 7, 2002

^{BL}
ORIG AMENDMENT

RECEIVED
OCT 08 2002
MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products •
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: **Mentax® - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 020
Response to FDA Facsimile Transmission Dated 10/2/02
Proposed Final Labeling for Drug Product

Dear Dr. Wilkin:

Reference is made to NDA 21-408 for Mentax®-TC (butenafine HCl) Cream, 1% submitted to FDA on December 14, 2001, the FDA facsimile transmission received July 2, 2002, the Sponsor's response to the July 2, 2002 facsimile dated August 30, 2002 and the FDA facsimile transmission dated October 2, 2002, which contained the FDA proposed final labeling for the drug product.

The purpose of this amendment is notify FDA that the Sponsor agrees to accept the exact wording proposed by FDA in the October 2, 2002 facsimile for the package insert, immediate labels and unit cartons for Mentax®-TC (butenafine HCl) Cream, 1%. Twelve copies of each piece of labeling will be submitted to FDA, as required, in a subsequent submission.

We believe that this amendment completes the Sponsor response to all outstanding issues related to the approval of this NDA and we look forward to receiving an "approval" letter from FDA in the near future.

If you have any questions related to this amendment, please contact me directly at (919) 991-9878.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Sherron P. Wiechert, RAC
Director of Regulatory Affairs and Quality Assurance

BEST POSSIBLE COPY

6 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ ✓ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 2, 2002 Number of Pages (including cover sheet) – 22

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: For your review and comments, please find attached to this facsimile transmission our labeling for your NDA 21-408, MENTAX®-TC (butenafine HCl) Cream, 1%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

September 26, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED
SEP 27 2002
MEGA/CDER

NDA 019C AMENDMENT

BC

RE: Mentax[®] - TC (butenafine HCl) Cream, 1%
NDA #21-408, Amendment 019
Response to FDA Facsimile Transmission Dated 7/18/02

Dear Dr. Wilkin:

Reference is made to NDA 21-408 for Mentax[®]-TC (butenafine HCl) Cream, 1% submitted to FDA on December 14, 2001, and the FDA facsimile transmission dated July 18, 2002, which contained the reviewer's preliminary notes in preparation for an FDA-requested teleconference to be scheduled between the Sponsor and the Division's Review Team. This teleconference was conducted on July 19, 2002. Reference is also made to the response to the FDA facsimile that was submitted by the Sponsor on September 6, 2002.

The purpose of this amendment is to provide the UV-visible absorption spectra _____ nm) for the _____ new degradation products, _____
_____ These scans were not available at the time of the amendment on September 6, 2002.

We believe that this amendment completes the Sponsor response to the FDA facsimile transmission dated July 18, 2002.

If you have any questions related to this amendment, please contact me directly at (919) 991-9878.

Sincerely,

Sherron P. Wiechert

Sherron P. Wiechert, RAC
Enclosures

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

BEST POSSIBLE COPY



P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

September 23, 2002

NDA ORIG AMENDMENT
BL

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED
SEP 24 2002
MEGA/CDER

RE: **Mentax[®] - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 018
Response to FDA Telephone Conversation on September 5, 2002

Dear Dr. Wilkin:

Reference is made to a telephone call from Commander Frank Cross to Sherron Wiechert, Bertek Pharmaceuticals Inc., on September 5, 2002. Commander Cross requested that the Sponsor provide the Agency with color copies of the Sponsor's proposed trade dress for the immediate labels and unit cartons with the trade name "Mentax[®] - TC." On August 5, 2002 (Amendment #013), the Sponsor submitted proposed color copies of the unit carton and tube labels, as requested, using the term "TRADEMARK[®]" in place of "Mentax[®] - TC" since the trade name had not been approved by the FDA. The labeling is presented in the same proposed trade dress as submitted in Amendment #013 with the exception of this change (i.e., "TRADEMARK[®]" to "Mentax[®] - TC").

Enclosed in this submission are two color copies of the Sponsor's proposed carton and tube labels for the _____, 15-g and 30-g packaging sizes using the trademark "Mentax[®] - TC." This amendment is being submitted in duplicate with a completed Form FDA 356h. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5913.

Sincerely,

A handwritten signature in cursive script that reads 'Charity M. Schuller'.

Charity Metz Schuller, Pharm.D.
Senior Regulatory Affairs Associate

Enclosure

DUPLICATE



RECEIVED

SEP 10 2002

MEGA/CDER

P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

NEW CORRESPONDENCE

BC

September 9, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: Mentax® - TC (butenafine HCl) Cream, 1%
NDA #21-408, Amendment 017
Withdrawal of Contract Testing Laboratory

Dear Dr. Wilkin:

Reference is made to the above referenced NDA submitted on December 17, 2001 and to the phone conversation between Bertek Pharmaceuticals Inc. (Bertek) and the Division on September 9, 2002 at which time the Sponsor was advised to withdraw

_____ as an alternate testing site for the _____
_____ test and the _____ test on the drug product.

The purpose of this amendment is to officially withdraw _____
_____ as an alternate testing site for the _____
_____ test and the _____ test on the drug product. This
laboratory was not used to conduct any testing on the lots of drug product submitted
in support of the NDA. The Sponsor submitted this facility as an alternate laboratory
only for _____ testing. At this time the Sponsor plans to use only
_____ to perform _____ testing of the drug product.
Bertek will continue to use _____ to perform short-term
preclinical studies of less than 30 days duration.

The following are submitted in support of this amendment:

- A completed FDA form 356h
- The current NDA page with the revision indicated

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

BEST POSSIBLE COPY

- The revised NDA page with _____ eliminated from Contract Laboratories table (NDA table 4-8) and additional information on other contract testing laboratories.
- Field Copy Certification

A true and exact field copy of this amendment will be submitted to the FDA Office in Atlanta, GA.

If you have any questions concerning this submission, please contact Sherron Wiechert at (919) 991-9878.

Sincerely,



Sherron P. Wiechert, RAC
Director of Regulatory Affairs and Quality Assurance

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

September 5, 2002

NDA ORIG AMENDMENT

BL

RECEIVED

SEP 06 2002

MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N-115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: Mentax[®] - TC (butenafine HCl) Cream, 1%
NDA #21-408, Amendment 015
Additional Copies of Amendment 014; Electronic
Version of Red-Lined Mentax[®]-TC Package Insert

Dear Dr. Wilkin:

As requested by Commander Frank Cross in a teleconference today with Sherron P. Wiechert, Director of Regulatory Affairs for Bertek Pharmaceuticals Inc., enclosed is a diskette containing the red-lined version of the Mentax[®]-TC Package Insert that was submitted in Amendment 014 of the NDA in hard copy version.

Also enclosed in this submission are four additional copies of Amendment 014, which was submitted on August 30, 2002. The four copies are being sent to directly to the attention of Commander Cross as Desk Copies.

This amendment is being submitted with a completed Form FDA 356h. Should you need further information or clarification regarding this submission, please contact Sherron Wiechert at 919-991-9878.

Sincerely yours,

A handwritten signature in cursive script, appearing to read 'Paula Mueda'.

Paula A. Mueda
Regulatory Submissions Specialist

APPEARS THIS WAY
ON ORIGINAL

Enclosures

BEST POSSIBLE COPY ORIGINAL



P.O. Box 14149 • Research Triangle Park, NC 27709-4149 U.S.A. • (919) 991-9800 • (888) 5-BERTEK

NDA CRIG AMENDMENT

BZ

September 6, 2002

RECEIVED

SEP 09 2002

MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: **Mentax® - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 016
Response to FDA Facsimile Transmission Dated 7/18/02

Dear Dr. Wilkin:

Reference is made to NDA 21-408 for Mentax®-TC (butenafine HCl) Cream, 1% submitted to FDA on December 17, 2001 and the FDA facsimile transmission dated July 18, 2002 which contained the reviewer's preliminary notes in preparation for a FDA requested teleconference to be scheduled between the Sponsor and the Division's Review Team. This teleconference was conducted on July 19, 2002.

The FDA questions/statements are presented below in bold face type and immediately followed by the Sponsor's response.

Chemistry, Manufacturing and Controls:

1. Please submit UV-visible absorption spectra (———), nm for the new degradation products.

Attachment A contains copies of the UV spectrum for the new degradation products ———. These copies were obtained from a previous pharmaceutical development report written by BerTek. We will also provide the UV-visible absorption spectra (——— nm) of the ——— new degradation products as soon additional reference standard can be obtained and scanned.

— new degradation products are commercially available from —
We would also like to provide the following additional information on —
degradation products as provided on the —

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

BEST POSSIBLE COPY

BEST POSSIBLE COPY

Page 2 of 6
NDA 21-408, S-016



2. The TRADEMARK®(butenafine HCl) cream, 1%, specifications contained — new degradation products than those reported for Mentax Cream. They are

Acceptance criteria for the individual products were proposed as: — butenafine HCl, respectively. In this regard, the Applicant is advised to qualify these impurities as per ICH guidance titled "Guidance for Industry – Q3B Impurities in New Drug Products (1996)".

The Sponsor is currently conducting an extensive literature search to determine what information can be identified on the safety of these known impurities. If the Sponsor can not provide the FDA with sufficient information for the FDA to grant a waiver for this request, the Sponsor will submit a protocol to FDA (based on the ICH guidance) describing the qualification studies that they propose to conduct to support the safety of these two impurities and proceed with these studies only after concurrent by the Agency.

3. It is recommended that — expiration date be proposed for the drug product instead of the — expiration date as proposed in the NDA. The reason for this request is because the stability studies Lot# PEGF-2 revealed these degradation products at levels of — of butenafine HCl after —. By lowering the expiration to —, the Agency could approve the NDA without qualification data at this time. However, if a higher expiration date is required than —, an approvable action would be granted with a Phase 4 commitment to submit supporting data to qualify these impurities.

APPEARS THIS WAY
ON ORIGINAL

The Sponsor will accept a _____ expiration date for the drug product instead of the _____ expiration date as proposed in the NDA based on the fact that qualification data for the two new degradation impurities are not available at this time. It is the understanding of the Sponsor that an acceptance of the expiration date for the drug product does not require a commitment by the Sponsor to conduct Phase 4 studies post-approval safety studies unless a request is made by the Sponsor to extend the expiration date of the drug product beyond the _____ expiration date. The Sponsor also commits to only extending the expiration date of the drug product beyond the _____ test point after submission of a prior-approval supplement to the NDA (i.e., not by notification in the Annual Report).

4. In addition, the following CMC deficiencies were noted in the NDA:

- a. The TRADEMARK®(butenafine HCl) Cream, 1% specifications failed to include _____ Please submit _____ when available.

The Sponsor would like to propose the release and stability _____ limits for the drug product as _____. This is the same _____ specification as is approved for the marketed product, Mentax® (butenafine HCl) Cream, 1%. Please refer to Attachment B for the revised Release and Stability Specifications for the drug product.

- b. The specifications were found to be higher for _____ impurities _____ than those reported in the specifications for Mentax Cream (NDA 20-524), please justify.

The specifications for the _____ impurities _____ were proposed to be higher for the new drug product as compared to the specifications for the Mentax® Cream (NDA 20-524) because the analytical method _____ used to determine the level of these related impurities is different from the approved analytical method used to test the Mentax® Cream _____ and based on lack of experience with the new method the limits were set at a higher limit until more stability data could be collected with the new method.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

After reviewing the stability data submitted in the NDA, the Sponsor would like to propose that the specifications for the _____ impurities _____ be set at a limit of NMT _____ respectively, and the limit for the new impurities (_____ be set at NMT _____

_____ The limit for total degradation products is proposed to be set at NMT _____. Please refer to Attachment B for the revised Release and Stability Specifications for the drug product. These limits for the _____ impurities _____ are the same as for the approved drug product, Mentax® (butenafine HCl) Cream, 1% (NDA 20-524).

- c. Please give the reason for the two (2) new degradation products appearing at 18 months of storage.

The proposed degradation pathway of butenafine yielding the _____ new impurities _____ is considered to occur by _____

_____ and _____ The _____ are further _____ Please refer to Attachment C for the postulated degradation pathways of butenafine HCl.

- d. Please indicate if the TRADEMARK®(butenafine HCl) Cream, 1% specifications are your regulatory specifications for both the release and stability of the finished product.

The drug product specifications presented on page 263 of the NDA are for both the release and stability of the finished drug product. The proposed revised release and stability specifications are presented in Attachment B of this submission.

- e. The NDA failed to include a typical C.O.A for the drug product.

Please refer to the information beginning on page 449, Volume 1.2 of the NDA for the C.O.A. for each lot of drug product used in the clinical studies and GMP stability studies conducted in support of this NDA.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



Page 5 of 6
NDA 21-408, S-016

This information was reviewed during the FDA/Sponsor teleconference on July 19, 2002 and deemed by FDA to be adequate.

- f. The NDA failed to include the vendors' COAs for the inactive ingredients.

Please refer to the information provided on NDA pages 376 to 447. This information was reviewed during the FDA/Sponsor teleconference on July 19, 2002 and deemed by FDA to be adequate.

Pharmacology/Toxicology:

1. The degradant that were present in earlier formulations are considered to be qualified per ICH Q3B.

The Sponsor acknowledges that the degradants _____ that were present in earlier formulations are considered to be qualified per ICH Q3B.

2. _____ should be qualified before a shelf life of greater than _____ is approved.

The Sponsor agrees to qualify the new impurities (either by literature references or actual studies) prior to requesting a shelf-life greater than _____ for the drug product. If this request is made by the Sponsor, post-approval, the change will be requested in a "prior approval" supplement to the NDA.

3. For a shelf life of greater than _____, the Sponsor should propose how it will qualify the degradants _____

If the Sponsor decides to request an extension of the expiration date beyond _____ and if acceptable literature references are not identified, the Sponsor agrees to discuss the requirements for additional studies with the FDA and submit a protocol for qualifying the degradants, _____ to FDA in a "prior-approval" supplement before the studies are conducted. Any request to extend the expiration date beyond _____ post-approval, will be submitted in a "prior approval" supplement to the NDA.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

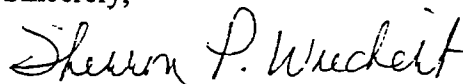
4. Toxicities of interest for _____ include genotoxicity, contact sensitization and general and dermal toxicity after repeated dose application (e.g., 28 days). Results of these studies will determine the need for further studies.

If the Sponsor decides to request an extension of the expiration date beyond _____ and if acceptable literature references are not identified, the Sponsor agrees to discuss the requirements for additional studies with the FDA and submit a protocol for qualifying the degradants, _____ to FDA in a "prior-approval" supplement before the studies are conducted.

This amendment to NDA 21-408 for Mentax®-TC (butenafine HCl) Cream, 1% is being submitted in triplicate with a completed FDA form 356h.

If you should have any questions concerning this response, please contact Sherro Wiechert directly at (919) 991-9878.

Sincerely,



Sherron P. Wiechert, RAC
Director of Regulatory Affairs and Quality Assurance

attachments

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

August 30, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED

SEP 03 2002

MEGA/CDER

NDA ORIG AMENDMENT
BL

RE: **Mentax[®] - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 014
Response to FDA Facsimile Dated July 2, 2002

Dear Dr. Wilkin:

Reference is made to a facsimile transmission received from the Agency on July 2, 2002. The facsimile provided the Agency's proposed labeling for the above referenced product. Enclosed are the following:

- The Sponsor's revised package insert based on the FDA suggested wording in the July 2, 2002 facsimile.
- An annotated version of the Sponsor's revised package insert.
- A comparison of the wording contained in the FDA proposed package insert to the proposed wording of the Sponsor's revised package insert. Red type and Strikethrough note differences in the wording.
- A diskette containing the proposed text of the Sponsor's revised package insert. The Sponsor's revised package insert is saved as a Word document entitled "Draft PI 8-02."

