CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205175Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205175 SUPPL # HFD # 540

Trade Name Ecoza

Generic Name (econazole nitrate) topical foam, 1%

Applicant Name AmDerma Pharmaceuticals, LLC

Approval Date, If Known 10/25/2013 (PDUFA)

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

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 ☒ 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 ☐

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

3 years

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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).

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 ☐

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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 8.

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

(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 8:

(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:

Study 079-2951-303 was a Phase 3 pivotal randomized, double-blind, parallel-group, vehicle-controlled, multi-center study of the safety and efficacy of Econazole Nitrate Foam 1% relative to Foam in subjects 12 years of age with interdigital tinea pedis. Econazole Nitrate Cream 1% was included as an evaluator-blinded comparator for safety purposes only to support a clinical bridge between Econazole Nitrate Foam 1% and Econazole Nitrate Cream 1%. The primary efficacy endpoint was the proportion of subjects who achieved complete cure at 2 weeks post-treatment (Day 43). Effective treatment and mycological cure were the secondary efficacy endpoints.

Study 079-2951-302 was a Phase 3 pivotal randomized, double-blind, vehicle-controlled, multi-center study of the safety and efficacy of Econazole Nitrate Foam 1% relative to Foam in subjects 12 years of age with interdigital tinea pedis. The primary efficacy endpoint was the proportion of subjects who achieved complete cure at 2 weeks post-treatment (Day 43). Effective treatment and mycological cure were the secondary efficacy endpoints.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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	079-2951-303	YES ☐	NO ☒
Investigation #2	079-2951-302	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:

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	079-2951-303	YES ☐	NO ☒
Investigation #2	079-2951-302	YES ☐	NO ☒

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

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"):

Study 079-2951-303
Study 079-2951-302

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 # 077523	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND # 077523	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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(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 ☒

If yes, explain:

==========

Name of person completing form: Matthew White
Title: Regulatory Health Project Manager
Date: 9/23/13

Name of Office/Division Director signing form: Susan J. Walker, MD, FAAD
Title: Director, DDDP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MATTHEW E WHITE
10/24/2013

SUSAN J WALKER
10/24/2013

1.3.3 DEBARMENT CERTIFICATION

AmDerma Pharmaceuticals, LLC 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.

Candis Edwards
Regulatory Agent
AmDerma Pharmaceuticals, LLC

December 19, 2012
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205175	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Ecoza Established/Proper Name: econazole nitrate Dosage Form: Foam, 1%		Applicant: AmDerma Pharmaceuticals, LLC Agent for Applicant (if applicable): Candis Edwards
RPM: Matthew White		Division: DDDP

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 018751 Spectazole (econazole nitrate) Cream, 1%

Provide a brief explanation of how this product is different from the listed drug.

Different dosage form

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 10/24/13

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is October 25, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 3

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	10/25/13
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval: 10/24/13
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	10/11/13
• Original applicant-proposed labeling	12/26/12
• Example of class labeling, if applicable	LD label included

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	10/4/13
• Original applicant-proposed labeling	12/26/12
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	9/20/13
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Final Review: 9/24/13 Conditionally Acceptable letter: 4/29/13 Review: 4/29/13
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 2/14/13 ☒ DMEPA 7/19/13 ☒ DMPP/PLT (DRISK) 8/22/13 ☒ ODPD (DDMAC) 8/21/13 ☒ SEALD 10/7/13 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review: 2/22/13
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 10/7/13
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 10/23/13
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 5/29/13 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Agency proposed PI-Track changes: 10/8/13 Agency proposed PI-Track changes: 10/3/13 PMR study comments: 9/30/13 Agency proposed PI-Track changes: 9/18/13 Agency proposed PI-Clean: 9/18/13 Carton/Container comments: 9/16/13 PMR study comments: 9/11/13 Carton/Container comments: 9/06/13 Carton/Container comments: 8/21/13 Information Request: 6/27/13 Information Request: 5/13/13 Advice: 3/19/13 Filing Communication: 3/8/13 Information Request: 2/12/13 Information Request: 2/8/13 Acknowledge NDA: 1/14/13
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 8/29/2012
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 4/15/2009
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Post-SPA Guidance mtg: 4/14/10 Pre-IND mtg: 9/10/07
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 10/24/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 9/30/13
PMR/PMC Development Templates *(indicate total number)*	☐ None 10/21/13
Clinical Information[6]	
❖ Clinical Reviews	

[6] Filing reviews should be filed with the discipline reviews.

• Clinical Team Leader Review(s) *(indicate date for each review)*	9/30/13
• Clinical review(s) *(indicate date for each review)*	Filing Review: 2/12/13 Final Review: 9/20/13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	9/20/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None Filing Review: 2/11/13 Discipline Review: 8/1/13
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None Filing Review: 2/8/13 Discipline Review: 8/27/13
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Filing Review: 2/12/13 Discipline Review: 8/29/13
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Filing review: 2/8/13 Discipline review: 8/2/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 10/16/13
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None **Biopharmaceutics:** Filing Review: 2/8/13 Discipline Review: 7/26/13 **Product Quality:** Filing Review: 2/8/13 Discipline Review #1: 8/20/13 Discipline Review #2: 9/30/13
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 6/25/13
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8/20/13
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 7/21/13 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

MATTHEW E WHITE
10/25/2013

From: White, Matthew
To: pamelaf@amderma.com; cedwards@amderma.com
Cc: Gould, Barbara
Subject: NDA 205175 for (econazole nitrate) topical foam, 1% Agency Proposed Label
Date: Tuesday, October 08, 2013 1:19:00 PM

Ms. Edwards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) topical foam, 1%.

The Agency proposed package insert in "track changes" is attached. Provide your concurrence with or a counterproposal to the Agency's comments by October 11, 2013.

NDA 205175_Ecoza
(econazole nitrate) Fc

Matthew White
Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research Food and Drug Administration
E-mail: matthew.white@fda.hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE
10/08/2013

From: White, Matthew
To: cedwards@amderma.com; pamelaf@amderma.com
Cc: Gould, Barbara
Subject: NDA 205175 for (econazole nitrate) topical foam, 1%: Agency Proposed Label
Date: Thursday, October 03, 2013 3:32:00 PM

Ms. Edwards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) topical foam, 1%.

The Agency proposed package insert in “track changes” is attached. Provide your concurrence with or a counterproposal to the Agency’s comments by October 8, 2013.


NDA 205175_Ecoza (econazole nitrate) Fo


NDA 205175_Ecoza (econazole nitrate) Fo


NDA 205175_Ecoza (econazole nitrate) Fo

Sincerely,

Matthew White
Regulatory Project Manager
Division of Dermatology and Dental Products Center for Drug Evaluation and Research Food and Drug Administration
E-mail: matthew.white@fda hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE
10/03/2013

From:	White, Matthew
To:	cedwards@amderma.com; pamelaf@amderma.com
Cc:	Gould, Barbara
Subject:	NDA 205175 for (econazole nitrate) topical foam, 1%
Date:	Monday, September 30, 2013 11:17:00 AM

Ms. Edwards,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) topical foam, 1%.

Also refer to your September 19, 2013 submission, which included the following proposal to conduct the postmarketing requirement study post approval:

Conduct in-vitro assessment to evaluate the following:

1. Inhibition potential of econazole nitrate for enzymes CVP1A2, (b) (4) 2C8, 2C9, 2C19, (b) (4) and 3A4.

   Final Protocol Submission: November 15, 2013
   Study/Trial Initiation: January 6, 2014
   Final Report Submission: March 28, 2014

2. Induction potential of econazole nitrate for enzymes CYP1A2, (b) (4) and 3A.

   Final Protocol Submission: November 15, 2013
   Study/Trial Initiation: January 20, 2014
   Final Report Submission: April 25, 2014

We have reviewed your proposal and we propose that in-vitro assessment to evaluate the inhibition potential and induction potential of the aforementioned enzymes be conducted in a single study with a single timeline.