Please note the Sponsor submitted the revised draft carton and tube labels as requested in the proposed trade dress with proposed trade name "Mentax[®] - TC" replaced with the word "TRADEMARK[®]" on August 5, 2002 as Supplement 013.

APPEARS THIS WAY
ON ORIGINAL

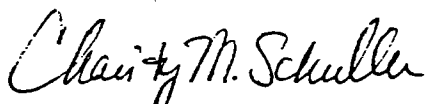
DUPLICATE

BEST POSSIBLE COPY

Jonathan Wilkin, MD
Page 2 of 2

This amendment is being submitted in duplicate with a completed Form FDA 356h. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5913.

Sincerely,



Charity Metz Schuller, Pharm.D.
Senior Associate
Regulatory Affairs

Enclosures

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Cross

Food and Drug Administration
Rockville MD 20857

AUG 22 2002

Terry M. Jones, M.D.
3204 University Avenue #475
Bryan, Texas 77802

Dear Dr. Jones:

Between June 5 and 7, 2002, Mr. James H. Robinson, representing the Food and Drug Administration (FDA), reviewed your conduct of protocol # PDC 010-036: A Multicenter, Double-Blind Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Butenafine HCl Cream 1% in the Treatment of Tinea Versicolor, performed for Bertek Pharmaceuticals Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to ensure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to pertinent federal regulations governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Robinson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

FEI: 1000306031

Field Classification: NAI

Headquarters Classification:

☒ 1)NAI

☐ 2)VAI- no response required

☐ 3)VAI- response requested

☐ 4)OAI

Deficiencies noted: None

cc:

HFA-224

HFD-540 Doc.Rm. NDA# 21-408

HFD-540 Review Div.Dir. Wilkin

HFD-540 MO Carr

HFD-540 PM Cross

HFD-46/47 c/r/s/ GCP File #10361

HFD-47 MTT/GRH

HFR-SW150 DIB Thornburg

HFR-SW1540 BIMO Monitor Martinez

HFR-SW1540 Investigator Robinson

r/d:GRH:8/14/02

revised:MTT:8/14/02

final:GRH:8/14/02

O:\GRH\JONES NAI.DOC

Reviewer's Note to Review Division Medical Officer

Of the 34 subjects enrolled in protocol PDC 010-036, 33 subjects completed the study and one dropped out because of lack of response. The informed consent forms for all 34 subjects and study-related records for 17 subjects were reviewed. No violations or deficiencies were noted.

The inspection included a comparison of the enrollment logs for study PDC 010-031 and study PDC 010-036, and did not reveal any duplication of subjects from one study to the other.

Thus, data from the 33 subjects at Dr. Jones' site can be used for evaluation of Protocol #PDC 010-036 in support of NDA 21-408 for review by FDA.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

August 5, 2002

NDA 21-408 AMENDMENT

BL

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED

AUG 06 2002

MEGA/CDER

RE: **Mentax[®] - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 013
Response to FDA Facsimile Dated July 2, 2002

Dear Dr. Wilkin:

Reference is made to a facsimile transmission received from the Agency on June 10, 2002 and the telephone call from Commander Frank Cross to Sherron Wiechert, Bertek Pharmaceuticals Inc., on June 26, 2002. The facsimile provided the Agency's labeling for the above referenced product. The Sponsor has revised the draft carton and tube labels as requested to replace the trademark "Mentax[®] - TC" with "TRADEMARK[®]." Enclosed are two color copies of the Sponsor's proposed carton and tube labels for the 2-g - professional sample, 15-g and 30-g packaging sizes. The labels are presented in the proposed trade dress. Please note that the Sponsor plans to comment on the Agency's package insert in a separate submission.

This amendment is being submitted in duplicate with a completed Form FDA 356h. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5913.

Sincerely,

A handwritten signature in cursive script that reads 'Charity M. Schuller'.

Charity Metz Schuller, Pharm.D.
Senior Regulatory Affairs Associate

Enclosure

DUPLICATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Bertek Pharmaceuticals Inc.

DATE OF SUBMISSION
August 5, 2002

TELEPHONE NO. (Include Area Code)
919-981-9800

FACSIMILE (FAX) Number (Include Area Code)
919-993-5913

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
and U.S. License number if previously issued):

Post Office Box 14149
Research Triangle Park, NC 27709-4149

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-408

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
butenafine HCl cream, 1%

PROPRIETARY NAME (trade name) IF ANY
Mentax Cream, 1%

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
N-4-tert-Butylbenzyl-N-methyl-l-naphthalenemethylamine hydrochloride

CODE NAME (If any)
KP-363

DOSAGE FORM:
Cream

STRENGTHS:
1%

ROUTE OF ADMINISTRATION:
Topical

(PROPOSED) INDICATION(S) FOR USE:
Tinea versicolor

APPLICATION INFORMATION

APPLICATION TYPE
(check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50)

☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

☒ 505 (b)(1)

☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)

☐ ORIGINAL APPLICATION

☒ AMENDMENT TO A PENDING APPLICATION

☐ RESUBMISSION

☐ PRESUBMISSION

☐ ANNUAL REPORT

☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT

☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT

☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

☐ CBE

☐ CBE-30

☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to FDA request for revision of Sponsor's draft carton and tube labels.

PROPOSED MARKETING STATUS (check one)

☒ PRESCRIPTION PRODUCT (Rx)

☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS

☒ PAPER

☐ PAPER AND ELECTRONIC

☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

APPEARS THIS WAY
ON ORIGINAL

RECEIVED

This application contains the following items: (Check all that apply)

- ☒ 1. Index
- ☒ 2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
- ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
- ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
- ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(l)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER (Specify) Cover letter and Form FDA 356h

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

Sherron P. Wiechert for

TYPED NAME AND TITLE

Sherron P. Wiechert, RAC
Director, Regulatory Affairs

DATE

August 5, 2002

ADDRESS (Street, City, State, and ZIP Code)

Post Office Box 14149

Research Triangle Park, NC 27709-4149

TELEPHONE NUMBER

919-991-9878

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services

Food and Drug Administration

CBER, HFM-99

1401 Rockville Pike

Rockville, MD 20852-1448

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.

APPEARS THIS WAY
ON ORIGINAL

FORM FDA 356h (4/00)

PAGE 2

BEST POSSIBLE COPY



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 31, 2002

Number of Pages (including cover sheet) - 1

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: For your NDA 21-408, Mentax-TC (butenafine HCl cream,) Cream, 1%, we have the following informational request from the Clinical reviewer:

In response to an Agency request for several patient diaries, you stated in Amendment 006 (dated April 10, 2002) that, "The diary cards are not available, as they were subject aids that were not collected by the study sites."

However, Section VI of the protocols for both pivotal trials states that, "The Subject Diary Card will be used to monitor the subject's compliance, and will serve as an appointment card for the subject's Day 8 visit." Thus, the diary cards served as both subject and investigator aids. Additionally, among the study procedures for Day 8 (Section VI of both protocols) is that, "The Subject Diary Card is collected..."

As the protocol specified that the diary cards were to have been collected, please explain why these subject and investigator aids are "not available."

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.



P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

April 18, 2002

NDA ORIG AMENDMENT

BC

RECEIVED

APR 19 2002

MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Subject: Mentax[®]-TC (butenafine HCl) Cream, 1%
NDA 21-408, Amendment 007
Minor Amendment for the Deletion of Alternate Release and Stability
Testing Site for the Drug Product

Dear Dr. Wilkin:

Pursuant to 21 CFR, part 314.60, we are submitting this amendment to NDA 21-408. This NDA for Mentax[®]-TC (butenafine HCl) Cream, 1% was submitted to FDA on December 17, 2001 and is currently under review. The purpose of this amendment is to delete Bertek Pharmaceuticals Inc. in Durham, NC as an alternate site for the release and stability testing of the drug product. Due to a management decision, the laboratories at this Bertek facility will be closed. The Bertek FDA Establishment License has also been revised to reflect this change.

In support of this amendment, the revised NDA pages are attached and immediately followed by the current NDA pages with the changes indicated directly on each page. Please note that Appendix 10 to Section 4.0, which is related to the qualification of the laboratory at the Bertek facility, is no longer relevant to the review and approval of the NDA.

This amendment is being submitted in duplicate with a completed FDA form 356(h).

A true and exact copy of this amendment is also being submitted to the Sponsor's home district office in Atlanta, GA.

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

BEST POSSIBLE COPY

Page 2 of 2
NDA 21-408, Amendment 007

If you should have any questions related to this amendment, please contact me directly at (919) 991-9878.

Sincerely,

A handwritten signature in cursive script that reads "Sherron P. Wiechert".

Sherron P. Wiechert, RAC
Director of Regulatory Affairs

Attachment

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

August 5, 2002

NDA 0210 AMENDMENT
BL

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED

AUG 06 2002

MEGA/CDER

RE: **Mentax[®] - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 013
Response to FDA Facsimile Dated July 2, 2002

Dear Dr. Wilkin:

Reference is made to a facsimile transmission received from the Agency on June 10, 2002 and the telephone call from Commander Frank Cross to Sherron Wiechert, Bertek Pharmaceuticals Inc., on June 26, 2002. The facsimile provided the Agency's labeling for the above referenced product. The Sponsor has revised the draft carton and tube labels as requested to replace the trademark "Mentax[®] - TC" with "TRADEMARK[®]." Enclosed are two color copies of the Sponsor's proposed carton and tube labels for the 2-g – professional sample, 15-g and 30-g packaging sizes. The labels are presented in the proposed trade dress. Please note that the Sponsor plans to comment on the Agency's package insert in a separate submission.

This amendment is being submitted in duplicate with a completed Form FDA 356h. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5913.

Sincerely,

Charity Metz Schuller, Pharm.D.
Senior Regulatory Affairs Associate

Enclosure

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

DUPLICATE



P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

July 12, 2002

RECEIVED

JUL 15 2002

MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

NDA 0181 AMENDMENT
BC

RE: **Mentax® - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 012
Environmental Assessment Request for Categorical Exclusion with
Supporting EIC Calculation

Dear Dr. Wilkin:

Reference is made to the NDA 21-208 for Mentax®-TC (butenafine HCl) Cream, 1% and to the request from FDA on June 21, 2002 to provide the Expected Introduction Concentration (EIC) calculation in support of the categorical exclusion that was requested in the NDA.

Please note that we were instructed by the FDA to include the impact from all of our approved drug products that contained butenafine HCl as the active ingredient. However,

the calculation is based on the impact of butenafine HCl in only Mentax®-TC (butenafine HCl) Cream, 1%. Since Mentax®-TC (butenafine HCl) Cream, 1% will have only one indication compared to the Mentax® (butenafine HCl) Cream, 1% that has four indications and the fact that a butenafine HCl 1% cream is now available as an OTC product, Bertek expects the quantity of butenafine HCl in the environment from our product to decline from current levels with the approval of this NDA.

This amendment contains a revised Categorical Exclusion Statement (NDA page 557) and a copy of the EIC calculation (NDA page 557a). Please note that the EIC equals — ppb and this is well below the maximum allowable concentration of 1 ppb.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

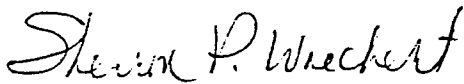
ORIGINAL

Jonathan Wilkin, MD
July 12, 2002
Page 2 of 2

This amendment is being provided in duplicate with a completed FDA form 356h.

If you have an questions concerning this amendment, please contact me directly at (919) 991-9878.

Sincerely,



Sherron P. Wiechert, RAC
Director, Regulatory Affairs

Attachment

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: July 2, 2002 Number of Pages (including cover sheet) – 36

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: For your review and comments, please find attached to this facsimile transmission our labeling for your NDA 21-408, TRADEMARK® (butenafine HCl) Cream, 1%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



P.O. Box 14149 • Research Triangle Park, NC 27709-4149 U.S.A. • (919) 991-9800 • (888) 5-BERTEK

June 18, 2002

NDA ORIG AMENDMENT
BZ

RECEIVED

JUN 19 2002

MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Subject: Mentax®-TC (butenafine HCl) Cream, 1%
NDA 21-408, Amendment 011
Submission of Additional Information for Bertek Study PDC 010-046

Dear Dr. Wilkin:

Reference is made to the pending NDA referenced above and to a phone call from Frank Cross, Senior Regulatory Project Manager, on June 14, 2002 at which time he requested additional information on Bertek Clinical Study PDC 010-046. Specifically, the biopharmaceutical reviewer at FDA had requested additional sample and standard stability information for — analytical method — which was used to analyze the blood plasma samples for the Bertek Study entitled, "Determination of Butenafine and its Metabolite, M2, in Heparinized Human Plasma Samples by LC-MS-MS." This study report was submitted on page 2072 of NDA 21-408 for Mentax®-TC (butenafine HCl) Cream, 1%. The method validation report for method — was referenced in the study but not included in the NDA submission. The stability information requested by FDA is contained in this method validation report.

Attached please find the method validation report — dated November 1995 and the First Amendment to this report, dated April 2001. The amendment contained additional stability information.

This validation report and first amendment are being submitted in duplicate, as required, along with a completed FDA Form 356(h).

**APPEARS THIS WAY
ON ORIGINAL**

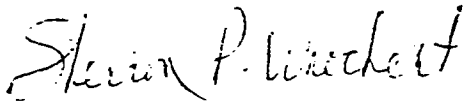
BEST POSSIBLE COPY

DUPLICATE

Page 2 of 2

If after reviewing this information you have additional questions, please do not hesitate to contact me at (919) 991-9878.

Sincerely,

A handwritten signature in black ink, reading "Sherron P. Wiechert". The signature is written in a cursive style with a large initial 'S'.

Sherron P. Wiechert, RAC
Director of Regulatory Affairs

enclosures

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

June 11, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED
JUN 12 2002
MEGA/CDER

ORIGINAL

*Noted
Blair
26 June 02*

RE: **Mentax® - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 010
Response to FDA Questions Received by Facsimile Transmission on
June 10, 2002

BS
ORIG AMENDMENT

Dear Dr. Wilkin:

Reference is made to a facsimile transmission received from the Agency on June 10, 2002. The facsimile requested clarification of the design of the Sponsor's pivotal study PDC 010-033 submitted in the original NDA. For ease of review, the FDA questions will be presented in bold type followed by the Sponsor's response in normal type. In addition, a copy of the Agency's facsimile is provided.

It is not clear from the Sponsor's submission whether study PDC 010-033 was originally designed as a Phase 2 or Phase 3 trial.

Study PDC 010-033 was planned and executed as a Phase II study. Since qualifying subjects were available, enrollment was increased above the 72 subjects called for in the original protocol to obtain greater power than the 53% 72 subjects would provide.

1. **The justification for having the date of amendment following the dates of the additional randomization codes related to the increase of the study enrollment.**

The date of the amendment follows the dates of generating the additional randomization codes because of error on the part of the clinical team. The team was familiar with the procedures for allowing increased enrollment at a given site to compensate for lack of enrollment at another study site. Typically, the rate limiting factors for allowing increased enrollment at one or more sites are obtaining additional labeled drug product and renegotiating investigator agreements. Since no difference in total number of

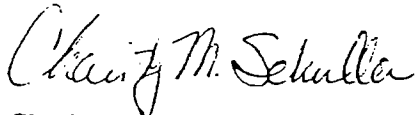
subjects occurs, there is no need to amend the protocol. In this instance, the clinical team focused on the mechanics of enabling increased enrollment at the individual sites, and lost sight of the fact that enrollment overall would increase, necessitating a protocol amendment. When the error was detected, the Sponsor consulted with — IRB, and a one-page amendment was issued changing the number of subjects enrolled from 72 to 130. At the recommendation of the IRB, no change was made to the informed consent.