Conduct in-vitro assessment to evaluate the following:

1. Inhibition potential of econazole nitrate for enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4.
2. Induction potential of econazole nitrate for enzymes CYP1A2, 2B6 and 3A.

Further in-vivo assessment to address drug interaction potential may be needed based on the results of the in-vitro assessment.

Final Protocol Submission:_____
Study/Trial initiation:_____
Final Report Submission:_____

Please submit your concurrence to conduct the postmarketing requirement study to be conducted post approval and your proposed timeline by Wednesday, October 2,

2013.

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: matthew.white@fda hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE
09/30/2013

Ms. Edwards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) Foam, 1%.

We also refer to your September 12, 2013 submission, containing updated carton and immediate container labeling.

Below are the Agency's comments regarding the proposed carton and immediate container labels. Provide your concurrence with or a counterproposal to the Agency's comments by September 20, 2013.

Proposed Container Labels and Carton Labeling (all packaging sizes)

1. (b) (4)

2. Revise the presentation of the established name to ensure that it is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). We recommend you relocate the dosage form and strength statements to appear on the same line; this will allow you to increase the size of the established name, dosage form and strength statements. For example:

   Ecoza
   (econazole nitrate)
   topical foam, 1%

   Note: The dosage form statement should be in lower case.

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/s/

MATTHEW E WHITE
09/16/2013

Ms. Edwards,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) topical foam, 1%.

The Agency has identified the following postmarketing requirement study to be conducted post approval:

Conduct in-vitro assessments to evaluate the following:

1. Inhibition potential of econazole nitrate for enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4.
2. Induction potential of econazole nitrate for enzymes CYP1A2, 2B6 and 3A.

Further in-vivo assessment to address drug interaction potential may be needed based on the results of the in-vitro assessment.

Final Protocol Submission: _____
Study/Trial Initiation: _____
Final Report Submission: _____

Submit to your NDA by Friday, September 20, 2013 your proposed dates for final protocol submission, study/trial completion, and final report submission for the required postmarketing study. Contact me if you have any questions.

Matthew White
Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research Food and Drug Administration
E-mail: matthew.white@fda hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE
09/11/2013

Ms. Edwards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) Foam, 1%.

We also refer to your August 30, 2013 submission, containing updated carton and immediate container labeling.

Below are the Agency's comments regarding the proposed carton and immediate container labels. Provide your concurrence with or a counterproposal to the Agency's comments by September 12, 2013.

Proposed Container Labels and Carton Labeling (all packaging sizes)

1. Reduce the size (b) (4) of the company name. (b) (4) We recommend (b) (4) reducing the size of the font.

2. In order to implement comment no. 3 without crowding the labels, delete or reduce the size of the inverted can graphic.

3. Change the following statements from:

   (b) (4)

   to

   "Ecoza topical foam is flammable. Avoid heat, flame, and smoking during and immediately following application. Contents under pressure. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C) even when empty. Do not store in direct sunlight."

4. Change the presentation of the trade name, established name, dosage form and strength to "Ecoza (econazole nitrate) topical foam, 1%".

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/s/

MATTHEW E WHITE
09/06/2013

Ms. Edwards.

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) Foam, 1%.

Below are the Agency's comments regarding the proposed carton/container labels. Provide your concurrence with or a counterproposal to the Agency's comments by August 30, 2013.

A. <u>Proposed Container Labels and Carton Labeling (all packaging sizes)</u>

1. Relocate the strength statement, "1%" to appear below the established name to help increase the readability of this information.
2. (b) (4)
3. Reduce the size (b) (4) of the company name. (b) (4) We recommend (b) (4) reducing the size of the font.
4. Relocate the route of administration statement "For Topical Use Only" to the principal display panel and increase its prominence by increasing the font size, bolding, and/or using color. Place this statement in the space (b) (4)
5. Relocate the statement "Not for ophthalmic, oral or intravaginal use" to the principal display panel immediately below the statement "For Topical Use Only". Do not use bold font or color, as this statement should not be more prominent than the intended route of administration.
6. Revise and relocate the statement "Keep Out of Reach of Children" to the principal display panel immediately below and at the same prominence as the route of administration statement. For example:

For Topical Use Only
Not for ophthalmic, oral or intravaginal use
Keep Out of Reach of Children

7. Delete the (b) (4) statement (b) (4)

8. Revise the Usual Dosage statement to read "Apply once daily for 4 weeks. See Prescribing Information."
9. Change [redacted] to polysorbate 20.
10. Change the storage temperature to: [redacted]
11. Change [redacted] to "Do not refrigerate or freeze."

B. Proposed Carton Labeling (Sample package)

1. Revise the net quantity statement [redacted] to read "Contains 4 cans of 10 g").
2. Add barcode on the carton label for 10 g presentation.

Matthew White
Regulatory Project Manager
Division of Dermatology and Dental Products
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/s/

MATTHEW E WHITE
08/21/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205175

INFORMATION REQUEST

AmDerma Pharmaceuticals, LLC
Attention: Candis Edwards
Regulatory Agent
440 U.S. Highway 22 East, Suite 104
Bridgewater, NJ 08807

Dear Ms. Edwards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) Foam, 1%.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following information requests. We request a prompt written response by July 19, 2013 in order to continue our evaluation of your NDA.

1. Combine release and stability specification into one tabulated specification for both drug substance and drug product.

2. Revise the acceptance criterion for leak rate in drug product specification to numerical limit (e.g., NMT (b) (4) et al. as per USP <601>), and update all batch release and stability data accordingly with actual values.

3. Specify the acceptance criterion (numerical limit or specific descriptions) for appearance (b) (4), packaging/product interactions. (b) (4) in the drug product specification based on the actual data.

4. (b) (4) (b) (4) data has been provided for lot CIF-C, but not for the other two lots. Provide data at 18-month testing point in Section 3.2.P.8.3 for the other two lots.

5. Clarify the notation of each batch number. For example, what do 5C and 6C mean for drug product lot # CIF-C (5C, 6C)?

6. In your method validation report for quantification of econazole nitrate and its impurities in 1% econazole nitrate foam (Report #: 69.METH1956.01):

   - Clarify the theoretical concentration of econazole nitrate (b) (4) in Tables 10 and 11 on page 14.

- Update the RRF and RRT for all three (b) (4) impurities with the correct information in Table 20 and Figure 5 on page 21.

7. The conclusions in Table 3 of section 3.2.P.7 container-closure-system are incongruous with the data. For example, you purported that all tested components meet requirements for USP <381>, USP <87>, and USP <661> when the following test results were in fact out of the corresponding limit set by USP:

(b) (4)

Update Table 3 with the conclusion to be reflective of data and provide justifications as to why the packaging components are suitable for use from a safety and quality perspective.

8. It is noted that different contract labs were used to perform USP <381>, USP <87>, and USP <661> studies with confusing descriptions of the test articles. Provide a tabular summary of all test articles with identifiable and tractable descriptions used in all three USP tests, and confirm if they are the same components to be used in your to-be-marketed product.

9. Provide analytical procedures for 76.0008, 76.0009, and 76.0049 of the release testing for the actuator, valve, and cans. Specify the ID tests for these components. State whether you will test every batch (b) (4) or accept them based on certificate of analysis (COA). If it is the latter, provide testing methods and intervals for periodical verification of the COAs.

10. We cannot assess the in-use stability study results provided in your amendment dated June 21, 2013, due to the absence of sample description and experimental details. Provide experimental details and sample description for the in-use stability study. Summarize and tabulate the study results.

11. The solubility data provided in the most recent amendment do not support your statement (b) (4) Add (b) (4) to assure batch to batch consistency.

If you have any questions, call Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
06/27/2013
Signing for Susan Walker, MD, DDDP Division Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205175 **INFORMATION REQUEST**

AmDerma Pharmaceuticals, LLC
Attention: Candis Edwards
Regulatory Agent
440 U.S. Highway 22 East
Suite 104
Bridgewater, NJ 08807

Dear Ms. Edwards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) Foam, 1%.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by May 24, 2013 in order to continue our evaluation of your NDA.