2. **Whether the extension of study enrollment was based on any interim analysis for the data. In such case, please provide details about the number of interim analyses and number of patients completing the trial at each interim analysis.**

No interim analysis was conducted; it was only after study completion and statistical analysis that the Sponsor decided to submit the results as one of two pivotal Phase III studies.

This amendment is being submitted in duplicate. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5913.

Sincerely,



Charity Metz Schuller, Pharm.D.
Senior Regulatory Affairs Associate

Enclosure

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 10, 2002 Number of Pages (including cover sheet) – 1

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: For your NDA 21-408, Mentax-TC (butenafine HCl cream,) Cream, 1%, we have the following informational request from the Biostatistical Reviewer:

It is not clear from the Sponsor's submission whether study PDC 010-033 was originally designed as a Phase 2 or Phase 3 trial. According to the protocol dated 8/17/1999, sample size calculation for this study was based on estimated response rates of 60% and 30% for active and placebo, respectively, leading to an estimated sample size of 72 patients to ensure 53% power. Following the original 72 randomization codes generated on 8/25/1999 for centers G1-G4, the Sponsor on 9/22/1999 generated 36 additional codes for centers G1-G4 and 27 codes for an additional center G5. Also, another 9 codes were generated on 10/18/1999 for center G4. Later an amendment dated 11/16/1999 was issued in which patient enrollment was increased to 130 subjects to ensure 81% power. Please clarify:

1. The justification for having the date of amendment following the dates of generating the additional randomization codes related to the increase of the study enrollment.
2. Whether the extension of study enrollment was based on any interim analysis for the data. In such case, please provide details about the number of interim analyses and number of patients completing the trial at each interim analysis.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

NDA 21-408

Mentax-TC (butenafine HCl cream,) Cream, 1%

Facsimile of Clinical Informationa Requests

Page 2

FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Frank Cross

6/11/02 12:14:38 PM

CSO

Faxed to Sponsor on 6/10/02

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



NEW CORRESP
NC

P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

June 3, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED
JUN 04 2002
MEGA/CDER

RE: **Mentax[®] - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 009
Response to FDA Question Received by Facsimile Transmission on May 31, 2002

Dear Dr. Wilkin:

Reference is made to a facsimile transmission received from the Agency on May 31, 2002. The facsimile requested clarification of one of the Sponsor's statements submitted in Supplement 006 (dated April 10, 2002). For ease of review, a copy of the Agency's facsimile is provided.

In the above referenced facsimile, the Agency requested an explanation regarding the Sponsor's statement that, "The diary cards are not available, as they were subject aids that were not collected by the study sites." The Sponsor apologizes for this erroneous statement. The diary cards are source documents collected by the study sites, but not collected by the Sponsor. The diary cards are available upon request. However, the Sponsor would need at least a week to collect the diary cards from the study sites, if they are requested.

This amendment is being submitted in duplicate.

Again, we apologize for any inconvenience that this error may have caused the Agency. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5913.

Sincerely,

Charity Metz Schuller, Pharm.D.
Senior Regulatory Affairs Associate

Enclosure

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Bertek Pharmaceuticals Inc.

DATE OF SUBMISSION
June 3, 2002

TELEPHONE NO. (Include Area Code)
919-981-9800

FACSIMILE (FAX) Number (Include Area Code)
919-993-5913

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
and U.S. License number if previously issued):

Post Office Box 14149
Research Triangle Park, NC 27709-4149

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-408

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
butenafine HCl cream, 1%

PROPRIETARY NAME (trade name) IF ANY
Mentax Cream, 1%

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
N-4-tert-Butylbenzyl-N-methyl-L-naphthalenemethylamine hydrochloride

CODE NAME (If any)
KP-363

DOSAGE FORM:
Cream

STRENGTHS:
1%

ROUTE OF ADMINISTRATION:
Topical

(PROPOSED) INDICATION(S) FOR USE:
Tinea versicolor

APPLICATION INFORMATION

APPLICATION TYPE

(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to FDA question regarding Supplement 006 received by facsimile transmission on May 31, 2002.

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

APPEARS THIS WAY
ON ORIGINAL

RECEIVED
JUN 04 2002

BEST POSSIBLE COPY

MEGA/CDER

DUPLICATE

This application contains the following items: (Check all that apply)

- ☐ 1. Index
- ☐ 2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
- ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
- ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
- ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(i)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER (Specify) Cover letter; copy of 5/31/02 facsimile transmission from FDA to Sponsor.

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

Sherron P. Wiechert

TYPED NAME AND TITLE

Sherron P. Wiechert, RAC
Director, Regulatory Affairs

DATE

June 3, 2002

ADDRESS (Street, City, State, and ZIP Code)

Post Office Box 14149
Research Triangle Park, NC 27709-4149

TELEPHONE NUMBER

919-991-9878

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 31, 2002 Number of Pages (including cover sheet) – 1

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: For your NDA 21-408, Mentax-TC (butenafine HCl cream,) Cream, 1%, we have the following informational request from the Clinical reviewer:

In response to an Agency request for several patient diaries, you stated in Amendment 006 (dated April 10, 2002) that, "The diary cards are not available, as they were subject aids that were not collected by the study sites."

However, Section VI of the protocols for both pivotal trials states that, "The Subject Diary Card will be used to monitor the subject's compliance, and will serve as an appointment card for the subject's Day 8 visit." Thus, the diary cards served as both subject and investigator aids. Additionally, among the study procedures for Day 8 (Section VI of both protocols) is that, "The Subject Diary Card is collected..."

As the protocol specified that the diary cards were to have been collected, please explain why these subject and investigator aids are "not available."

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

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

/s/

Frank Cross

6/4/02 01:19:34 PM

CSO

Faxed to Applicant on 5/31/02.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

IND 60,471
butenafine hydrochloride cream, 1%
Pre-NDA Meeting Minutes
Page 8

Teleconference Date: May 18, 2001

Time: 1415

Location: N225

IND 60,471, butenafine hydrochloride cream, 1%

Indication: Tinea versicolor

Applicant: Bertek Pharmaceuticals, Inc.

Biopharmaceutics Discussion

Meeting Chair: Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader

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

FDA Attendees, titles and offices:

Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Markham Luke, M.D., Ph.D., Acting Clinical Team Leader, DDDDP, HFD-540
Brenda Vaughan, M.D., Medical Officer, DDDDP, HFD-540
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles, and offices:

Barbara Brennan, R.A.C., Executive Director, Clinical Operations
Bhaskar Chaudhuri, Ph.D., Vice President and General Manager
Elena Serbinova, Ph.D., R.A.C., Associate Director, Pharmacology/Toxicology
Daniel Bucks, Ph.D., Project Leader
Paula Mueda, Regulatory Affairs Associate

Agency:

Biopharmaceutics:

With regard to the Sponsor's Pharmacokinetics Section, p. 44, of the April 20, 2001, pre-NDA Meeting Briefing Package:

1. The Sponsor was advised that their proposal to treat a minimum of 50 cm² of diseased skin was inadequate.
2. One possible approach that the Sponsor can employ is to:
 - a. Review the design of the butenafine HCl drug product Phase 3 clinical trials,
 - b. take an average of the amount of butenafine drug product used and
 - c. calculate the related area of involvement based on standard formulae under labeled conditions with respect to:
 - i. diseased skin,
 - ii. maximal area of involved skin and
 - iii. dosing frequency.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

IND 60,471
butenafine hydrochloride cream, 1%
Pre-NDA Meeting Minutes
Page 9

Sponsor:

The Sponsor thanked the Agency for its advice and recommendations and will make the appropriate submission.

The meeting ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Jonathan Wilkin

8/12/01 06:39:43 PM

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**



NDA 010-AMENDMENT

B

P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

May 9, 2002

RECEIVED

MAY 10 2002

MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Subject: Mentax[®]-TC (butenafine HCl) Cream, 1%
NDA 21-408, Amendment 008
Minor Chemistry, Manufacturing and Controls Amendment

Subject: Stability Update

Dear Dr. Wilkin:

Reference is made to NDA 21-408 for Mentax[®]-TC (butenafine HCl) Cream, 1%, which was submitted to FDA on 12/7/01. The purpose of this amendment is to provide updated stability information in support of the approval of this NDA.

The following stability information is provided as an attachment to this letter:

Lot Number	Fill size	Stability Information
RDF	2 g	— at 25°C
RDF-1	15 g	— at 30°C
RDF-2	30 g	— at 35°C
		— at 40°C
PEGF	2 g	— at 4°C
PEGF-1	15 g	— at 25°C
PEGF-2	30 g	— at 30°C
		— at 35°C
		— at 40°C

ORIGINAL

BEST POSSIBLE COPY

Lot Number	Fill size	Stability Information
NEEC	2 g*	— at 4°C
NEEC-1	15 g	— at 25°C
NEEC-3	30 g	— at 30°C
		— at 35°C
		— at 40°C

* no studies conducted at 30 or 35°C

All stability data are within the proposed shelf life specifications submitted in NDA 21-408 for the Mentax®-TC (butenafine HCl) Cream, 1% drug product.

This Chemistry, Manufacturing and Controls amendment is being provided in duplicate with a completed FDA 356h form.

A true and exact copy of this supplement is being provided to the FDA District Office in Atlanta, GA.

If you have any questions related to this amendment, please contact me directly at (919) 991-9878.

Sincerely,

Sherron P. Wiechert

Sherron P. Wiechert, RAC
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

attachment

BEST POSSIBLE COPY

The following information does not include fileability issues, but should be completed to facilitate your review planning.

Table 2

STABILITY DATA REQUIRED FOR REVIEW

	Stability Data Requested	Yes	No
1	Does the NDA include — months of stability data?	X	
2	Do the stability data cover the expiry date?	X	
3	Do the stability data include only the largest & smallest container sizes?		X
4	Do the stability data include all package sizes?	X	
5	Are there tabular data for each size and batch?	X	
6	Are there graphical data for each size and batch?	X	
7	Is a statistical consult required?		X
8	Is a stability protocol included?	X	
9	Are the stability-indicating assays described?	X	
10	Is a three-point stability commitment given?	X	

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 3

DMF INFORMATION

DMF #	DMF Holder	TYPE	LOA Date	Date Of Last Review
[REDACTED]	[REDACTED]	II	11/19/99	9/11/95
		I	11/19/99	9/11/95
		III	6/26/01	3/27/01

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

April 12, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V, CDER
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

*Noted
Harris
16 Sept 02*

RECEIVED

APR 15 2002

MEGA/CDER

ORIGINAL

RE: **Mentax® - TC (butenafine HCl) Cream, 1% NDA ORIG AMENDMENT**
NDA #21-408, Amendment 006 — ADDENDUM

Bm

Dear Dr. Wilkin:

Reference is made to Amendment 006 submitted to NDA 21-408 on April 10, 2002. Amendment 006 was submitted in response to the Agency's request for additional information in support of the approval of NDA 21-408 submitted to the FDA on December 14, 2001.

In reviewing the materials submitted on April 10, the Sponsor discovered that there had been an inadvertent omission of a piece of information which the Agency had requested in question #5. The underlined portion of the request which follows identifies the portion of the request that the Sponsor inadvertently omitted from the Amendment 006 submission on April 10, 2002: *"5. Please provide a list of any subject who participated in more than one of the studies listed below (i.e., PDC 010-033, PDC 010-036, PDC 010-031, PDC 010-032). For any subject listed, please identify the studies in which they participated, and their dates of participation."*

A table identifying subjects who participated in more than one of the designated clinical studies was included as Attachment 2 in the Amendment 006 submission. The Sponsor requests that Attachment 2 submitted on April 10 be replaced with the updated Attachment 2, enclosed, which contains the all-inclusive information requested by the Agency in its facsimile transmission received by the Sponsor on March 27, 2002. Further, the Sponsor apologizes for any inconvenience this omission may have caused the Agency and its reviewers.

This Addendum to Amendment 006 is being submitted in duplicate. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9878 or by facsimile at (919) 993-5910.

Sincerely,

Sherron P. Wiechert

Sherron P. Wiechert
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Enclosure



BM

P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

April 10, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED

APR 11 2002

MEGA/CDER

*Noted
3/16/02
16 Sept 02*

RE: **Mentax[®] - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 006
Response to FDA Questions Received by Facsimile Transmission on
March 27, 2002

Dear Dr. Wilkin:

Reference is made to a facsimile transmission received from the Agency on March 27, 2002. The facsimile requested additional information in support of the approval of NDA 21-408. For ease of review the FDA questions will be presented in bold type followed by the Sponsor's response in normal type.

1. Please "clarify the "Race" data presented in Table 8.5, Vol. 13.

The number of subjects with "Effective Treatment post hoc" in Study PDC 010-033 was corrected on Table 8.5. The corrected copy of NDA Page 4841 is provided as Attachment 1. The corrections were made based on study statistical tables 3.1.4 on Pages 3228 and 3809 and ISE statistical table B.3.1.4 on NDA Page 4866.

2. Please provide the mean amounts of study drug used in trials, PDC 501-005 and PDC 501-006.

The extent of exposure in PDC 501-005 for butenafine and vehicle was an average of 17.78 g and 17.98 g, respectively. The extent of exposure in PDC 501-006 for butenafine and vehicle was an average of 15.53 g and 16.02 g, respectively.

ORIGINAL

BEST POSSIBLE COPY

For studies PDC 010-033 and PDC 010-036, please provide the scientific procedures followed for collection of adverse event data "by another route such as telephone (Sec. XII of both protocols)." Please include the circumstances under which the adverse event data was collected by telephone (or other means), rather than in a study visit, and how subjects were queried. Also, please provide the CRF's for subjects who had such assessments done, including the day of the assessment, Day 28.

Adverse events were collected by telephone (or other means) in either studies PDC 010-033 or PDC 010-036. Adverse events were only collected during study visits. However, the Sponsor wanted to provide a mechanism by which a physician could capture an adverse event via telephone or other means in between study visits. This mechanism was in place to ensure that all adverse events were collected in a manner that facilitated expedited reporting of any serious adverse events.

In the conduct of studies PDC 010-33 and PDC 010-036 (Section VI of both protocols), the first procedure is "Telephone Screening" of an existing population. Details were found in either protocol, as to the nature of this population, e.g., who constituted the population. Please provide specifics of how subjects were initially accrued for possible participation in the pivotal studies, i.e., the population of subjects who was screened by telephone prior to the Day 1/Baseline visit.

Used on the manner in which an investigator recruited patients (i.e., radio, newspaper, office records), a Day 1/Baseline visit would be set up via telephone. The primary purpose of the call was to schedule the visit and to instruct the patient not to bathe for at least 24 hours prior to the visit. At the Day 1/Baseline visit, the subject would be examined with a Wood's lamp for the presence of yellow fluorescence indicating the presence of *Malassezia furfur*. (Note: The fluorescing pigment produced by *M. furfur* is water soluble.)

Please provide a list of any subject who participated in more than one of the studies listed below. For any subject listed, please identify the studies they participated, and their dates of participation.