Biopharmaceutics

1. Indicate [redacted (b) (4)] with proper documentation.
2. There is an apparent discrepancy [redacted (b) (4)] used for the IVRT study. [redacted (b) (4)] Explain this discrepancy.
3. Submit the raw data for the IVRT studies [redacted (b) (4)] he raw data can be submitted in the following format:

[redacted (b) (4)]

(b) (4)

Chemistry, Manufacturing and Controls

Regarding Drug Product Characterization and Process:

4. In the formulation development (on page 25 of 82) you have provided the following data (b) (4) in the final drug product:

(b) (4)

5. Provide the following information for Manufacturing Process in Section 3.2.P.3.3:

    a. Equipments used in packaging/filling operation

    b. Operation parameters and (b) (4) controls with acceptance criteria in packaging/filling operations, such as filling rate and fill weight (b) (4)

Regarding the Finished Drug Product Specification:

6. Resubmit the drug product specification in tabular form including attributes, acceptance criteria (descriptive or numerical), and testing methods. The specification should include microbial controls.

7. Revise the drug product specification to include ID test.

8. [redacted] (b) (4)

Regarding the Container Closure System:

9. In your report entitled "Product and Component Interaction Study Report", out-of-specification results were observed for appearance, assay, and impurities for multiple components of the container/closure system. Investigate the nature and root causes of the observations, and indicate whether drug/components interactions or leachable/extractables have any adverse impact on the quality, safety, and efficacy of the drug product during its entire shell life and in-use period.

Additional Requests:

10. Provide forced degradation study report: Method development technical report 54.1488.

11. Tabulate all differences between the two different manufacturing sites, including equipment, if different.

12. Tabulate information for all clinical batches and registration batches, including batch size, manufacturing date, drug substance lot number, manufacturing site, and purpose of use etc.

13. Your drug product release specifications do not include microbial limits testing, but your post-approval stability protocol states that finished product testing is performed. Clarify whether you will perform microbial limits testing for drug product release, and if so, provide updated specifications.

Clinical Microbiology

14. For mycological testing, you state that *T. rubrum* MYA 4438 strain was used for testing of isolates from patients in Phase 2 trials and *T. rubrum* MYA 4498 strain for testing of isolates from patients in Phase 3 trials. Clarify if this was a typographical error and *T. rubrum* MYA 4438 strain was used for testing of isolates from Phase 3 trials as recommended by the CLSI (CLSI M38-A2).

Clinical Pharmacology

15. Reorganize Section 12 of the Package Insert into subsections (12.1, 12.2, 12.3 and 12.4) and propose labeling language for each of these subsections with data obtained using your Foam formulation. For additional information, you are referred to the draft guidance

for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (February 2009).*

If you have any questions, call Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
05/13/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205175

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

AmDerma Pharmaceuticals, LLC
440 US Highway 22 East, Suite 104
Bridgewater, NJ 08807

ATTENTION: Candis Edwards
Regulatory Agent

Dear Ms. Edwards:

Please refer to your New Drug Application (NDA) dated December 21, 2012, received December 26, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Econazole Nitrate, Topical Foam 1%.

We also refer to your January 29, 2013, correspondence, received January 30, 2013, requesting review of your proposed proprietary name, Ecoza. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Ecoza, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 29, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet L. Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact Cristina Attinello, Regulatory Project Manager in the Office of New Drugs (OND) at (301) 796-3986.

Sincerely,
{See appended electronic signature page}
Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/29/2013

Attinello, Cristina

From: Attinello, Cristina
Sent: Tuesday, March 19, 2013 10:27 AM
To: 'Pamela Fitzpatrick'; C. Edwards
Cc: Folkendt, Michael M; Tran-Zwanetz, Catherine; Gould, Barbara
Subject: RE: NDA 205175 Econazole Nitrate Foam 1% Questions for ONDQA (Biopharmaceutics)

Hello,

In regards to the clarifying questions you submitted via email;

Submit to us all of the IVRT method validation information you currently have. We will review this information with the IVRT method development report and IVRT method validation report that you submitted in the original submission. We will inform you if further information is required during the review process.

Regarding #18 in the filing communication, we will review the video or photographs that demonstrate how the foam was applied (b) (4) However, we also request that you submit a written description of how the foam product was applied (b) (4) each time with proper documentation.

We look forward to your response, and the responses to the other review comments, by this Friday.

Thank you,

Cristina

From: Pamela Fitzpatrick [mailto:pamelaf@amderma.com]
Sent: Friday, March 15, 2013 4:43 PM
To: Tran-Zwanetz, Catherine
Cc: Attinello, Cristina; Gould, Barbara; C. Edwards; Folkendt, Michael M
Subject: NDA 205175 Econazole Nitrate Foam 1% Questions for ONDQA (Biopharmaceutics)

Dear Cathy,

I am a Regulatory Consultant for AmDerma Pharmaceuticals. AmDerma is in receipt of a (74 day) Filing Communication dated March 8 which includes a request for Biopharmaceutics information. In the letter, AmDerma was advised to contact ONDQA for specific guidelines regarding this request.

Per my discussion this afternoon with Michael Folkendt, attached please find our CMC consultant's request for clarification on these issues. Please be advised that these questions have already been forwarded to the OND Project Manager, Cristina Attinello.

Our response is due back to the Agency by next **Friday, March 22** (AmDerma was granted a one week extension from the original date).

We are happy to arrange a teleconference, or to receive the Agency's response via email. Your assistance with expediting this matter is greatly appreciated.

If you have any questions or need any further information, please contact me via email or by phone at (631) 952-0214 Ext 104.

Thank you again for your help.

Kind Regards,

Pam

Pamela Fitzpatrick
Regulatory Consultant for AmDerma Pharmaceuticals
pamelaf@amderma.com

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/s/

CRISTINA Petruccelli Attinello
03/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205175

FILING COMMUNICATION

AmDerma Pharmaceuticals, LLC
Attention: Candis Edwards
Regulatory Agent
440 U.S. Highway 22 East
Suite 104
Bridgewater, NJ 08807

Dear Ms. Edwards:

Please refer to your New Drug Application (NDA) dated December 22, 2012, received December 26, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (econazole nitrate) Foam, 1%.

We also refer to your amendments dated February 7, 14, and 15(2), 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 16, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Chemistry, Manufacturing, and Controls

1. Submit the following samples for dosage form evaluation:
   - A representative sample of U.S. registration stability batches for each packaging configuration.
   - A representative sample of (b) (4) batches.

   Each sample should be accompanied with corresponding certificate of analysis.

2. Provide method procedure with method number for the test on appearance (b) (4) Currently, the referenced method (b) (4) contains no procedural information, which is unacceptable.

3. Revise the acceptance criterion for the test on appearance (b) (4)

4. Summarize batch release results in one table for the Phase 3 clinical and registration stability batches.

5. Summarize registration stability data into tables. Each table should cover multiple time points.

6. Revise Table 1 of Section 3.2.P.1.1 by assigning a function for each inactive ingredient based on physicochemical properties of the ingredient (b) (4) We have noted that the function of dimethicone (b) (4) in the formulation has not been assigned, and the functions of propylene glycol and glycerin have been assigned (b) (4)

7. Revise Master Batch Records by adding information regarding (1) the targeted value and allowable range for operational parameters (b) (4) and (2) (b) (4) tests with acceptance criteria.

8. Clarify whether the proposed starting material, (b) (4) is commercially available. Provide a justification to support the proposed starting material designation for this compound.

9. Provide the following solubility information for econazole nitrate: pH-solubility profile, solubility (b) (4) and solubility (b) (4)

Clinical Pharmacology

10. Provide storage stability data of internal standard miconazole to support the duration of bioanalysis.

11. According to your reports, trial 0792951-109 (Pediatric PK) was initiated on September 21, 2011 (first informed consent) and as per your bioanalytical study report (MC11B-0109) the sample analysis was completed on May 16, 2012, i.e. a total duration of 238 days. The extended stability of econazole in human plasma (as per report MC08B-088) of 188 days will be inadequate to support the stability of PK samples for the entire duration from initiation of the trial to completion of bioanalysis. Provide additional stability data to support storage stability of at least 238 days or provide detailed data to support that all samples were analyzed within 188 days of sample collection.

12. According to the report for trial D79-2902-07 the trial completion date provided is September 25, 2008 and according to your pharmacokinetics report (MC08B-0089 – Appendix A), the bioanalysis project completion date is stated as September 8, 2008. Clarify how the bioanalysis project completion date is before the trial completion date.

13. For trial D79-2902-07, add a column to provide identification of the treatment administered for each subject (Foam or Cream) in your raw data set file pc.xpt.

14. For trial D79-2902-07, provide the relative bioavailability data between foam and cream as ratio of the geometric mean as well as 90% confidence interval of the ratio of the geometric mean for AUC and C_{max} for the entire population. In addition, provide descriptive statistics and statistical analysis comparing the foam and the cream formulation by calculating 90% confidence interval for the geometric mean of C_{max} and AUC stratified by subject disease type (i.e. interdigital only, moccasin only and subjects having both interdigital and moccasin).

15. We note that PK following drug administration was assessed only on the final day of the study after 4 weeks of drug application in trial D79-2902-07 and 0792951-109. We also note that the proposed treatment duration with your product is 4 weeks. Hence, the systemic exposure information obtained on the final day of treatment could be from subjects that have healed skin and this may not represent maximal use conditions. For trial D79-2902-07, provide a sub-group analysis (both descriptive statistics and relative bioavailability analyses) of your PK data by categorizing the data from subjects with healed skin and data from subjects that have not yet healed. For trial 0792951-109, provide comparative systemic concentrations by categorizing the data from subjects with healed skin and data from subjects that have not yet healed. Also provide a table for each of these 2 trials showing information on disease severity at baseline and on the day of PK assessment for each subject.

16. For your Phase 3 trial (0792951-303), provide bioanalytical method validation and bioanalysis reports.

Biopharmaceutics

17. The applicant validated the IVRT method based on specificity, linearity, LOD, LOQ, and stability of solutions. The IVRT method development and validation report should contain (but not limited to) the following information:

    - Choice of (b) (4) apparatus (b) (4) and condition
    - Linearity and Range
    - Accuracy/Precision and Reproducibility
    - Recovery, Mass Balance & Dose Depletion
    - Sensitivity
    - Specificity
    - Selectivity
    - Robustness
    - Membrane Inertness
    - Receptor Solution Solubility/Stability

    The sensitivity, specificity, selectivity and robustness of the methods need to be performed (b) (4) You may consult ONDQA for specific guidelines in this respect.

18. Explain precisely how the foam was applied (b) (4)

Clinical Microbiology

19. Provide analysis datasets that include subject and site identifiers, treatment arm, and fungal species identified at different visits (e.g., baseline, day 29, and day 43), as well as clinical cure, mycological response, and antifungal susceptibility test results for each of the clinical studies (Study 302, 303, and 07). It will aid in our review if the datasets can be organized as shown in Table 1 (attached).

20. Provide tables summarizing clinical and mycological response by fungal species as well as clofazimine MIC by fungal species at different visits as shown in Tables 2 and 3 (attached); a separate Table should be created for each study.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

21. In Highlights, all headings must be presented in the center of a horizontal line, in upper case letters and bolded. Re-center the headings for Indications and Usage and Contraindications.

22. In Highlights, white space must be present before each major heading. Add white space between each major heading in Highlights.

23. In Highlights, each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. Add a reference to the end of the summarized statement under the Adverse Reactions heading.

24. In Highlights, section headings must be presented in the appropriate order. Add a product title following the Highlights Limitation Statement.

25. In Highlights, the product title must be bolded. Bold the newly added product title.

26. A horizontal line must separate the Highlights from the Table of Contents (TOC). Add a line that separates Highlights from the TOC.

27. In Highlights, the Highlights Limitation Statement must appear with the drug product name in upper case. Revise this statement to include only the proposed proprietary name in upper case.

28. In Highlights, Initial U.S. Approval must be placed immediately beneath the product title. Remove the space between the product title and the Initial U.S. Approval statement.

29. In Highlights, if a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section: [(Product) is a (name of class) indicated for (indication)]. Add a pharmacologic class statement to the Indications and Usage section of Highlights.

30. In Highlights, the Adverse Reactions statement should include the name of the manufacturer and the manufacturer's U.S. phone number. Remove the manufacturer's website following the phone number of the manufacturer.

31. In Highlights, the Patient Counseling Information statement should include the following bolded verbatim statement (without quotations) "**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."** Replace the Patient Counseling Information statement you proposed with the one provided above.

32. In Highlights, the revision date must appear bolded and in a month/year fashion. Edit the revision date to reflect "XX/2013."

33. A horizontal line must separate the TOC from the FPI. Add a line that separates the TOC from the FPI. Additionally, move the beginning of the FPI to the following page of the proposed label.

34. In the TOC, the section headings and subheadings must match the section headings and subheadings in the FPI. Remove the headings for section 7 Drug Interactions and section

15 References form the TOC. Edit the subheading for section 6.1 Clinical Trials Experience and the heading for section 16 How Supplied/Storage and Handling to match in the TOC and FPI.

35. In the FPI, the bolded section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1). In the FPI, the subheading for 13.2 is not named in accordance with this CFR citation. Consider removing 13.2 as a subsection and placing as text beneath section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. Edit section 16 How Supplied/Storage and Handling in the FPI so that no ampersand appears in the heading.

36. In the FPI, the preferred presentation for cross-references is the section heading (not subsection heading) followed by the numerical identifier in italics. Edit the microbiology reference in section 12 Clinical Pharmacology to match the above convention.

37. In the FPI, Patient Counseling Information must reference any FDA-approved patient labeling, including the type of patient labeling at the beginning of section 17. Replace the current Patient Counseling Information statement with "See FDA-approved patient labeling (Patient Information)."

38. Consider the removal of patent information at the end of the FPI.

39. Remove "DRAFT December 2012" from the end of the FPI.

We request that you resubmit labeling that addresses these issues by March 15, 2013. The resubmitted labeling will be used for further labeling discussions. To guide you in making the above revisions, a sample tool illustrating the format of Highlights and the TOC is available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm.

Please respond to all the above requests for information by March 15, 2013. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

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

Table 1: CL Clinical microbiology dataset sample template for Study 302 (separate Tables for Study 303 and 07)

PtID	Center/ Study Site	Treatment Group	ITT/PP Flag	Phase/Visit	Organism	Econazole MIC	Clinical Response	Mycological Response**	
								KOH	Culture
101		E		Baseline					
101		E		Day 29					
101		E		Day 43					
102		E		Baseline					
102		E		Day 29					
102		E		Day 43					
103		P		Baseline					
103		P		Day 29					
103		P		Day 43					
103		P		Baseline					
103		P		Day 29					
103		P		Day 43					

* If more than one species was identified in a specimen from a patient then that should be identified
**If both KOH and culture was performed on specimens then please show the results separately
E= econazole; P = Placebo

Table 2: Clinical and mycological response by fungal species for Study 302 (separate Tables for Study 303 and 07)

Treatment Group/Species	Day 29 n /N (%)			Day 43 n /N (%)		
	Clinical Success	Proven Mycological Eradication	Presumed Mycological Eradication	Clinical Success	Proven Mycological Eradication**	Presumed Mycological Eradication
ITT						
Econazole						
US sites						
T. rubrum						
Non US sites						
T. rubrum						
T. mentagraphytes						
Total						
Placebo						
US sites						
T. rubrum						
Non US sites						
T. rubrum						
T. mentagraphytes						
Total						
PP						
Econazole						
US sites						
T. rubrum						
Non US sites						
T. rubrum						
T. mentagraphytes						
Total						
Placebo						
US sites						
T. rubrum						
Non US sites						
T. rubrum						
T. mentagraphytes						
Total						

**If both KOH and culture was performed on specimens then please show the results separately

Comment [SB1]: Add rows for additional species as needed

Comment [SB2]: Add rows for additional species as needed

Comment [SB3]: Add rows for additional species as needed

Comment [SB4]: Add rows for additional species as needed

Table 3: Clofazimine MIC range and MIC_{90} at different visits by fungal species for Study 302 (separate Tables for Study 303 and 07)

Organism	**US/nonUS site**	**Clofamizine MIC range (MIC_{90})**		
		Baseline (n=)	**Day 29 (n=)**	**Day 43 (n=)**
T. rubrum	US			
	nonUS (Dominican republic)			
T. mentagraphytes				

Comment [SB5]: Add rows for additional species as needed

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/s/

TATIANA OUSSOVA
03/08/2013
Signed on behalf of Dr. Susan Walker

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205175 **INFORMATION REQUEST**

AmDerma Pharmaceuticals, LLC
Attention: Candis Edwards
Regulatory Agent
440 U.S. Highway 22 East
Suite 104
Bridgewater, NJ 08807

Dear Ms. Edwards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) Foam, 1%.