- a. PDC 010-033
- b. PDC 010-036
- c. PDC 010-031
- d. PDC 010-032

Seventeen patients participated in both studies PDC 010-032 and PDC 010-036. There were no duplicate participants in studies PDC 010-031 and PDC 010-033. A list of duplicate participants is provided in Attachment 2.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table of Contents

Form FDA 356b

Attachment 1
Revised NDA Page 4841

Attachment 2
Subjects in More Than One

Attachment 3
Selected PDC 010-033 CRFs

6. Please provide indexed copies of the CRF and diary cards for the following subjects:

PDC 010-033

G102, G104, G125, G201, G214, G305, G308, G313, G327, G401, G406,
G408, G409, G414, G507, G511, G521, G524

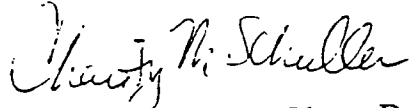
PDC 010-036

B101, B102, B105, B112, B114, B205, B214, B218, B302, B304, B315, B318,
B401, B403, B408, B412, B516, B517, B524, B606, B609, B611, B614, B615,
B707, B711, B718, B734, B801, B802, B809, B812, B823, B832

The requested CRFs are indexed and provided as Attachments 3 and 4. The diary cards are not available, as they were subject aids that were not collected by the study sites.

This amendment is being submitted in duplicate. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5910.

Sincerely,



Charity Metz Schuller, Pharm.D.
Senior Regulatory Affairs Associate

Enclosures

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Carol Anne Currier/Dr. Matthew Thomas/ Dr. El Hage - DSI, HFD-45		FROM: HFD-540 (Division of Dermatologic and Dental Drug Products) Frank Cross		
DATE: April 8, 2002	IND NO.:	NDA NO.: 21-408	TYPE OF DOCUMENT : New NDA	DATE OF DOCUMENT: 12/14/01
NAME OF DRUG: Mentax-TC (butenafine HCl cream) Cream, 1%		PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 3	DESIRED COMPLETION DATE: 8/5/02
NAME OF FIRM: Bertek Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☐ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:		☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:		
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES		☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
☒ CLINICAL		☐ PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: For this New NDA: Inspection Request, for: Inspecting the data collected and submitted in support of NDA #21,408, from the following four study sites: Thanks, Frank cc: Original NDA 21-408 HFD-540/Div. Files HFD-540/Cross				
SIGNATURE OF REQUESTER:		METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND		
SIGNATURE OF RECEIVER:		SIGNATURE OF DELIVERER:		

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 27, 2002 Number of Pages (including cover sheet) – 2

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs

COMPANY: Bertek Pharmaceuticals, Inc.

FAX #: 919-993-5910

MESSAGE: For your NDA 21-408, Mentax-TC (butenafine HCl cream,) Cream, 1%, we have the following informational requests from the Clinical reviewer:

1. Please clarify the "Race" data presented in Table 8.5, Vol. 13.
2. Please provide the mean amounts of study drug used in trials, PDC 501-005 and PDC 501-006.
3. For studies PDC 010-033 and PDC 010-036, please provide the specific procedures followed for the collection of adverse event data "by another route such as telephone (Sec. XII of both protocols)." Please include the circumstances under which the adverse event data was collected by telephone (or other means), rather than a study site visit, and how subjects were queried. Also, please provide the CRF's for subjects who had such assessments done, including the day of the assessment, e.g. Day 28.
4. In the conduct of studies PDC 010-033 and PDC 010-036 (Section VI of both protocols), the first procedure is "Telephone Screening" of an existing population. No details were found in either protocol, as to the nature of this population, e.g. who constituted this population. Please provide the specifics of how subjects were initially accrued for possible participation in the pivotal studies, i.e. the population of subjects who was screened by telephone prior to the Day 1/Baseline visit.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 20, 2002 Number of Pages (including cover sheet) – 1

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: For your NDA 21-408, Mentax-TC (butenafine HCl cream,) Cream, 1%, we have the following request from the Clinical Microbiology reviewer:

Please provide the number of *M. furfur* isolates that were tested to determine the MIC range for butenafine indicated in Volume 1.7 pg. 2182.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY



BT

P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

March 21, 2002

RECEIVED

MAR 22 2002

MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: **Mentax® - TC (butenafine HCl) Cream, 1%**
NDA 21-408, Amendment 005
Response to FDA Question Received by Facsimile
Transmission on March 20, 2002

Dear Dr. Wilkin:

Reference is made to a facsimile transmission received from the Agency on March 20, 2002. The facsimile requested additional information in support of the approval of NDA 21-408. For ease of review the FDA question is presented in bold type followed by the Sponsor's response in normal type.

Please provide the number of *M. furfur* isolates that were tested to determine the MIC range for butenafine indicated in Volume 1.7 pg. 2182.

Table 7.1 (*In Vitro* Activity of Antifungal Agents against *M. furfur*) lists Minimum Inhibitory Concentration range based on six isolates of *Malassezia furfur*. The isolates are as follows:

<i>Malassezia furfur</i>	IFO 0656
<i>Malassezia furfur</i>	No 25
<i>Malassezia furfur</i>	No 942
<i>Malassezia furfur</i>	No 1202
<i>Malassezia furfur</i>	No 1203
<i>Malassezia furfur</i>	No 1210

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

ORIGINAL

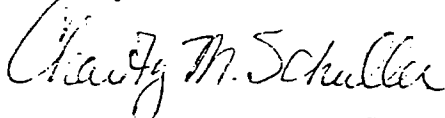
Jonathan Wilkin, MD

Page 2 of 2

In the review of this question, the Sponsor noted an error in the description of the composition of the medium. The medium contains 0.04% Tween 80 instead of 0.4% Tween 80 as listed. A corrected page 2182 is provided as Attachment 1.

This amendment is being submitted in duplicate. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5910.

Sincerely,

A handwritten signature in cursive script that reads "Charity M. Schuller".

Charity M. Schuller, PharmD
Senior Associate
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



NEW ORIG AMENDMENT
BC

Form FDA 356h

Drug Formulation
Quantitative Composition

Drug Product Lots Used
(from Application Summary)

Drug Product Lots Used
(from "Drug Facts")

P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

February 27, 2002

RECEIVED

FEB 28 2002

MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Subject: NDA 21-408 – Mentax®-TC (butenafine HCl) Cream, 1%
Amendment 004: FDA Request for Location in NDA of
Investigation Formulations

Dear Dr. Wilkin:

Reference is made to a telephone conversation held on February 25, 2002 between Commander Frank Cross and myself regarding information Bertek faxed to him on February 21, 2002 concerning investigation formulations listed in NDA 21-408, which was submitted to the FDA on December 14, 2001.

During that conversation, Commander Cross requested that Bertek submit the faxed information as an official amendment to the NDA. The enclosed materials, therefore, are being submitted as Amendment 004 to NDA 21-408.

This amendment is being submitted in duplicate, along with a Form FDA 356h. In addition, a desk copy is being sent to the attention of Commander Cross.

If you need additional information concerning the product formulations used during development of this drug product, please contact me at (919) 991-9878.

Sincerely,

Sherron P. Wiechert, RAC
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

/pm
Enclosures

DUPLICATE

BEST POSSIBLE COPY



P.O. Box 14149 • Research Triangle Park, NC 27709-4149 U.S.A. • (919) 991-9111 • (888) 5-BERTEK

February 20, 2002

RECEIVED

ORIG AMENDMENT

FEB 21 2002

BZ

MEGA/CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

ORIGINAL

RE: Mentax[®] - TC (butenafine HCl) Cream, 1%
NDA #21-408, Amendment 003
Response to FDA Questions Received by Facsimile Transmission on
February 7, 2002

Dear Dr. Wilkin:

Reference is made to a facsimile transmission received from the Agency on February 7, 2002. The facsimile requested additional information in support of the approval of NDA 21-408. For ease of review the FDA questions will be presented in bold type followed by the Sponsor's response in normal type.

Chemistry, Manufacturing and Controls:

Please provide the location of the "Investigational Formulations section" in your original NDA submission.

The Sponsor did not include an "Investigational Formulations section" in the original NDA submission, as the same active and vehicle formulations were used throughout all of the Sponsor's clinical investigations for Mentax[®] - TC (butenafine HCl) Cream, 1%.

Clinical:

1. Please provide sample tubes of the active and vehicle study creams

The Sponsor mailed one tube each of the active and vehicle study creams via Federal Express to Sr. Comdr. Frank Cross' attention on January 31, 2002. The Sponsor was notified on February 8, 2002 that Sr. Comdr. Cross had not received the tubes. Subsequently, the Sponsor sent two additional tubes of the active and vehicle study

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

creams on February 8, 2002 via Federal Express to Sr. Comdr. Cross' attention as "Desk Copies."

2. For Clinical Protocols PDC 010-033 and PDC 010-036, please provide:

a. The date that the first patient was enrolled in each protocol and the date that the last patient was evaluated in each protocol.

In study PDC 010-033, the first subject was enrolled 9/03/99 as stated in the Clinical Study Report (CSR). In addition, the CSR states that the last subject completed on December 28, 1999. However, even though that is the date the last subject (Subject G526) completed the study per the protocol, one subject was actually evaluated for an "out of window" Day 49 visit at a date subsequent to 12/28/99. Specifically, Subject G521 was seen on 1/14/00, which is the last day any subject was evaluated in study PDC 010-033. (Source: Line Listing 6 on NDA page 3510). Please refer to the CSR on page 3150 of the NDA.

In study PDC 010-036, the first subject was enrolled July 24, 2000, as stated in the CSR for this study, and the last subject was evaluated November 20, 2000, which is the date stated in the CSR for last subject completed. Please refer to the CSR on page 3726 of the NDA.

b. date each protocol was finalized and

The final protocol for study PDC 010-033 was issued on August 17, 1999. Please refer to page 3251 of the NDA. The final protocol for study PDC 010-036 was issued on June 23, 2000. Please refer to page 3832 of the NDA.

c. the date of each amendment to each protocol and the reason(s) for each amendment.

There were no amendments to protocol PDC 010-036. Study protocol PDC 010-033 was amended once. The issue date for Amendment 1 was November 16, 1999. Amendment 1 to study PDC 010-033 increased the number of subjects to be enrolled from 72 to approximately 130. The Sponsor and study investigators were initially conservative in estimating the number of eligible subjects available for enrollment due to the fact that tinea versicolor is typically most prevalent in warmer weather and the study enrollment was not expected to begin until early Fall. As study enrollment approached the original target, investigators reported that an excess of available subjects had materialized in response to their recruiting efforts. Therefore, the protocol was amended to authorize the enrollment of these additional subjects. The original protocol had only 53% power to detect a difference between the active and vehicle groups given the cure rate assumptions utilized. Increasing the number of subjects to 130 increased the power to 80% using the same cure rate assumptions.

Jonathan Wilkin, MD

Page 3 of 6

BEST POSSIBLE COPY

Biostatistics:

1. There is an inconsistency of protocol amendment dates for study PDC 010-033, i.e., 11/11/99 on page 6222, Volume 17 vs. 11/16/99 on page 6333, Volume 17.

Please provide a clarification and submit a copy of the amendment with the original signatures and dates.

Amendment 1 to study protocol PDC 010-033 was issued November 16, 1999. This amendment date is correctly shown in the CSR in the Synopsis section on NDA page 6191, and in Section 9.3 of the CSR, Selection of Study Population, on NDA page 6207. However in Section 9.8.1 (NDA page 6222), Amendment of the Protocol, a typo resulted in the date being incorrectly shown as November 11, 1999. A copy of the original amendment with the original Bertek Pharmaceuticals Approval Form with signatures and dates is provided as Attachment 1. Please note that all signature dates on the Approval Form are equal to or greater than 11/16/99. Amendment 1 was issued in its final form on 11/16/99 and then circulated within the company for approval. The Bertek-approved Amendment was then submitted to — IRB for approval and distribution to the study sites.

2. Randomization:

a. Please provide details about your randomization procedure performed in the two pivotal trials. The details should include, but not limited to, the methods used for the randomization procedure, the number of subjects and sites pre-planned, the actual enrollments, and any randomization deviation and justification, if any.

A randomization schedule is used in all clinical studies conducted by Bertek Pharmaceuticals to randomly allocate subjects to the treatment groups of the study. The randomization procedure is described in Bertek Pharmaceutical SOP — and is as follows: A request for randomization is generated —

The request for randomization specifies the number of sites participating in the study, the number of subjects to be enrolled at each site, the ratio of active to placebo at each site, the number of drug units (e.g., tubes) in each subject's individual medication set, and the quantity of any replacement drug supplies to be provided to each site.

— is also responsible for the design of the labels to be utilized in the study, including the specific numbering system to be utilized to identify each medication set/subject.

For studies PDC 010-033 and PDC 010-036, the numbering system consisted of a two-digit number that identified the site (G1 through G5, and B1 through B8, respectively) combined with a two digit number corresponding in ascending numerical order to the number of medication sets assigned to the study site.

The Bertek — generates a randomization schedule for treatment allocation or delegates the responsibility to a contract facility. If Bertek generates the

APPEARS THIS WAY
ON ORIGINAL

randomization schedule (as was the case in studies PDC 010-033 and PDC 010-036), a computer program, *Mathematica*, is utilized to generate a series of random numbers of three digits. In order to achieve balance, the sequence of random numbers is divided into smaller groups (blocks), with typically 3, 4, or 6 numbers comprising a block. Ranks are then assigned to the numbers in each block, with the smallest number ranked first and the largest number ranked last within the group. Treatments are assigned based on rankings within the block.

To illustrate, in studies PDC 010-033 and PDC 010-036, block size is three and there are two treatment groups, A and B, where the allocation is to be 2:1, active to placebo. If the first three random numbers generated are 238, 561, 381, for example, their rank assignments will be 1, 3, 2. These ranks are considered to be random permutations of numbers 1 to 3. The first two ranks in each group are assigned Treatment A, and the last rank in each group is assigned Treatment B, or vice versa. The same method is used to allocate drug assignments for each additional block of three.

is responsible for labeling each medication set according to the randomization schedule using the numbering system to be employed in the study.

As a clinical study progresses, it sometimes happens that an individual site is not able to meet its enrollment target and a new study site may then be recruited to produce the required number of subjects. Alternatively, existing study sites may be allowed to "over-enroll" beyond their original target to make up for the deficit in study subjects at sites underachieving their targeted goal. In both of these cases,

, and a new randomization schedule for drug to supply additional study subjects would be generated according to the procedure described above.

In study PDC 010-033, in order to increase the study power, as explained in Section 1. c above, the protocol was amended to change the targeted enrollment from 72 subjects to approximately 130 subjects. In order to enable this additional enrollment, new randomization schedules were generated to accommodate the enrollment of additional study subjects at four original study sites G1, G2, G3, G4, as well as, to allow enrollment at a new study site, G5, with Dr. Suzanne Bruce as principal investigator. Dr. Bruce had just completed a tinea versicolor study for Bertek Pharmaceuticals (Study PDC 010-032) and had screened more patients with tinea versicolor than could be enrolled in that study. These subjects were , therefore, available for enrollment into study PDC 010-033.

There were no changes in the planned enrollment or number of sites for study PDC 010-036. Randomization schedules were appropriately generated for eight study sites. As the study progressed, four of the sites received additional drug supplies to allow for additional enrollment to balance four sites with less than targeted enrollment. New randomization schedules were appropriately generated for the additional drug supplied.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

BEST POSSIBLE COPY

Jonathan Wilkin, MD
Page 5 of 6

In studies PDC 010-033 and PDC 010-036, the subjects were identified by the number of the medication sets dispensed to them. Each medication set was to be dispensed in ascending sequential order as eligible subjects presented at the clinic for enrollment into the study. As can be seen on Listing 10 of PDC 010-033 and PDC 010-036 (beginning on NDA pages 6409 and 7020, respectively), almost 100% of the medication sets were dispensed appropriately as subjects presented at the clinic. In study PDC 010-033, Subject G408 appears to have been dispensed drug out of order when dispensation dates are reviewed (see Listing 9, NDA page 6601). The comment page of the Case Report Form (CRF) for subject G408 is provided as Attachment 2. However, as explained in the comment section of the subject's CRF, after the subject presented at the clinic and was assigned the next sequential medication set, it was learned that due to a work conflict, the subject could not return on the appropriate day for study visit 2. The medication was withheld and the subject returned several days later for his Day 1 visit on September 20, 1999 so that his visit 2 could take place according to protocol on Day 8. There were no other anomalies in dispensation of study medication sets in study PDC 010-033. In study PDC 010-036, one medication set, B213, was dispensed out of order due to site error.

b. Please provide the listing of treatment allocation in sequential order of patient IDs, supported by documentation, for each pivotal study, i.e., the treatment allocation lists generated prior to start of the trials.

The listing of treatment allocation in sequential order of patient IDs (recall that the medication set number becomes the subject ID number when the medication set is dispensed to a patient) has been presented for each study as an attachment to the CSR, Appendix 16.1.7 (NDA pages 6399 and 7010), entitled, Computer Generated Scheme for Study Randomization. This list is comprehensive and shows all medication allocated to an individual study site. However, not every medication set sent to a study site was actually dispensed to a subject. Listing 7, Drug Accountability (beginning on NDA pages 6519 and 7165), and Listing 10, Randomization (beginning on NDA pages 6409 and 7020) both show the ID numbers of medication sets actually dispensed to subjects, and the date of their dispensation. Records of all medication shipped to study sites, whether or not dispensed to a subject, were reconciled accurately, and the study medication was collected and returned to the Sponsor at study completion.

c. Please clarify the difference between the two listings in your randomization documents (i.e., pages 6399-6408, Volume 17, and pages 7010-7021, Volume 18), where one labels as "treatment" and the other as "replacement tubes".

Two tubes of study medication were thought to be an adequate supply for most subjects to be enrolled into the pivotal tinea versicolor studies. However, recognizing that the area of involvement might vary greatly from patient to patient, provision was made to supply each site with additional medication should the subject require it to complete his/her treatment regimen. The tube numbers for replacement medication used the same general format as the individual medication sets, except that an "R" was inserted after the site number to indicate replacement tube. However, since the numbers were randomized

APPEARS THIS WAY
ON ORIGINAL

Jonathan Wilkin, MD

Page 6 of 6

separately from the study medication sets, there is no relationship between medication set number and replacement tube number. Sites were required to contact the Sponsor to obtain the correct replacement tube number to be dispensed to a subject who required additional medication. Bertek — provided documentation of the appropriate replacement tube to dispense to the subject so that the treatment group assignment was not compromised. This system maintained the blind while minimizing the amount of extra drug at a given study site.

This amendment is being submitted in duplicate. Should you need further information or clarification regarding this submission, please contact me at (919) 991-9827 or Sherron Wiechert at (919) 991-9878. I can also be contacted by facsimile at (919) 993-5910.

Sincerely,



Charity-Anne Metz Schuller, Pharm.D.
Senior Regulatory Affairs Associate

Enclosures

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 7, 2002 Number of Pages (including cover sheet) – 2

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: For your NDA 21-407, Mentax-TC (butenafine HCl cream,) Cream, 1%, we have the following requests.

Chemistry, Manufacturing and Controls:

Please provide the location of the "Investigational Formulations section in your original NDA submission.

Clinical:

1. Please provide sample tubes of the active and vehicle study creams.
2. For Clinical Protocols PDC 010-033 and PDC 010-036, please provide:
 - a. The date that the first patient was enrolled in each protocol and the date that the last patient was evaluated in each protocol,
 - b. date each protocol was finalized and
 - c. the date of each amendment to each protocol and the reason(s) for each amendment.

Biostatistics:

1. There is an inconsistency of protocol amendment dates for study PDC 010-033, i.e., 11/11/99 on page 6222, Volume 17 vs. 11/16/99 on page 6333, Volume 17.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Please provide a clarification and submit a copy of the amendment with the original signatures and dates.

2. Randomization:

- a. Please provide details about your randomization procedure performed in the two pivotal trials. The details should include, but not limited to, the methods used for the randomization procedure, the number of subjects and sites pre-planned, the actual enrollments, and any randomization deviation and justification, if any.
- b. Please provide the listing of treatment allocation in sequential order of patient IDs, supported by documentation, for each pivotal study, i.e., the treatment allocation lists generated prior to start of the trials.
- c. Please clarify the difference between the two listings in your randomization documents (i.e., pages 6399-6408, Volume 17, and pages 7010-7021, Volume 18), where one labels as "treatment" and the other as "replacement tubes".

Thank you in advance for your timely response.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

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

/s/

Frank Cross

2/22/02 02:35:19 PM

CSO

Faxed to Applicant on 2/7/02.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 7, 2002 Number of Pages (including cover sheet) – 4

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: Our minutes of today's Biostatistics teleconference regarding your NDA 21-407, Mentax-TC (butenafine HCl cream,) Cream, 1%, follow on page 2 of this facsimile transmission.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Teleconference Date: February 8, 2002
Meeting ID#

Time: 1100

Location: N229

NDA 21-408, Mentax-TC (butenafine HCl cream) Cream, 1%

Indication: Tinea versicolor

Applicant: Bertek Pharmaceuticals, Inc.

Biostatistics Discussion of SAS Datasets

Meeting Chair: Frank Cross, Jr., M.A., CDR

Meeting Recorder (Project Manager

FDA Attendees, titles and offices:

Mohamed Alosch, Ph.D., 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

Applicant Attendees, titles and offices:

Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs

Brenda Van Lunen, M.S., Statistician

Barbara Brennan, Executive Director, Clinical Research

Patrick McGrath, Ph.D., Director, Clinical Operations

Sherron Weichert, R.A.C., Director, Regulatory Affairs

With regard to the SAS Datasets submitted to this NDA 21-408, on December 20, 2001,

Background:

During the fileability meeting of February 7, 2002, for NDA 21-408, Mentax-TC (butenafine HCl cream) Cream, 1%, the Biostatistics team had a concern in regards to the date format of a portion of the Applicant's electronic SAS data submission dated December 20, 2001. The Agency subsequently conveyed this concern to the Applicant during a brief teleconference at the conclusion of the NDA fileability Meeting and requested a revised SAS Data submission.

The Applicant requested a follow-up teleconference on February 8, 2002, to clarify the Agency's request of February 7, 2002.

Agency:

Biostatistics:

The Agency indicated that there are some inconsistencies in the aforementioned electronic SAS data set submitted on December 20, 2001. For example:

1. Patients' date of births (DOB) have "negative" values and
2. Dates of adverse event (AE) onset, resolution, signature, comment, visits, drug dispensed, last dose, drug replacement, drug returned, etc., are not identifiable.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

NDA 21-408

Mentax-TC (butenafine HCl cream) Cream, 1%

Biostatistics Teleconference Minutes

Page 2

The Agency mentioned that all the above data are not in the format of MMDDYYYY and requested that the Applicant submit a revised electronic SAS data set that presents the above data in the MMDDYYYY format.

Applicant:

The Applicant agreed with the Agency and will submit the revised electronic SAS data set per Agency request later today, February 8, 2002.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

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

/s/

Frank Cross

2/8/02 05:28:10 PM

CSO

Faxed to Applicant on 2/8/02.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

1 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

FORWARD PLANNING MEETING CHECKLIST

NDA 21-408

Mentax – TC (butenafine hydrochloride cream) Cream, 1%

February 7, 2002

Applicant: Bertek Pharmaceuticals, Inc.
Pharmacologic class: Antifungal
Type: 3S
Indication: topical treatment of Tinea versicolor
Active ingredient: butenafine hydrochloride
Filing Date: February 15, 2002
Labeling Day: September 4, 2002
User Fee Due Date: October 17, 2002

On initial overview of the NDA application:

YES NO

PROJECT MANAGEMENT:

(1) Do any of the following apply to this application (i.e., if YES, the application MUST BE REFUSED TO FILE under 314.101 (e) and there is no filing over protest):

- | | | |
|-----|--|----|
| (a) | Is the drug product already covered by an approved application? | NO |
| (b) | Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)? | NO |
| (c) | Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter 1 of Title 21 of the CFR? | NO |

(2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.101(d) and there is the potential for filing over protest):

- | | | |
|-----|--|-----|
| (a) | Does the application contain a completed application form as required under 314.50 or 314.55? | YES |
| (b) | On its face, does the application contain the sections of an application required by regulation and Center guidelines? | YES |

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

NDA 21-408

Mentax -TC (butenafine hydrochloride cream) Cream, 1%

Treatment of Tinea versicolor

Project Management Fileability Checklist

Page 2

- (c) Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is under 25.24 of the CFR? YES

Request for Categorical Exclusion is at Volume 1.3, p. 557

- (d) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries? YES

- (e) Is the NDA indexed and paginated? YES

- (f) On its face, is the NDA legible? YES

- (g) Has the applicant submitted all required copies of the submission and various sections of the submission? YES

- (h) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? N/A

- (i) Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements? YES

Per the January 11, 2002, submission, this statement can be found with each Nonclinical Study Report in the Nonclinical Pharmacology and Toxicology Section of the NDA.

- (j) If required, has the applicant submitted carcinogenicity studies? YES

- (k) On its face, does the application contain at least two adequate and well-controlled clinical trials? YES

**APPEARS THIS WAY
ON ORIGINAL**

PDC 010-033: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream, 1% for Seven Days

PDC 010-036: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream, 1% for Seven Days

- (l) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?

YES

Per the January 11, 2002, submission, this statement Can be found with each Clinical Study Report in the Clinical Data Section of the NDA.

- (m) Have all articles/study reports been submitted whether in English or translated into English?

YES

- (n) Has the applicant submitted draft labeling in compliance with 201.56 and 201.57 of the CFR?

YES

- (o) Has the applicant submitted the required FRAUD POLICY notice?

YES

Volume 1.1, p. 18

- (p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated?

N/A

- (q) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS?

YES

November 20, 2001.

APPEARS THIS WAY
ON ORIGINAL

- (r) If this is an Electronic NDA Submission, has the Applicant submitted a statement to the archival NDA that the text, tables, and data in the Electronic Submission and the archival hardcopy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions? YES

This original NDA is a partial Electronic NDA Submission, i.e., the SAS Datasets, have only been electronically submitted. Per the Applicant's January 11, 2002, submission, the proposed Package insert, Application Summary Section, Clinical Data Section, ISS and ISE electronically submitted as well as in hard copy are identical to each other.

- (s) Pediatric Use Section: Has the Applicant requested Pediatric Exclusivity? NO

The Applicant has requested "a partial waiver for pediatric subjects of 11 years or less..., because the proposed new drug product is not likely to be used in a substantial number of patients in that age group."

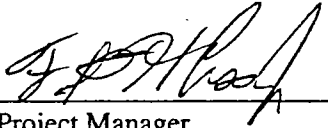
- (t) Financial Disclosure: Has the Applicant included Form 3454? YES

Volume 1.1, p. 29, signed by the responsible party of the Applicant

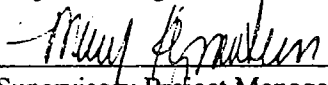
- (u) Does the Applicant have or intend to have a Patient Package Insert? NO

Applicant does not intend to have a PPI, per January 11, 2002, submission.

- (3) From a project management perspective, is this NDA fileable? If "no", please state why it is not. YES


Project Manager

Date 2/7/02


Supervisory Project Manager

Date 2/7/02

APPEARS THIS WAY
ON ORIGINAL

NDA FILEABILITY CHECKLIST

NDA Number: 21-408

Drug Name: Mentax (butenafine HCl) Cream 1%

Applicant: Bertek Pharmaceuticals Inc.

IS THE CMC SECTION OF THIS APPLICATION FILEABLE? (Yes or No) Yes

Table 1

The following parameters are necessary for initiating a full review, e.g. complete enough for review but may have deficiencies.

	Parameter	Yes	No	Comment
1	Is the NDA organized adequately for its CMC content?	X		
2	Are the CMC sections adequately indexed & paginated?	X		
3	Is the CMC sections legible?	X		
4	Are all facilities identified with full street addresses, contact names & CFN#s?	X		
5	Is there a statement that all facilities are prepared for GMP inspections?	X		
6	Has an environmental assessment or categorical exclusion been provided?	X		
7	Does the drug substance section contain controls?	X		
8	Does the drug product section contain controls?	X		
9	Have stability data been submitted to justify the requested expiry date?	X		
10	Has the applicant provided all requested data by the division during the IND & pre-NDA phases?	X		
11	Have draft container labels been provided?	X		
12	Has a draft package insert been provided?	X		
13	Has an Investigational Formulations section been included?			Not sure
14	Are there three Methods Validation documents?	X		
15	Is a statistical consult required?		X	
16	Is there a separate microbiological section? Is a micro consult required?	X		No information

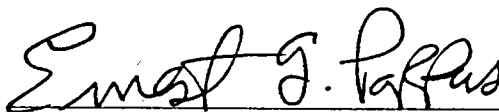
APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

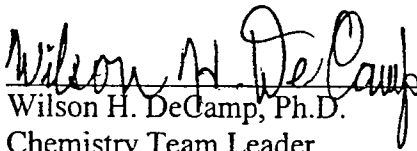
EER REPORT ATTACHED

Explanation of why this NDA is not fileable (if applicable): N.A.