We are reviewing the Clinical section of your submission and have the following comments and information request. We request a prompt written response by February 14, 2013 in order to continue our evaluation of your NDA.

Your application does not identify the requirements for certain 505(b)(2) applications as described at 21 CFR 314.54. A 505(b)(2) application should include the following:

- Identification of those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference (for example, for reproductive toxicity studies).

- If the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy for a listed drug or drugs, identification of any and all listed drugs by established name, proprietary name (if any), dosage form, strength, route of administration, name of the listed drug's sponsor, and the application number (21 CFR 314.54(a)(1)(iii)).

If there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.

Identify how your bridge is established to the referenced product.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
02/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205175 **INFORMATION REQUEST**

AmDerma Pharmaceuticals, LLC
Attention: Candis Edwards
Regulatory Agent
440 U.S. Highway 22 East
Suite 104
Bridgewater, NJ 08807

Dear Ms. Edwards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) Foam, 1%.

We are reviewing the Clinical Microbiology section of your submission and have the following comments and information requests. We request a prompt written response by February 15, 2013 in order to continue our evaluation of your NDA.

1. In the mycology study report the results of *in vitro* susceptibility testing of clinical isolates performed (b) (4) were summarized as the range of minimum inhibitory concentration (MIC), MIC_{50} and MIC_{90} values irrespective of the fungal species and the time of collection of the isolate. It is unclear if these include results of patients who failed therapy. The results by different fungal species and isolates collected from patients enrolled at different sites and at different visits could not be found. Clarify if these results (summary tables and analysis datasets) have been submitted. If yes, then identify their location. If these results have not been submitted, provide us with the following:
    i. Summary tables that include MIC_{50}, MIC_{90}, and MIC range by fungal species, different sites, and different visits (e.g., baseline, day 29, and day 43).
    ii. Analysis data sets that include subject and site identifiers, treatment arm, and fungal species identified at different visits (e.g., baseline, day 29, and day 43), as well as clinical cure, mycological response, and antifungal susceptibility test results.

    The results of each of the clinical trial should be presented separately. We encourage you to share examples of tables with us using sham datasets for our comment and feedback.

2. You state that the Clinical and Laboratory Standards Institute (CLSI) method was used for *in vitro* susceptibility testing. Provide a reference to the CLSI method used; any deviations from the CLSI method should also be specified. Additionally, provide results of the quality control strains included for testing.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
02/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205175

NDA ACKNOWLEDGMENT

AmDerma Pharmaceuticals, LLC
Attention: Candis Edwards
Regulatory Agent
440 U.S. Highway 22 East
Suite 104
Bridgewater, NJ 08807

Dear Ms. Edwards:

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

Name of Drug Product: (econazole nitrate) Foam, 1%

Date of Application: December 22, 2012

Date of Receipt: December 26, 2012

Our Reference Number: NDA 205175

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 22, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Cristina Attinello, MPH
Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

CRISTINA Petruccelli Attinello
01/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077523

MEETING MINUTES

AmDerma Pharmaceuticals, LLC
c/o Amneal Enterprises
Attention: Candis Edwards
Regulatory Affairs Consultant
85 Adams Avenue
Hauppauge, NY 11788

Dear Ms. Edwards:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (econazole nitrate) Foam, 1%.

We also refer to the teleconference between representatives of your firm and the FDA on August 29, 2012. The purpose of the meeting was to discuss the planned NDA submission for IND 077523.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 29, 2012, 9 AM
Meeting Location:	Teleconference
Application Number:	IND 077523
Product Name:	(econazole nitrate) Foam, 1%
Proposed Indication:	For the treatment of interdigital tinea pedis
Sponsor Name:	AmDerma Pharmaceuticals, LLC
Meeting Chair:	Tatiana Oussova, MD
Meeting Recorder:	Cristina Attinello

FDA ATTENDEES

Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Amy Woitach, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jerry Wang, PhD, Nonclinical Reviewer, DDDP
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
Cristina Petruccelli Attinello, MPH, Regulatory Project Manager, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Tarun Mehta, PhD, Chemistry Reviewer, DPA II, Branch III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP 3
Carolyn McCloskey, PharmD, Safety Evaluator, OSE
Jessica Weintraub, PharmD, Safety Evaluator, OSE
Lois LaGrenade, PharmD, Safety Evaluator, OSE
Roy Blay, OSI Reviewer

SPONSOR ATTENDEES

Candis Edwards, Regulatory Affairs Consultant, AmDerma Pharmaceuticals
Shankar Hariharan, PhD, Advisor Scientific Strategy, AmDerma Pharmaceuticals
Todd Kays, PhD, Clinical Consultant, AmDerma Pharmaceuticals
Pamela Fitzpatrick, Regulatory Affairs Consultant, AmDerma Pharmaceuticals
Arlin Frias, Regulatory Affairs Consultant, AmDerma Pharmaceuticals
Vincent Manetta, Director, Product Development, Quinnova Pharmaceuticals
(b) (4) Nonclinical Consultant
(b) (4) Biostatistician Consultant (b) (4)

(b) (4) Clinical Consultant (b) (4)

Purpose of the Meeting:
The purpose of the meeting is to discuss the planned NDA submission for IND 077523.

Regulatory Correspondence History

We have had the following meetings with you:
- Post-SPA Guidance Meeting: April 14, 2010
- End of Phase 2 Meeting: April 15, 2009
- Pre-IND Meeting: September 10, 2007

We have sent the following correspondences:
- Advice Letter: March 2, 2012
- Advice Letter: February 18, 2011
- Advice Letter: October 1, 2010
- Post-SPA Guidance Meeting Minutes: April 21, 2010
- SPA Agreement (2): January 7, 2010
- End of Phase 2 Meeting Minutes: April 27, 2009
- Advice/Information Request: May 30, 2008
- Advice/Information Request: May 13, 2008
- Advice/Information Request: May 5, 2008
- Advice/Information Request: March 20, 2008
- Pre-IND Meeting Minutes: October 2, 2007

Regulatory

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 draft guidance for industry *Applications Covered by Section 505(b)(2)* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Question 1:
Does the Agency agree that AmDerma's 505(b)(2) NDA, which includes clinical data, is eligible for a 3-year exclusivity term pursuant to 21 CFR 314.108?

Response:
The Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until approval of an NDA. As described in 21 CFR 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it **is entitled. FDA will consider the applicant's** assertions regarding exclusivity following approval of the application.

For further information regarding exclusivity, refer to
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm.

Question 2:
Based on the letter received from the Agency on April 27, 2009 describing the Pediatric Research Equity Act of 2003, which requires all applications for new active ingredients, new dosage form, new indication, new routes of administration, and new dosing regimens to contain assessment of the safety and effective of the product in pediatric patients, AmDerma conducted a pharmacokinetic study on patients 12 to 18 years of age. Does the Agency agree that **AmDerma's 505(b)(2) NDA is eligible for an additional** 6 month pediatric exclusivity term pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a)?