Planned Completion Date: July 17, 2002

 1/31/02

Ernest G. Pappas
Review Chemist

 1/31/02

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader

Attachment

Cc: Original NDA
HFD-540/Division File
HFD-540/Chm/Pappas
HFD-540/ChmTL/DeCamp
HFD-540/ProjMgr/
HFD-830/DivDir/Chen

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 1.A Location of GCP Compliance Statements for Pivotal Clinical Studies
Presented in the Clinical Data Section of NDA #21-408

Study Number	Title	Location of GCP Compliance Statement
PDC 010-033	A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream, 1% for Seven Days	NDA #21-408; Pg. 3148
PDC 010-036	A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream, 1% for Seven Days	NDA #21-408; Pg. 3724

Table 1.B Location of GCP Compliance Statements for Supportive Domestic Clinical Studies Referenced in the Clinical Data Section of NDA #21-408

Study Number	Title	Location of GCP Compliance Statement
PDC 010-037	A 21-Day Cumulative Irritation Study in Humans	NDA #21-408; Pg. 2378
PDC 010-038	Repeated Insult Patch Test	NDA #21-408; Pg. 2525
PDC 010-047	Evaluation of Phototoxicity in Humans Using Butenafine HCl Cream 1%, Butenafine HCl Cream Vehicle, Butenafine HCl Solution 1% and Butenafine HCl Solution Vehicle	NDA #21-408; Pg. 2675
PDC 010-048	Evaluation of Human Photoallergy by Repeated Insult Patch Test Using Butenafine HCl cream, 1%, Butenafine HCl Cream Vehicle, Butenafine HCl Solution 1% and Butenafine HCl Solution Vehicle	NDA #21-408; Pg. 2787
PDC 010-046	A Single-Center, Open-Label Study to Determine the Plasma Levels of Butenafine and a Primary Metabolite, M-2, Following Topical Applications of Butenafine HCl Cream, 1%, to Patients with Severe Tinea Versicolor	NDA #21-408; Pg. 2914 and Pg. 1911

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Study Number	Title	Location of GCP Compliance Statement
PDC 010-031	A Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of Mentax [®] (Butenafine HCl) Cream 1% in the Treatment of Tinea Versicolor	NDA #20-524; Suppl. 005; Vol. 2, Pg. 2-078
PDC 010-032	A Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of Mentax [®] (Butenafine HCl) Cream 1% in the Treatment of Tinea Versicolor	NDA #20-524; Suppl. 005; Vol. 5, Pg. 5-043

Table 1.C Location of GCP Compliance Statements for Supportive Foreign Clinical Studies Referenced in the Clinical Data Section of NDA #21-408

Study Number	Title	Location of GCP Compliance Statement
G-5	Clinical Evaluation of Butenafine HCl Cream in Dermatophytosis-Comparison with Bifonazole Cream in a Well-Controlled Comparative Study	NDA #21-408; Uncontrolled Study – No GCP Statement
G-4	Clinical Evaluation of Butenafine Hydrochloride (KP-363), a New Antifungal Agent, Cream and Lotion on Dermatomycosis in a Multicenter Open Study	NDA #21-408; Uncontrolled Study – No GCP Statement
G-7	Clinical Effect of 1% Butenafine Hydrochloride (KP-363) Cream on Dermatomycosis	NDA #21-408; Uncontrolled Study – No GCP Statement

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 2.A Location of GLP Compliance Statements for Nonclinical Study Reports in the Nonclinical Pharmacology & Toxicology Section of NDA #21-408

Study Number	Title	Location of GLP Compliance Statement
TOX 010-067	Primary Skin Irritation Potential of a 1% Butenafine HCl Formulation	Pg. 1160
TOX 010-068	Primary Eye Irritation of 1% Butenafine HCl Cream Formulation in Rabbits	Pg. 1196
TOX 010-069	Acute Oral Toxicity in Rats Using 1% Butenafine HCl Cream PD 010-C-009 Formulation	Pg. 1223
TOX 010-056	A 21-Day Dermal Toxicity Study in Rats with PD-501-C-004, PD-501-C-005, PD-010-C-008 and PD-003-C-002	Pg. 1239

Table 2.B Location of GLP Compliance Statements for Referenced Supportive Nonclinical Studies in the Nonclinical Pharmacology & Toxicology Section of NDA #20-524

Study Number	Title	Location of GLP Compliance Statement
Kaken E-2	Effects of Butenafine Hydrochloride, a New Benzylamine Derivative, on Experimental Dermatophytosis in Guinea Pigs	Published Study
	<i>In Vitro</i> and <i>In Vivo</i> Anti- <i>Candida albicans</i> Activities of Butenafine Hydrochloride	No GLP Statement
Kaken E-5	Effects of Butenafine Hydrochloride, a New Benzylamine Derivative, on Experimental Tinea Pedis in Guinea Pigs	Published Study
	General Pharmacological Studies of Butenafine Hydrochloride	No GLP Statement
	Studies of Hormone Levels in Rats Treated Subcutaneously with KP-363 for 6 Weeks	No GLP Statement
	Percutaneous Acute Toxicity of Degradation Products of Butenafine Hydrochloride in Rats	Vol. 1.12, Pg. 3-2916

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Study Number	Title	Location of GLP Compliance Statement
	Intra-Peritoneal Administration Acute Toxicity Studies of Metabolites Butenafine Hydrochloride in Rats	Vol. 1.12, Pg. 3-2949
	Primary Dermal Irritation Study of Deteriorated Butenafine Hydrochloride in Rabbits	Vol. 1.12, Pg. 3-3008
	Acute Toxicity Studies of Butenafine Hydrochloride in Mice and Rats	Vol. 1.6, Pg. 3-0276
	Acute Toxicity Study of Butenafine Hydrochloride in Dogs	Vol. 1.7, Pg. 3-0380
TOX 010-001	Acute Toxicity Study of Butenafine Hydrochloride in Dogs	Vol. 1.7, Pg. 3-0441
TOX 010-043	Acute Oral Toxicity in Rats - Limit Test of: PD-010-C-003	Vol. 1.7, Pg. 3-0476
	Acute Oral Toxicity in Rats - Limit Test of: PD-010-C-003	Vol. 1.7, Pg. 3-0516
	Subacute Toxicity Study of Butenafine Hydrochloride in Dogs	Vol. 1.8, Pg. 3-0868
	Three-Month Subacute Subcutaneous Toxicity Study of Butenafine Hydrochloride in Rats	Vol. 1.7, Pg. 3-0786
	Six-Month Chronic Subcutaneous Toxicity Study of Butenafine Hydrochloride in Rats	Vol. 1.8, Pg. 3-1019
	Chronic Toxicity Study of Butenafine Hydrochloride in Dogs	Vol. 1.9, Pg. 3-1400
TOX 010-002	Primary Skin Irritation Study in Rabbits of: PD-010-C-001	Vol. 1.10, Pg. 3-1839
TOX 010-045	Primary Skin Irritation Study in Rabbits of: PD-010-C-003	Vol. 1.10, Pg. 3-2030
	Dermal and Ocular Irritation Study of Butenafine Hydrochloride in Rabbits	Vol. 1.10, Pg. 3-1906
TOX 010-003	Primary Eye Irritation Study in Rabbits of: PD-010-C-001	Vol. 1.10, Pg. 3-1872
TOX 010-044	Primary Eye Irritation Study in Rabbits of: PD-010-C-003	Vol. 1.10, Pg. 3-1995
	Contact Allergenicity, Phototoxicity and Photocontact Allergenicity Test of Butenafine Hydrochloride	Vol. 1.9, Pg. 3-1572

**APPEARS THIS WAY
ON ORIGINAL**

Study Number	Title	Location of GLP Compliance Statement
	Fertility Study of Butenafine Hydrochloride in Rats	Vol. 1.10, Pg. 3-2065
	Reproduction Study by Percutaneous Administration of Butenafine Hydrochloride During the Fetal Organogenesis Period in Rabbits	Vol. 1.11, Pg. 3-2456
	Primary Skin Irritation Study in Rabbits of: PD-010-C-003	Vol. 1.12, Pg. 3-2544
	Mutagenicity Test of Butenafine Hydrochloride - Reverse Mutation Test in Bacteria and Chromosome Aberration Test in CHL Cells	Vol. 1.12, Pg. 3-2777
TOX 010-046	<i>In Vivo</i> Rat Micronucleus Assay	Vol. 1.12, Pg. 3-2808
	Biological Fate of Butenafine Hydrochloride (KP-363) - Absorption, Distribution and Excretion in Rats, Guinea Pigs and Dogs After Single Administration of ¹⁴ C-KP-363	Non-GLP Study
	Biological Fate of Butenafine Hydrochloride (KP-363) - Absorption, Distribution and Excretion in Rats after Repeated Administration	Non-GLP Study
	Penetration in Skin after Dermal Application of Butenafine HCl	Non-GLP Study
	Metabolism of Butenafine Hydrochloride	Non-GLP Study

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

45-DAY MEETING: Checklist for filing NDA

NDA #: 21-408 Drug: Mentax^R TC

On initial overview of the NDA application:

PHARMACOLOGY/TOXICOLOGY:

	<u>Yes</u>	<u>No</u>
(1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin?	X	
(2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review begin?	X	
(3) On its face, is the pharmacology section of the NDA legible so that substantive review can begin?	X	
(4) Are all required(*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, Juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?	X	
(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required?	X	
(6) Are the proposed labeling sections relative to pharmacology appropriate (including humandose multiples expressed in either mg/m or comparative serum/plasma levels) and in accordance with 201.57?	X	
(7) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	N/A	No such studies were requested
(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X	
(9) Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X	
(10) Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	X	
(11) From a pharmacology perspective, is this NDA fileable? If "no", please state	X	

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

below why it is not.

Kumar D. Mainigi 02/04/2002
Reviewer: Kumar D. Mainigi

Supervisor: A. Jacobs *A. Jacobs 2/14/02*

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



NEW CORRESP

HSC

P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

January 31, 2002

Senior Commander Frank Cross
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N229
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED
FEB 01 2002
MEGA/CDER

**Subject: NDA 21-408 – Mentax®-TC (butenafine HCl) Cream, 1%
FDA Request for Samples of Active Drug Product and Vehicle**

Dear Commander Cross:

Per your request to Sherron Wiechert on January 30, 2002, labeled tubes of active drug product, butenafine HCl cream 1%, and of butenafine HCl cream vehicle are enclosed. The enclosed active drug product is from Lot NEEC-3. The enclosed vehicle is from Lot NEED. Lot NEEC-3 and Lot NEED were the lots used in the conduct of both of the Sponsor's pivotal studies, PDC 010-33 (*A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream, 1% for Seven Days*) and PDC 010-036 (*A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream, 1% for Seven Days*).

Should you have any questions or require additional information, please contact me at (919) 991-9827 or by facsimile at (919) 993-5910 or Sherron Wiechert by telephone at (919) 991-9878.

Sincerely,

Charity-Anne Metz Schuller, Pharm.D.
Senior Associate
Regulatory Affairs

Enclosure: Active drug product, butenafine HCl cream 1%, and butenafine HCl cream vehicle

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL



NEW CORRESP
NC

P.O. Box 14149 • Research Triangle Park, NC 27709-4149 U.S.A. • (919) 991-9800 • (888) 5-BERTEK

January 11, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED
JAN 14 2002
MEGA/CDER

RE: **Mentax[®] - TC (butenafine HCl) Cream, 1%**
NDA #21-408, Amendment 002
Request for Further Clarification of Original Submission

Dear Dr. Wilkin:

Reference is made to a telephone conversation that occurred on January 9, 2002 between FDA and Bertek Pharmaceuticals Inc. to discuss NDA #21-408 submitted on December 14, 2001. The participants in this phone conversation were Frank Cross of the FDA and Sherron Wiechert of Bertek Pharmaceuticals Inc (Bertek). The purpose of the telephone call was to confirm that all the sections and/or statements required to file the application were present in the NDA. Senior Commander Cross requested that we identify the location of these sections and/or statements by page number within the NDA and submit this information as an amendment to the application. Sr. Comdr. Cross also requested that we provide a certification that all electronic information submitted was identical to the information provided in the paper NDA.

The Bertek responses are provided below:

Certification of Accuracy of Electronic Documents

Reference is made to the electronic copies of the proposed package insert, Application Summary Section, Clinical Data Section, Integrated Summary of Efficacy and Integrated Summary of Safety supplied to Sr. Comdr. Cross in a submission dated December 31, 2001. To the best of the Sponsor's knowledge, the electronic documents are identical to their counterpart paper versions submitted in our original NDA #21-408 dated December 14, 2001.

Integrated Summary of Safety Time Frame

The Integrated Summary of Safety portion of the Clinical Data Section describes information obtained by Sponsor through clinical studies ending on November 20, 2000. Since the completion of the last pivotal study, no further safety studies have been conducted with Mentax - TC (butenafine HCl) Cream, 1%. Therefore, November 20, 2000 should be considered the "cut-off" date for the safety data. This statement was not included in the original NDA. Additional safety data is provided in Section 9.0, Safety Update, of the original NDA regarding similar butenafine HCl 1% cream formulations.

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

BEST POSSIBLE COPY

Patient Leaflet

The Sponsor did not submit a patient leaflet for Mentax® - TC Cream, 1% in the original NDA. The Sponsor has no plans at this time to develop patient leaflet for this product.

Verification of Pivotal Study Titles

The Sponsor verified that the clinical study titles supplied in Section 8.3.5 are indeed the full, correct titles of the pivotal studies. They are as follows:

- PDC 010-033: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream, 1% for Seven Days
- PDC 010-036: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream, 1% for Seven Days

Location of Good Clinical Practices (GCP) Compliance Statements

Enclosed you will find three tables listing studies that were used to supply efficacy and/or safety data in support of this NDA. Table 1.A lists the pivotal clinical study titles along with the page numbers on which the GCP compliance statements are located. Table 1.B lists the supportive domestic clinical study titles along with the page numbers on which the GCP compliance statements are located. Table 1.C lists the supportive foreign clinical study titles along with the page numbers on which the GCP compliance statements are located. The full titles of each clinical study are provided.

Location of Good Laboratory Practices (GLP) Compliance Statements

Enclosed you will find two additional tables of studies that were used to supply safety data in support of this NDA. Table 2.A lists the nonclinical study titles of the study reports supplied in the original NDA #21-408 along with the page numbers on which the report GLP compliance statements are located. Table 2.B lists the referenced supportive nonclinical study titles (NDA #20-524) along with the page numbers on which the GLP/non-GLP compliance statements are located. The full titles of each nonclinical study are provided.

This amendment is being submitted in duplicate. Should you need further information or clarification regarding this submission, please contact Sherron Wiechert at 919-991-9878.

Sincerely,



Charity-Anne Metz Schuller, Pharm.D.
Senior Regulatory Affairs Associate

**APPEARS THIS WAY
ON ORIGINAL**

Enclosures

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
Bertek Pharmaceuticals Inc.

DATE OF SUBMISSION
January 11, 2002

TELEPHONE NO. (Include Area Code)
(919) 991-9800

FACSIMILE (FAX) Number (Include Area Code)
(919) 993-5910

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
and U.S. License number if previously issued):
Post Office Box 14149
Research Triangle Park, NC 27709-4149

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-408

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
butenafine HCl cream 1%

PROPRIETARY NAME (trade name) IF ANY
Mentax-TC Cream 1%

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine hydrochloride

CODE NAME (If any)
KP-363

DOSAGE FORM:
Cream

STRENGTHS:
1%

ROUTE OF ADMINISTRATION:
Topical

(PROPOSED) INDICATION(S) FOR USE:
Tinea versicolor

APPLICATION INFORMATION

APPLICATION TYPE
(check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50)

☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

☒ 505 (b)(1)

☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)

☐ ORIGINAL APPLICATION

☒ AMENDMENT TO A PENDING APPLICATION

☐ RESUBMISSION

☐ PRESUBMISSION

☐ ANNUAL REPORT

☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT

☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT

☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

☐ CBE

☐ CBE-30

☐ Prior Approval (PA)

REASON FOR SUBMISSION

Submission of requested information

PROPOSED MARKETING STATUS (check one)

☒ PRESCRIPTION PRODUCT (Rx)

☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

☒ PAPER

☐ PAPER AND ELECTRONIC

☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF
DMF
DMF

RECEIVED

JAN 14 2002

PAGE 1

APPEARS THIS WAY
ON ORIGINAL

MEGA/CDER

DUPLICATE

This application contains the following items: (Check all that apply)

- ☐ 1. Index
- ☐ 2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
- ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
- ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
- ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(l)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER (Specify) Location of GCP & GLP statements; verification of study titles; additional information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

Sherron P. Wiechert

TYPED NAME AND TITLE

Sherron P. Wiechert, RAC
Director Regulatory Affairs

DATE

January 11, 2002

ADDRESS (Street, City, State, and ZIP Code)

Post Office Box 14149

Research Triangle Park, NC 27709-4149

TELEPHONE NUMBER

(919) 991-9878

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

**APPEARS THIS WAY
ON ORIGINAL**



NDA CRIS. ATTACHMENT
BZ

P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

December 31, 2001

Commander Frank Cross
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N229
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED

JAN 03 2002

MEGA/CDER

Subject: NDA 21-408 – Mentax®-TC (butenafine HCl) Cream, 1%
FDA Request for New Compact Disc (CD) Containing Product
Labeling, Application Summary and Clinical Sections of NDA

Dear Commander Cross:

In a teleconference between Agency representatives Frank Cross and Randy Levin and representatives of Bertek Pharmaceuticals on December 20, 2001, it was determined that the CD submitted with original NDA 21-408 on December 14, which contained Product Labeling, Application Summary, ISE, ISS, and Clinical Data sections of the NDA, was inadequate. The Sponsor has, therefore, "burned" a new CD containing the relevant sections, saving the sections in PDF and Microsoft WORD® format, as requested by the Agency. It is anticipated that this new electronic version will meet the Agency's requirements for review of the Labeling, Application Summary, ISE, ISS, and Clinical sections and will expedite overall review of NDA 21-408.