Response:
No, we do not agree. The Pediatric Exclusivity provision under the Best Pharmaceuticals for Children Act allows sponsors to qualify for an additional six months of marketing exclusivity, which attaches to any existing patent or exclusivity for the active moiety. It is not a stand-alone exclusivity. To qualify for pediatric exclusivity, a sponsor must:

1) be in receipt of a Written Request from FDA;
2) submit study reports to the NDA **after** receipt of the Written Request; and
3) meet the terms of the Written Request.

If you wish to qualify for pediatric exclusivity, submit a "Proposed Pediatric Study Request" requesting a Written Request from FDA. For further information, refer to the guidance for industry *Qualifying for Pediatric Exclusivity* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078751.pdf .

Question 3:
AmDerma intends to file the NDA in eCTD format. Are there any electronic filing requirements that are specific to the Division?

Response:
The Division does not have any requirements for electronic submission that differ from those at the CDER eCTD webpage for all current versions of specifications and guidances related to the eCTD:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm.

Contact esub@fda.hhs.gov for questions related to preparing or submitting your eCTD submission.

Question 4:
AmDerma intends to request a Prescription Drug User Fee Waiver, based on its small business status. The waiver will be submitted to the Agency prior to submission of the 505(b)(2) NDA and the anticipated favorable response may not be received until after its 505(b)(2) NDA is submitted. Does the Agency agree that AmDerma can file the 505(b)(2) NDA without paying the filing fee at the time of submission, based on the waiver request?

Response:
No, we do not agree. The Food, Drug, and Cosmetic Act does not provide for deferral of user fees, and FDA does not grant deferrals of user fees based on pending waiver or reduction requests. FDA therefore expects that all product and establishment fees will be paid without regard to a pending request for a fee waiver or reduction.
Refer to the guidance for industry *User Fee Waivers, Reductions, and Refunds for Drug and Biological Products* **for further information. You may also refer to "Frequently Asked Questions on Prescription Drug User Fees (PDUFA)" at**
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069943.htm#P227_18912.

If you have any questions (e.g., waiver request, refund request) you should contact:

Michael Jones
Food and Drug Administration
10903 New Hampshire Ave, Building 51, Room 6288
Silver Spring, MD 20993-0002

Phone: 301-796-3602
Email: michael.jones@fda.hhs.gov
Fax: 301 847-8711

or

Beverly Friedman
Food and Drug Administration
10903 New Hampshire Ave, Building 51, Room 6284
Silver Spring, MD 20993-0002

Phone: 301-796-3602
Email: beverly.friedman@fda.hhs.gov
Fax: 301 847-8711

Chemistry, Manufacturing and Controls (CMC)

Question 1:
AmDerma has updated the Drug Substance specifications to comply with the Agency's previous requests. Does the Agency agree that the proposed drug substance tests and specifications are acceptable for filing?

Response:
We agree that the proposed drug substance specification is acceptable for filing.

However, the test method validation for the related substances is inadequate. We refer you to the validation of (b) (4) impurities (b) (4)

Meeting Discussion:
The sponsor (b) (4) questioned how method validation can be accomplished for these three impurities. The Agency responded that the method validation can be accomplished by using response factors if the sponsor is able to determine the response factors for these three impurities. The sponsor replied that they are able to determine the response factors and accepted the Agency's recommendation.

Question 2:
AmDerma has updated the Finished Product release and Stability specifications to comply with the Agency's previous requests. Does the Agency agree that the proposed Finished Product release and Stability specifications are acceptable for NDA filing?

Response:
Yes, we agree.

Question 4:
AmDerma has updated the container/closure specifications to comply with the Agency's previous requests. Does the Agency agree that the proposed container/closure specifications are acceptable for NDA filing?

Response:
Yes, we agree.

Meeting Discussion:
The sponsor proposed to submit USP test results on container/closure within one month after the NDA submission. The Agency agreed that this would be acceptable.

Question 5:
Section 13.2.6.2 provides a listing of the proposed USP safety testing that is being conducted for the container/closure system. Does the Agency agree that the tests described in this table are adequate for characterization of the safety of the container/closure system in support of the 505(b)(2) NDA filing?

Response:
Yes, we agree.

Question 6:
In the event of any changes to the container/closure system components (i.e materials of constructions, manufacturer, etc.), AmDerma intends to include a packaging component comparability protocol in the 505(b)(2) NDA filling. Can the Agency provide guidance on the testing that would be recommended to be included in the comparability protocol?

Response:
The comparability requirements are largely dependent on the kind of changes being implemented. Therefore, the recommendation of the testing is a review issue.

Question 7:
Does the Agency agree that adequate safety information is provided in support of the proposed container/closure configuration that will be used for commercial distribution, and this information is sufficient for NDA filing?

Response:
Yes, we agree.

Question 8:
Does the Agency agree that the executed stability protocol provides sufficient information for NDA filing?

Response:
Yes, we agree.

Conform to the ICH conditions for the intermediate stability testing; as opposed to your statement of 30^0 C/60% RH, it should be 30^0C/65% RH per ICH Q1A (R2).

Question 9:
AmDerma has manufactured 3 batches each of Econazole Nitrate Foam, 1% using 3 different lots of API. At the time of filing AmDerma will submit 6 months of Accelerated and 12 months of Controlled Room Temperature stability data, which will be updated during review process. AmDerma intends to request a 24 months expiration date based on the available stability data. Does the Agency agree that this data is sufficient for NDA filing?

Response:
Your stability data plan is acceptable, if the three lots of API were manufactured with the same manufacturing processes (b) (4) . If not, we would expect the typical stability data from two batches of drug product from each API lot.

According to SUPAC SS guidance, the change in the manufacturing site (b) (4) to USA will be a (b) (4) change. To support the approval of the new site, along with other CMC requirements, you would need to conduct an in-vitro drug release test comparing the in-vitro release rate from the product manufactured at the new site in USA versus the in-vitro release rate of a recent lot of comparable age of the dosage form manufactured at the prior site (b) (4) Also, depending on the nature of the differences in the manufacturing process, you may need to support your NDA application with an in-vitro release test comparing the in-vitro release rate of the products using the current process versus the product using the revised process. Provide the complete information/data supporting these changes in your NDA.

Meeting Discussion:
The sponsor proposes not to conduct bridging studies (as recommended by SUPAC SS guidance) to bridge the two manufacturing sites, since pivotal trials were conducted with product batches from the new U.S. manufacturing site. The Agency noted that product batches produced at the original (b) (4) manufacturing site were used in the pivotal PK study D79-2902-07 where the PK profile was characterized. The sponsor proposes to submit a rationale to review prior to NDA submission. The Agency recommended that such rationale should address the potential for any differences in drug absorption.

Pharmacology/Toxicology

Question 1:
For the inactive ingredient Povidone (b) (4), AmDerma provided a reference to a transdermal route of administration and a vaginal route of administration from the Inactive Ingredient Database posted on the Office of Generic Drugs website, in order to establish the safety of the concentration of this ingredient in the formulation. Does the Agency agree that the IID limit for the transdermal and vaginal route of administrations are acceptable to establish the safety of the level of Povidone (b) (4) on the topical foam formulation?

Response:
Yes, we agree.

Question 2:
AmDerma has conducted the following nonclinical studies on Econazole Nitrate 1% Foam: primary dermal irritation study in rabbits, delayed contact hypersensitivity study in guinea pigs, phototoxicity study in rabbits, 4-week repeat-dose dermal toxicity study in minipigs, maximum feasible dose study in minipigs, and 13-week repeat-dose dermal toxicity study in minipigs. No unexpected or unique toxicities were observed in these studies. Furthermore, at the End of Phase 2 meeting, it was agreed that the 13-week repeat-dose study would be adequate for the 505(b)(2) NDA assuming that a clinical bridge was established with the reference listed drug; this has been done as part of the clinical program. Based on this, does the Agency agree that no additional nonclinical studies are required to support the NDA?

Response:
The study report for the 13-week minipig study has not been received by the Agency. No additional nonclinical studies are recommended at this time.

Question 3:
AmDerma intends to rely on nonclinical safety data provided in Fougera's ANDA # 076065 for Econazole Nitrate Cream, 1%, the current Reference Listed Drug. Does the Agency agree?

Response:
While it is acceptable to use the ANDA product designated as the RLD in the Orange Book for your bridging studies when the innovator product has been discontinued, you will need to identify the NDA product that was the basis for submission of the ANDA product as the listed drug relied upon to support your proposed 505(b)(2) application (see our response to question 3 in the Clinical/Biostatistics section below). It should be noted that you may rely only upon FDA's finding of safety and/or effectiveness as is reflected in the approved labeling for the innovator drug, provided an adequate clinical bridge was established between your drug product and ANDA product designated as the RLD. You can not directly cite data to which you do not have a right to refer. You may not reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries for support of safety and/or efficacy of your proposed product.

Clinical Pharmacology/Clinical/Biostatistics

Question 1:
Does the Agency agree that the clinical data package described in the briefing document, subject to review, is sufficient for submission and filing of the Econazole Nitrate Foam 1% 505(b)(2) NDA?

Response:
We have the following comments with regards to Clinical Pharmacology Trials D79-2902-07 and 079-2951-109:

1. You stated that the composition of your product formulation did not change during development and will remain the same for the proposed commercial product. (b) (4) [redacted] The applicability of data from study D79-2902-07 using the previous manufacturing site will be a review issue. In your NDA submission, provide a comparison of the manufacturing process between the 2 sites and data and/or scientific rationale to support the applicability of data from study D79-2902-07 to support your NDA application.

2. We note that PK following drug administration was assessed only on the final day of the study after 4 weeks of drug application. We also note that the proposed treatment duration with your product is 4 weeks. Hence, the systemic exposure information obtained could be from subjects that have healed skin and this would not represent maximal use conditions. Provide in your NDA submission a sub-group analysis (both descriptive PK and relative bioavailability analyses) of your PK data by categorizing as data from subjects with healed skin and data from subjects not healed. Also provide information on disease severity at baseline and on the day of PK assessment for all subjects.

3. Confirm that (b) (4) [redacted] used the to-be-marketed formulation manufactured (b) (4) [redacted]

4. You should present the relative bioavailability data as 90% confidence interval of the ratio of the geometric mean of AUC and C_{max}.

5. Submit electronic data sets in SAS transport format with your NDA.

6. Submit bioanalytical method validation and bioanalysis reports with your NDA submission.

Question 2:
Does the Agency agree that the Econazole Nitrate Foam 1% data from the development program described in the briefing document, subject to review, support the proposed indication and dosing regimen?

Response:
A determination that your proposed product is safe and effective for the indication sought in the population studied will be the subject of the NDA application review.

Question 3:
AmDerma intends to request a waiver for the lower age group (less than 12 years old) by providing scientific and medical rationale given the low incidence of the disease in these younger age groups. Does the Agency agree with the Sponsor's proposal for a waiver of pediatric studies using Econazole Nitrate Foam 1% in subjects less than 12 years of age?

Response:
Your rationale for a waiver for the age group less than 12 years of age appears reasonable. Your waiver request should include data that supports your rationale, as well as labeling from any precedent approved products that support your position. Decisions regarding waivers or deferrals of pediatric studies are made during the NDA review process.

Question 4:
AmDerma has included a draft labeling in Physician Labeling Rule (PLR) format for the Agency's consideration. Does the Agency agree that the proposed labeling in the PLR format provides all of the required components for NDA filing?

Response:
Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. Labeling content and format will be reviewed during the NDA review.

You should describe information in Section 12: Clinical Pharmacology in specific sub-sections. For further information, you are referred to the draft guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products - Content and Format*, February 2009.

Question 5:
Does the Agency agree that the relevant information from the clinical studies conducted by AmDerma can be incorporated in the appropriate PLR sections of AmDerma's proposed labeling?

Response:
The clinical study section of your proposed label should contain information from adequate and well-controlled studies that support effectiveness of your drug for the labeled indication(s), including discussion of study design, population, endpoints, and results, and relevant safety experience.

Question 6:
Since the brand product, SPECTAZOLE® Cream, 1% was discontinued by the NDA holder, AmDerma used the current Reference Listed Drug, Econazole Nitrate Cream, 1%, manufactured by Fougera under ANDA 076075, as the basis for the 505(b)(2) filing and as the basis for the labeling information. AmDerma would like to confirm that the Agency's position has not changed with regard to this prior agreement.

Response:
While it is appropriate to use the ANDA product designated as the RLD as the comparator in bridging studies when the innovator product has been discontinued, you will need to identify the NDA product (i.e., Spectrazole Cream, 1%) that was the basis for submission of the ANDA product as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide a patent certification or statement with respect to each patent listed in the Orange

Book for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)). Note also that **reliance on FDA's finding of safety and/or effectiveness** for a discontinued listed drug is **contingent on FDA's finding that** the drug was not discontinued for reasons of safety or effectiveness.

Question 7:
Statistical analysis of the efficacy data for the Phase 3 trials Studies 079-2951-302 and 079-2951-303 conducted with the to-be-marketed formulation will be pooled and presented in the Integrated Summary of Efficacy (ISE). Only the foam vehicle and Econazole Nitrate Foam 1% treatment groups will be included in the pooled analyses; the Econazole Nitrate cream 1% and Placebo Cream treatment groups will be included only in the analyses for the 079-2951-303 study. Does the Agency agree?

Question 8:
Statistical analysis of the safety data for Studies 079-2951-302 and 079-2951-303 conducted with the to-be-marketed formulation will be pooled and presented in the Integrated Summary of Safety (ISS). In this pooling analysis we are not planning to include the safety data from the Phase 2 Study D79-2902-07. We plan to use the tables from this pooled analysis for describing the adverse events commonly reported at 1% or more. Only the foam vehicle and Econazole Nitrate Foam 1% treatment groups will be included in the pooled analyses; the Econazole Nitrate Cream 1% and Placebo Cream treatment groups will be included only in the analyses for the 079-2951-303 study. Does the Agency agree?

Response to Questions 7 and 8:
Your proposal of pooling efficacy results for the Integrated Summary of Efficacy (ISE) appears to be acceptable. However, for establishing efficacy claim, results of individual studies would be required. The ISE should discuss the effectiveness of the drug across the studies and comment on the consistency of the findings.

In addition to the information required in the Integrated Summary of Effectiveness (ISE), to aid our review, provide the following:

- a detailed analysis for race and ethnicity (i.e., beyond white vs. non-white).
- a detailed analysis for age subgroups (subgroups over 65 and under 18, in addition to above and below the median age).
- a rationale for why the data presented represents a demonstration of substantial evidence of effectiveness for the proposed indication.

You should provide information in the submission regarding the basis for determining patients to be a screening failure.

Refer to the *Guidance for Industry: Integrated Summary of Effectiveness* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf) for additional information on what to include in the ISE and discussions about integrating efficacy across studies.

In addition to the information required in the Integrated Summary of Safety (ISS) to aid our review, provide the following:

- Shift tables for all laboratory values for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.

Question 9:
In accordance with the ICH E3 Guidelines for Industry: Structure and Content of Clinical Study Reports, the NDA will be included only for deaths, other serious adverse events, and withdrawals for adverse events. Does the Agency agree?

Response:
The following data should be included:

- Subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation from the trials conducted with your product.
- The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.
- Case report forms (CRFs) for all serious AEs, all severe AEs, and for all subjects who discontinued from the studies for any reason. A study's CRFs should be placed in a CRF folder under the applicable study with a file tag of "case-report-forms." Also provide the following:
    - Electronic links for:
        a. all serious AEs
        b. all severe AEs
        c. all patients discontinued regardless of reason
        d. all deaths
    - CRFs should be referenced under the study in which it belongs and tagged as "casereport-forms" in that study's stf.xml file.
    - CRFs that are not submitted should be readily available upon request.
- Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) $\geq$ 1%.
- Adverse event tables $\geq$ 1% regardless of causality.
- Line listings for all safety data.
- Group means for irritancy safety study results.
- Frequency tables for sensitivity safety study results. Define and justify the threshold for calling a score positive (or negative) for sensitization.