Should you need further information or clarification regarding this submission, please contact Sherron Wiechert at 919-991-9878.

Again, have a very Happy New Year!

Sincerely,

Paula Mueda
Regulatory Submissions Specialist

APPEARS THIS WAY
ON ORIGINAL

/pm

Enclosure: Compact Disc Formatted in PDF and MS WORD

ORIGINAL

BEST POSSIBLE COPY



P.O. Box 14149 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

RECEIVED

DEC 21 2001

MEGA/CDER

December 20, 2001

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Subject: Mentax[®]-TC (butenafine HCl) Cream, 1%
 NDA 21-408, Amendment 001
 Submission of Replacement Statistical Data

Dear Dr. Wilkin:

Reference is made to a conversation that occurred on December 20, 2001 between FDA and Bertek Pharmaceuticals Inc. to discuss the CD submitted with NDA 21-408 on December 14, 2001 and the fact that the FDA was unable to open the file to view the SAS statistical data. The participants in this phone conversation were Frank Cross and Randy Levin of the FDA and Sherron Wiechert, Brenda VanLunen, Dr. Patrick McGrath, Charity Schuller and Richard Boyce of Bertek Pharmaceuticals Inc. Following a detailed conversation between Mr. Levin and Brenda VanLunen, the Bertek statistician, it was decided that Bertek would resubmit the CD containing the SAS data file to determine if the problems created with the initial CD submitted with the NDA could be corrected. Bertek was also instructed to submit the data definitions in PDF not in MS Word. Bertek agreed to make this correction when the new CD was submitted.

Enclosed in this submission is the new CD containing the statistical data files in support of the approval of NDA 21-408 for Mentax[®]-TC (butenafine HCl) Cream, 1%. This CD was created as a SAS transport file in XPORT using PROC copy with XPORT engine version in SAS Unix 6.12. When we contacted SAS to ask for suggestions for a resolution to our problem, they suggested downloading the newest version of the SAS system viewer from the internet. When we downloaded this version of the SAS system viewer from the internet, we were able to open and read the files.

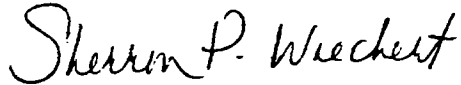
APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

If this CD is not satisfactory to FDA, please notify Sherron Wiechert immediately at (919) 991-9878 and we will attempt to make any changes necessary to fulfil the FDA requirements.

The amendment is being submitted in triplicate with a completed FDA Form 356h.

Sincerely,

A handwritten signature in cursive script that reads "Sherron P. Wiechert".

Sherron P. Wiechert, RAC
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



BERTEK
PHARMACEUTICALS INC.

19 ♦ Research Triangle Park, NC 27709-4149 U.S.A. ♦ (919) 991-9800 ♦ (888) 5-BERTEK

er 14, 2001

Wilkin, MD, Director
of Dermatologic and Dental Drug Products
Drug Evaluation V
Drug Evaluation and Research
Drug Administration
Mail Room N115
Corporate Blvd., HFD-540
e, MD 20850

Original New Drug Application
Mentax[®] -TC (butenafine HCl) Cream, 1%
NDA 21-408

Wilkin:

to section 505(b) of the Federal Food, Drug and Cosmetic Act and 21 CFR,
we are submitting the enclosed New Drug Application (NDA) for
-TC (butenafine HCl) Cream, 1%. This new drug is an optimized formula
Mentax[®] (butenafine HCl) Cream, 1% that is the subject of approved NDAs
and 20-663. This formulation was studied under IND 60,471 for the
t of tinea versicolor.

re and mailing address of the applicant are as follows:

Pharmaceuticals Inc.
x 14149
h Triangle Park, NC 27709-4149

ne and phone number of the primary contact person within Bertek
ceuticals Inc. is:

P. Wiechert, RAC
r of Regulatory Affairs
(919) 991-9878
(919) 993-5910

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Index, Forms and
Certifications

Form FDA 356h
(Application to Market)

Index to the Application

User Fee Form -
Form FDA 3397

Department Statement

Jonathan Wilkin, MD

December 14, 2001

Page 2

This submission contains the required archival and review copies and a methods validation package, as well as a completed FDA Form 356(h). In addition, a complete copy of the Chemistry, Manufacturing and Controls section has been submitted to the FDA District Office in Atlanta, Georgia.

This original new drug application is being provided entirely as a paper copy except for the following sections that are also being provided electronically on disk: draft package insert, Application Summary, Clinical Section including ISS and ISE, and the raw statistical data using SAS in a transport file.

Please note that the User Fees of \$309,647 for this application (as described in the 12/18/00 *Federal Register* notice) were previously submitted to the FDA in August of 2001. Since this NDA was not submitted as expected by October 1, 2001, it is our understanding that Bertek will be billed for any additional fees related to the review of this application.

This submission contains confidential commercial and/or trade secret information that is exempt from public disclosure under the Freedom of Information Act. No portion of this submission should be disclosed to anyone outside of the Food and Drug Administration without prior notification to, and the written consent of Bertek Pharmaceuticals Inc.

If you should have any questions concerning this submission, please contact the undersigned at the numbers provided above.

Sincerely,

Sherron P. Wiechert

Sherron P. Wiechert, RAC
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Index, Forms and
Certifications

Form FDA 356h
(Application to Market)

Index to the Application

User Fee Form -
Form FDA 3397

Debarment Statement

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 010-033	See attached
	Clinical Study PDC 010-036	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
Sherron P. Wiechert, RAC	Director Regulatory Affairs
FIRM/ORGANIZATION	
Berek Pharmaceuticals Inc.	
SIGNATURE	DATE
Sherron P. Wiechert	December 14, 2001

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

BEST POSSIBLE COPY

Automatic Renewal -
Request for Waiver

APPEARS THIS WAY
ON ORIGINAL

Printed by: PDC Media Arts/3011443-2454 EF

Form FDA 3454 Attachment

NDA 21-408

Clinical Study PDC 010-033

Principal Investigators without Financial Interest:

David Tashjian, MD	Site G1
Mark Ling, MD	Site G2
David Rodriguez, MD	Site G3
Dow Stough, MD	Site G4
Suzanne Bruce, MD	Site G5

Financial Disclosure:

None

Clinical Study PDC 010-036

Principal Investigators without Financial Interest:

Robert Pariser, MD	Site B1
Kimberly Butterwick, MD	Site B2
David Whiting, MD	Site B3
Stephen Horwitz, MD	Site B4
Michael Jarratt, MD	Site B5
Terry Jones, MD	Site B6
Ronald Savin, MD	Site B7
Joel Shavin, MD	Site B8

Financial Disclosure:

None

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Pediatric Patients -
Request for Waiver

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

N21-408

APPLICANT INFORMATION

NAME OF APPLICANT
Bertek Pharmaceuticals Inc.

DATE OF SUBMISSION
December 14, 2001

TELEPHONE NO. (Include Area Code)
(919) 991-9800

FACSIMILE (FAX) Number (Include Area Code)
(919) 993-5910

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
and U.S. License number if previously issued):
Post Office Box 14149
Research Triangle Park, NC 27709-4149

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-408

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Mentaxine HCl cream 1%

PROPRIETARY NAME (trade name) IF ANY
Mentax Cream 1%

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
4-tert-Butylbenzyl-N-methyl-L-naphthalenemethylamine hydrochloride

CODE NAME (If any)
KP-363

DOSE FORM:
Cream

STRENGTHS:
1%

ROUTE OF ADMINISTRATION:
Topical

PROPOSED INDICATION(S) FOR USE:
Acta versicolor

APPLICATION INFORMATION

APPLICATION TYPE
(check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50)

☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF ANDA, IDENTIFY THE APPROPRIATE TYPE

☒ 505 (b)(1)

☐ 505 (b)(2)

IF ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Holder of Approved Application

TYPE OF SUBMISSION (check one)

☒ ORIGINAL APPLICATION

☐ AMENDMENT TO A PENDING APPLICATION

☐ RESUBMISSION

RESUBMISSION

☐ ANNUAL REPORT

☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT

☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT

☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

☐ OTHER

SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

☐ CBE

☐ CBE-30

☐ Prior Approval (PA)

TYPE OF SUBMISSION

Drug Application

PROPOSED MARKETING STATUS (check one)

☒ PRESCRIPTION PRODUCT (Rx)

☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 28 (archive)

THIS APPLICATION IS ☐ PAPER

☒ PAPER AND ELECTRONIC

☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

RECEIVED

RECEIVED

DEC 20 2001

DEC 17 2001

DA 356h (4/00)

APPEARS THIS WAY
ON ORIGINAL

MEGA/CDER

CDR/CDER

PAGE 1

This application contains the following items: (Check all that apply)

- ☐ 1. Index
- ☐ 2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
- ☒ 3. Summary (21 CFR 314.50(c))
- ☒ 4. Chemistry section
 - ☒ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - ☒ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☒ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☒ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☒ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☒ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☒ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☒ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☒ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☒ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☒ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☒ 16. Debarment certification (FD&C Act 306(k)(1))
- ☒ 17. Field copy certification (21 CFR 314.50(l)(3))
- ☒ 18. User Fee Cover Sheet (Form FDA 3397)
- ☒ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER (Specify) Environmental Impact

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

NATURE OF RESPONSIBLE OFFICIAL OR AGENT

Sherron P. Wiechert

TYPED NAME AND TITLE

Sherron P. Wiechert, RAC
Director Regulatory Affairs

DATE

December 14, 2001

ADDRESS (Street, City, State, and ZIP Code)

Office Box 14149
Research Triangle Park, NC 27709-4149

TELEPHONE NUMBER

(919) 991-9878

The reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden to:

Department of Health and Human Services
Food and Drug Administration
R, HFM-99

Rockville Pike
Silver Spring, MD 20852-1448
Form FDA 356h (4/00)

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.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY 2 3

Cross Jr, Frank H

From: RCV_SIMMS@OCOFM.FDA.GOV
Sent: Tuesday, August 28, 2001 1:44 PM
To: KACUBAA@CDER.FDA.GOV; LUTWAKV@CDER.FDA.GOV;
WRIGHTM@CDER.FDA.GOV; KOZMAFORNARO@CDER.FDA.GOV;
CROSSF@CDER.FDA.GOV; ZECCOLAA@CDER.FDA.GOV;
CATTERSOND@CDER.FDA.GOV; KLUNKK@CDER.FDA.GOV;
STATEND@CDER.FDA.GOV; LAMBERTM@CDER.FDA.GOV;
STRONGINB@CDER.FDA.GOV; KUZMIKB@CDER.FDA.GOV;
HOLMESJ@CDER.FDA.GOV; ROBERTSK@CDER.FDA.GOV;
YOKOYAMAJ@CDER.FDA.GOV; OLIVERK@CDER.FDA.GOV;
BARNES@CDER.FDA.GOV; WILLIAMSJS@CDER.FDA.GOV; LESANE@CDER.FDA.GOV;
MOODY@CDER.FDA.GOV; PEASE@CDER.FDA.GOV; SCHMIDTS@CDER.FDA.GOV;
VACCARIL@CDER.FDA.GOV; CARTERL@CDER.FDA.GOV;
BUEHLER@CDER.FDA.GOV; JANIP@CDER.FDA.GOV; MCDONALDZ@CDER.FDA.GOV;
MORGENSTERN@CDER.FDA.GOV; ROEDERD@CDER.FDA.GOV;
DAVID@CDER.FDA.GOV; HARDEMANS@CDER.FDA.GOV;
HIGGINSK@CDER.FDA.GOV; MILLEM@CDER.FDA.GOV;
NIGHSWANDER@CDER.FDA.GOV; PURVISJ@CDER.FDA.GOV;
SCHUMAKER@CDER.FDA.GOV; BLAYR@CDER.FDA.GOV
Subject: USER FEE PAYMENT & ARREARS LIST

Effective January 1, 2001, applicants must send the full Fiscal Year 2001 application fee at the time of submission for fee liable applications and supplements. The fees for Fiscal Year 2001, as announced in the Federal Register on December 18, 2000 (Vol. 65, No. 243 page 79107) are:

Application/Clinical Data Required..... \$ 309,647
Supplement/Clinical Data Required..... \$ 154,823
Application/No Clinical Data Required... \$ 154,823

An application should be accepted for filing if a fee is submitted even if the amount of the fee is incorrect. The firm should be contacted and told to promptly remit the balance (same user fee ID number). As before, applications for which NO FEE has been received by FDA within 5 days of the receipt date of the application should not be accepted for filing.

NOTE: * denotes entries since last report

APPLICATION PAYMENTS

The following application payments have been received:

Date Payment	Firm	Userfee ID	Application #
-----------------	------	------------	---------------

* 28-AUG-2001 BERTEK PHARMACEUTICA 4178
309,647

N021408

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Bertek Pharmaceuticals Inc.
530 Davis Drive
Durham, NC 27709

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N021408

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA)

2. TELEPHONE NUMBER (Include Area Code)

(919) 991-9800

3. PRODUCT NAME

Mentax (butenafine HCl cream) Cream 1%
for the treatment of tinea versicolor

6. USER FEE I.D. NUMBER
4178

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

RECEIVED

DEC 17 2001

CDR/CDER

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

9. Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Form HFD-94
1 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

APPEARS THIS WAY
ON ORIGINAL

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE
Sharon P. Wiechert, RAC

TITLE
Director Regulatory Affairs

DATE
December 7, 2001

FDA 3397 (4/01)

BEST POSSIBLE COPY



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: August 20, 2001 Number of Pages (including cover sheet) - 11

TO: Sherron P. Weichart, RAC, Director of Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: Attached to this facsimile transmission please find our minutes of our May 21, 2001, Pre-NDA Meeting for your IND 60,471, butenafine hydrochloride cream, 1%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Meeting Date: May 21, 2001
Meeting ID# 6904

Time: 1000

Location: N225

IND 60,471, butenafine hydrochloride cream, 1%

Indication: Tinea versicolor

Applicant: Bertek Pharmaceuticals, Inc.

Pre-NDA Meeting

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
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Kumar Mainigi, Ph.D., M.P.H., Pharmacologist/Toxicologist, DDDDP, HFD-540
Markham Luke, M.D., Ph.D., Acting Clinical Team Leader, DDDDP, HFD-540
Brenda Vaughan, M.D., Medical Officer, DDDDP, HFD-540
Mohamed Alosch, Ph.D., 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:

Barbara Brennan, R.A.C., Executive Director, Clinical Operations
Bhaskar Chaudhuri, Ph.D., Vice President and General Manager
Elena Serbinova, Ph.D., R.A.C., Associate Director, Pharmacology/Toxicology
John Quigley, Jr., Ph.D., Scientific Coordinator, Research and Development
Sherron Weichert, R.A.C., Director, Regulatory

With regard to the April 3 and 20, 2001, Meeting Request and Meeting Briefing Package, respectively, the following discussion took place:

Agency:

Chemistry, Manufacturing and Controls:

Sponsor:

1. Chemistry Question 1 of Sponsor's April 20, 2001, Meeting Briefing Package: "...Does the Agency have any comments on the proposed manufacture, specifications, and analytical test methods?"

Agency:

Since NDA 20-524 and DMF — have been cross-referenced to support the proposed new NDA submission for the manufacture and control of the drug substance, this is acceptable to support the new NDA. However, assurance should be given that butenafine HCl drug substance will be —
We recommend that in-process tests be performed during the manufacture of the cream to assure either (1)

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

Sponsor:

2. Chemistry Question 2 of Sponsor's April 20, 2001, Meeting Briefing Package: "...Does the Agency agree that the stability program will be sufficient to support a — expiration dating?"

Agency:

The Sponsor's stability program is acceptable. However, this stability program is not a stability protocol. A stability protocol should be included in the NDA submission for the batches to be marketed for commercial use in the proposed package sizes. This stability protocol should include the specification for long term and accelerated studies, including quality attributes to be tested, time points, three point stability commitment, etc.

The Agency encourages the Sponsor to submit as much data as possible. If less than full term data are submitted, the proposed expiration dating should be supported by a statistical analysis of the data available to support the proposed expiration date.

3. Additional comments regarding the CMC section for the proposed NDA,
- a. A — should be included among the — tests for the finished product regulatory specifications.
 - b. A statement should be provided that all facilities involved in the manufacturing, packaging and testing of the drug substance and finished product are ready for FDA inspection.
 - c. We recommend that an additional trade name be proposed for the new formulation of butenafine hydrochloride cream, 1%, at the earliest possible time for trade name review. In general, two (2) trade names should be proposed at the time of NDA submission.

Pharmacology/Toxicology:

At this time, no additional animal studies are required for the submission of NDA.

Clinical Microbiology:

The Sponsor proposes to identify the presence of an associated organism microscopically before and to look for eradication after treatment. Since the associated organism of *Tinea versicolor*, i.e., *Malassezia furfur*, is difficult to grow; microscopic identification is an acceptable method.

Biopharmaceutics:

The Biopharmaceutics issue raised in this April 20, 2001, Meeting Briefing Package was previously discussed during a May 18, 2001, teleconference (minutes attached).

Clinical:

Sponsor:

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

1. Clinical Question 1 of Sponsor's April 20, 2001, Meeting Briefing Package: "...No additional clinical studies are planned for this submission. Does the Agency agree?"

Agency:

It appears that the Sponsor has conducted an appropriate number of Phase 3 studies required for NDA submission; however, the quality of the data is a review issue. However, the Sponsor is reminded that:

- a. No End of Phase 2 meeting was held between the Sponsor and the Agency for this formulation for this indication.
- b. No commitments regarding this formulation for this indication were made by the Agency.
- c. Statistical plans not stated *a priori* in the study protocol are considered post hoc analyses and may not meet the Agency's requirement for NDA approval.

Sponsor:

2. Clinical Question 2 of Sponsor's April 20, 2001, Meeting Briefing Package: "...Does the Agency concur with this format of presentation in the NDA?"

Agency:

Acceptable.

3. Clinical Question 3 of Sponsor's April 20, 2001, Meeting Briefing Package: "...Is this approach acceptable for the Integrated Summary of Safety?"

Agency

Acceptable.

Sponsor:

4. Other Question 1 of Sponsor's April 20, 2001, Meeting Briefing Package: "...Does the Agency agree with retention of the Mentax name for the new formulation?"

Agency:

Retention of the Mentax name for the new formulation is a review issue. If no comparative studies were conducted between the new formulation and currently marketed formulation for this indication, then the Sponsor should indicate how a clinician might be able to distinguish between the two products. The trade name for such a product in the absence of comparative studies should be sufficiently distinguishable from the trade name of the currently marketed formulation. The Sponsor should not make any comparative claims for safety or efficacy between the two formulations.

Sponsor:

The Sponsor said that they will

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

5. Other Question 2 of Sponsor's April 20, 2001, Meeting Briefing Package: "Does the Agency have any additional comments or recommendation?"

Agency:

- a. The Sponsor has not included a control arm to isolate the contribution of polyolprepolymer-2 (PPP-2)
- b. Percent involvement at baseline should be specified as an entry criterion, data collected and tabulated.
- c. Since the area of involvement might be inferred from the amount of drug applied, please provide the amount of drug applied for each patient.
- d. Any new lesions occurring on or adjacent to the same anatomical location of prior treatment should be considered a treatment failure.
- e. Unless confirmatory cultures are performed, the signs and symptoms score for scaling should be 0 at the end of the treatment and study endpoint for Effective Treatment and Complete Cure.
- f. KOH results should be negative at the end of treatment and negative at each post-treatment assessment.
- g. Proposed tables or line listings for the clinical study reports for the pivotal Phase 3 studies, should include "outcome" group data for each visit (e.g., complete cure, effectively treated, dropout) for all treated lesions and also sorted by "outcome" by patients and site.
- h. Provide on-treatment summary of All Adverse Events by Treatment and Body System [Number (%) of Patients] Safety Population without respect to causality or severity.
- i. Application site reactions should be presented separately and characterized (mild, moderate, severe) for the new formulation.
- j. On-treatment summary Adverse Events by Treatment and Body System [Number (%) of Patients] Safety Population Tables should be presented separately for each study and integrated for the ISS.
- k. Submit all CRFs including all body diagrams (e.g., Baseline Body Diagrams and diagrams indicating new lesions) for patients with application site reactions.
- l. In addition to CRF for deaths, other serious adverse experiences and for discontinuations due to adverse experiences, please provide the following:
 - i. CRF for all drop-outs
 - ii. A copy of a blank CRF
 - iii. Include a copy of the protocol in the study report section
 - iv. Index the investigators, appendices, tables, etc. for ease of location during review

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

- v. CRF for all patients who develop new lesions
- vi. Baseline Body Diagrams and New Lesion Diagrams should accompany all submitted CRFs.
- vii. 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.
- viii. To facilitate the review process, it is helpful to submit electronic files. Text and in-text tables in MS Word 97 on CD and diskette files are requested for the following sections:
 - Package Insert
 - Application Summary
 - Clinical Sections
 - Clinical Study Protocols
 - Clinical Study Reports
 - ISS and ISE
- m. The Sponsor should note that topical safety studies should be conducted with the final "to-be-marketed formulation" including phototoxicity and photosensitization topical safety studies in humans. The following phototoxicity and photosensitization studies are recommended:
 - i. Phototoxicity (25-30 subjects needed)
 - ii. Photocontact allergy (30 - 50 subjects needed)

Biostatistics:

The following statistical comments are based on the Sponsor's briefing package (IND 60,471/SN 009):

1. The Sponsor has proposed the analysis of combined studies (PDC-010-033 and PDC-010-036) to demonstrate efficacy and safety of the test drug. Following the Agency's Guidance, two independent, well-controlled and multi-center studies are required to support the efficacy claim of the test drug. The analysis of combined studies has little regulatory utility for establishing efficacy. Efficacy results for each individual study should be submitted in the NDA in addition to the combined studies.
2. Study PDC-010-033 was proposed as one of the two pivotal studies. It was conducted during 9/3/99 - 12/28/99. The original protocol, which did not pre-specify statistical analysis plan for the efficacy endpoints, was dated 8/17/99. The final version of the protocol with a statistical analysis plan was dated 2/10/00. It should be noted that the efficacy results would be considered to be post hoc which may not be acceptable for the efficacy and safety claims to be made for the test drug. During the meeting the Sponsor indicated that the statistical plan was finalized prior to unblinding the data. The Division requested that the Sponsor provide a chronological listing of all changes that occurred to the statistical plan.

**APPEARS THIS WAY
ON ORIGINAL**

BEST POSSIBLE COPY

3. For superiority comparisons in the pivotal studies (PDC-010-033 and PDC-010-036), both intent-to-treat (ITT) and per-protocol (PP) analyses should be submitted in the NDA.
4. The tables listed on pages 190-197 of the briefing package are the analysis excluding each individual center (B1-B8) for Study PDC-010-036. However, it is not clear to this Agency the purpose of such analysis. Please provide rationale for this analysis.
5. The Sponsor's submission (page 229 of the Sponsor's April 20, 2001, Meeting Briefing Package) included a list with the title of "Listing 10 – Randomization", which showed patient ID, randomization date and treatment. This list should also include the time of enrollment for each patient in addition to the date. Additionally, the computer-generated randomization list that showed the sequential treatment allocation prior to the initiation of each study should be included. A detailed description of randomization should be provided for each individual study in the NDA submission.
6. An endpoint "effective clinical response", which was defined as the total signs/symptoms scores ≤ 1 , is also listed in the tables of the briefing package (e.g., page 126 and thereafter of the Sponsor's April 20, 2001, Meeting Briefing Package). It should be noted that this efficacy endpoint was not pre-specified in the protocol (PDC-010-036) reviewed by the Agency. It might not be used in the labeling claim for the test drug.
7. In addition to the above statistical comments, the NDA submission should also include the patient data listings by center, CRT, study protocols (both original, and revised), and electronic raw data sets in SAS transport file format.

Project Management:

1. 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."

Waivers are requested in accordance with 21CFR 314.55(c).

2. 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.
3. If the Sponsor has an Information for Patients leaflet/labeling, please submit it with the proposed NDA.

**APPEARS THIS WAY
ON ORIGINAL**

The meeting ended amicably.

Signature, minutes preparer: _____

BEST POSSIBLE COPY

IND 60,471
butenafine hydrochloride cream, 1%
Pre-NDA Meeting Minutes
Page 7

Concurrence Chair (or designated signatory): _____

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Filability Checklist:

45 DAY MEETING CHECKLIST

FILEABILITY: NDA 21-408 (butenafine cream 1%)

On initial overview of the NDA application: **(YES)** NO

CLINICAL:

1. On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? *yes*
2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? *yes*
3. On its face, is the clinical section of the NDA legible so that substantive review can begin? *yes*
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose- ranging studies)? *Dose- ranging does not appear to have been done*

Study Number:

Study Title:

Sample Size:

Arms:

NDA Volume:

Pages:

5. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? *yes*

Application Type: 505(b)(1) **(Y/N)**

505 (b) (2) (Y/N) Reference drug:

Identification of pivotal trials:

Pivotal Study #1: Protocol Number: PDC 010-033

Page Location in NDA: Protocol: p. 3,252 Study Report: p. 3,148

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Is this an adequate multi-centered trial?

yes

Center	Patients Enrolled
G5 Suzanne Bruce, M.D.	27 (20.9%)
G2 Mark Ling, M.D.	18 (14.0%)
G3 David Rodriguez, M.D.	27 (20.9%)
G4 Dow Stough, M.D.	32 (24.8%)
G1 David Tashjian, M.D.	25 (19.4%)

Study Title: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream 1% for Seven Days

Study design: Randomized (Y/N) Double Blind (Y/N) Placebo controlled (Y/N)
Multicentered (Y/N)

Indication: Tinea versicolor

Study arms (dosage, duration, treatment length for each arm):

two treatment arms: butenafine HCl cream and vehicle applied topically once daily for 7 days

Efficacy endpoints (Primary and secondary):

Primary: the proportion of subjects with Effective Treatment

Secondary:

- proportion of subjects with Negative Mycology
- proportion of subjects with Complete Cure
- mean change from baseline in signs and symptom scores

How measured:

Effective Treatment: Negative Mycology + Total Signs and Symptoms score ≤ 1
(Effective Clinical Response) at Day 49

Negative Mycology: absence of hyphae in a KOH preparation of skin scrapings,
i.e., no fungal forms seen or the presence of yeast cells
(blastospores) only in the KOH preparation

Complete Cure: Negative Mycology + Total Signs and Symptoms score of zero at Day 49

Pivotal Study #2: Protocol Number: PDC 010-36

Location in NDA: Protocol: p.3,832 Study Report: p. 3,724

Has the sponsor stated that this protocol is identical in design to Study #1? Yes/No/Unknown

Is this an adequate multi-centered trial?

yes

APPEARS THIS WAY
ON ORIGINAL

Center	Patients Enrolled
B2 Kimberly Butterwick, M.D.	19 (8.8%)
B4 Stephen Horwitz, M.D.	15 (6.9%)
B5 Michael Jarratt, M.D.	27 (12.4%)
B6 Terry M. Jones, M.D.	34 (15.7%)
B1 Robert J. Pariser, M.D.	24 (11.1%)
B7 Ronald Savin, M.D.	34 (15.7%)
B8 Joel Shavin, M.D.	33 (15.2%)
B3 David Whiting, M.D.	31 (14.3%)

Study Title: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Butenafine HCl Cream 1% in the Treatment of Tinea Versicolor

Study design: Randomized (Y/N) Double Blind (Y/N) Placebo controlled (Y/N)
Multicentered (Y/N)

Indication: Tinea versicolor

Study arms (dosage, duration, treatment length for each arm):
two treatment arms: butenafine HCl cream and vehicle applied topically once daily for 7 days

Efficacy endpoints (Primary and secondary):

Primary: the proportion of subjects with Effective Treatment

"Other variables of interest":

- proportion of subjects with Negative Mycology
- proportion of subjects with Complete Cure
- mean change from baseline in signs and symptom scores
- percent change from baseline in signs and symptom scores

How measured:

Effective Treatment: Negative Mycology + Total Signs and Symptoms score ≤ 1
(Effective Clinical Response) at Day 49

Negative Mycology: absence of hyphae in a KOH preparation of skin scrapings,
i.e., no fungal forms seen or the presence of yeast cells
(blastospores) only in the KOH preparation

Complete Cure: Negative Mycology + Total Signs and Symptoms score of zero at Day 49

6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?

APPEARS THIS WAY
ON ORIGINAL

Proposed indication from sponsor's draft labeling: *tinea versicolor*

As designed, could endpoints in pivotal trial #1 support labeling?

As designed, could endpoints in pivotal trial #2 support labeling? *yes*

7. Are all data sets for pivotal efficacy studies complete for all indications (indications) requested? (this is a stat question?)

8. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? *yes*

PreIND Mtg: (Y/N)

IND number/s: 60,471

PreIND Mtg Date:

EP2 Meeting Date: no

Agency response to Phase 3 protocols:

PreNDA meeting date: May 21, 2001

Do endpoints as described by sponsor in pivotal Study 1 conform to previous agency commitments? (Y/N/No previous commitment)

Do endpoints as described by sponsor in pivotal Study 2 conform to previous agency commitments? (Y/N/No previous commitments)

Are the pivotal trials multi-centered? *Y/N*

Are there adequate numbers of patients enrolled? *Y/N* study 033 (#1) - 129 subjects
study 036 (#2) - 217 subjects

9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division? *yes*

10. Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population?

new formulation; no foreign data reported - this formulation

11. Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? *yes (Vol 22-27)*

12. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? *yes*

13. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? *yes*

14. Has the applicant submitted draft -labeling consistent with 21CFR 201.56 and 21CFR 201.57, current divisional policies, and the design of the development package? *yes*

APPEARS THIS WAY
ON ORIGINAL

15. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? *yes (cum. irr., repeat insult, absorption, phototox, photoall)*

16. Has the applicant complied with the requirements of the Pediatric Rule? *yes*

BEST POSSIBLE COPY

- a) Is this an indication that would be applicable to the pediatric population? *adolescents & up*
b) What pediatric ages are included in the protocol? *12 years and older*
c) Does the sponsor request pediatric labeling? What age groups? *12 to 16 years*

17. Financial disclosure of investigator *yes*

- a) Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for Investigators? *yes*

18. From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. *yes*

If certain claims are not fileable please state which claims they are and why they are not fileable.

Brando Cam m

Reviewing Medical Officer

Susan Walker MD

Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

100 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓
___ § 552(b)(5) Draft Labeling

72 Page(s) Withheld

☒ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling

1