Additional Comments

1. Submit clinical photographs obtained during the Phase 3 trials.

2. You should submit analysis datasets following the general guidelines specified by the CDISC Analysis Data Model (ADaM) Team (http://www.cdisc.org/adam). Note that:

- The electronic datasets should be submitted in SAS transport form (.xpt).
- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables.

3. The original raw datasets should be submitted as SAS transport (.xpt), as well as in SDTM Version 3.1.2, with accompanying Define.xml files. Definition files for raw datasets should **be modeled according to CDISC/SDTM. Refer to CDISC's Define.XML page** (http://www.cdisc.org/define-xml) for assistance/guidance related to creating Define.xml files for CDISC/SDTM data. Also, for ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

4. You are encouraged to submit sample electronic SDTM datasets to the Agency for testing prior to your NDA submission. Please refer to the FDA website on submitting a sample eCTD (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at esub@fda.hhs.gov, or for standardized data submission questions, contact edata@fda.hhs.gov.

5. In addition to the electronic datasets, for each Phase 3 trial include the study protocol, all protocol amendments (with dates), the statistical analysis plan, an annotated copy of the case report form, generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment). Statistical programs for any non-standard analyses should also be submitted.

Meeting Discussion:
The sponsor inquired whether in Additional Comment #3 (above) the Agency is requesting the raw datasets in two formats. In response, the Agency noted the request of one set of datasets and that the intended reading **in #3 should be: "The original raw datasets should be submitted as SAS transport (.xpt) files in SDTM format."**

Corrigendum:
The sponsor requested clarification regarding Attachment 1. The numbers in Exhibit 2 of the attachment are a sampling of a fictitious data set and do not provide the raw data from which the

standard deviation should be calculated. Use standard statistical software to calculate the standard deviations.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.

2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).

3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided **in the attachment titled, "Product name,** NDA/BLA 012345, Establishment Information for Form **356h."**

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

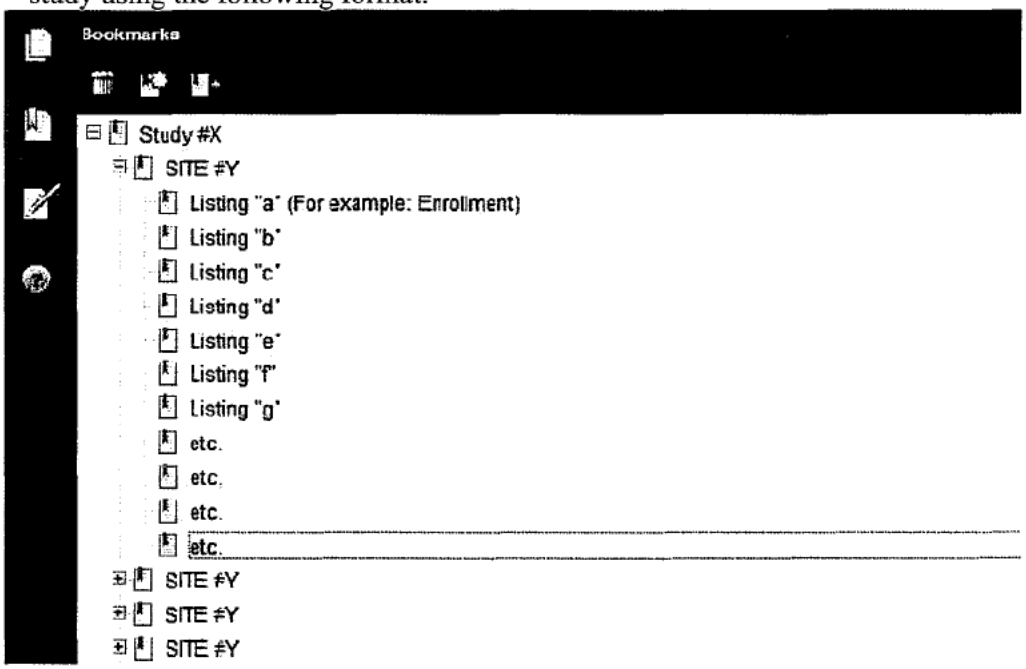
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.

- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.

- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).

- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

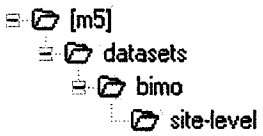
Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

TATIANA OUSSOVA
09/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077523

MEETING MINUTES

Quinnova Pharmaceuticals
Attention: Rhea N. Williams, M.P.H.
Acting Director, Regulatory Affairs
411 South State Street, 3rd Floor
Newton, PA 18940

Dear Ms. Williams:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for econazole nitrate foam, 1%.

We also refer to the teleconference between representatives of your firm and the FDA on April 14, 2010. The purpose of the meeting was to discuss any remaining points of clarification regarding the January 7, 2010 SPA responses provided by the Agency.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Post-SPA Guidance Meeting

Meeting Date and Time: April 14, 2010, 10AM
Meeting Location: Teleconference

Application Number: 077523
Product Name: econazole nitrate foam, 1%
Indication: treatment of interdigital tinea pedis
Sponsor/Applicant Name: Quinnova Pharmaceuticals

Meeting Chair: Susan Walker
Meeting Recorder: Cristina Attinello

FDA ATTENDEES
Susan J. Walker, M.D., Division Director, DDDP
David Kettl, M.D., Clinical Team Leader, DDDP
Amy Woitach, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Carmen Booker, Ph.D., Pharmacology Reviewer, DDDP
Margo Owens, Team Leader, Project Management Staff, DDDP
Cristina Petruccelli Attinello, MPH, Regulatory Project Manager, DDDP
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DB III
Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DB III
Julia Cho, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Tarun Mehta, Ph.D., Chemistry Reviewer, DPA II, Branch III

SPONSOR ATTENDEES
Charles Nomides, B.S., Senior Vice President, Research and Development
Linda Mahoney, Senior Director, Project Management and CMC
Brian Gallagher, Operations
Rhea Williams, M.P.H., Acting Director, Regulatory Affairs
(b) (4) Consultant, Clinical, Microbiology and Regulatory Affairs
(b) (4) Consultant, Biostatistics
(b) (4) Consultant, Clinical Affairs

Purpose of the Meeting:
Per *Guidance for Industry: Special Protocol Assessment*, this meeting is being held to discuss any remaining points of clarification regarding the January 7, 2010 SPA responses provided by the Agency.

Regulatory Correspondence History

We have had the following meetings with you:
- End of Phase 2 Meeting: April 15, 2009
- Pre-IND Meeting: September 10, 2007

We have sent the following correspondences:
- SPA Agreement (2): January 7, 2010
- Advice/Information Request: May 30, 2008
- Advice/Information Request: May 13, 2008
- Advice/Information Request: May 5, 2008
- Advice/Information Request: March 20, 2008

Clinical Pharmacology/Biopharmaceutics

Question 2:
As presented in the Type A briefing book [March 8, 2010], the clinical "bridge" will be based upon the Phase 2 comparative data along with data from the Phase 3 Study 303 that contains a comparative safety evaluation with Econazole Nitrate Cream, 1%. Efficacy will be established based upon demonstrating superiority of Econazole Nitrate Foam, 1% over Foam Vehicle in the two Phase 3 trials, Studies 302 and 303.

Does the strategy presented in the Type A briefing book represent an appropriate bridge between Econazole Nitrate Foam, 1% and Spectazole Cream, 1%?

Response:
A comparative pharmacokinetic study between Econazole Nitrate Foam versus Cream is one of the elements of a clinical bridge to assess systemic safety of your drug, provided that the study was conducted under "maximal use" conditions in the intended population. The adequacy of data is a review issue.

If your drug is being developed for patients 12 years and older, the PK study needs to have a sufficient number of subjects aged 12 and 18 years to allow meaningful analysis.

Meeting Discussion:
The sponsor asked for clarification whether PK studies in subjects aged 12 to 17 is necessary. The Agency stated that there is an informational need for bioavailability in the proposed labeled population. The sponsor agreed to submit protocols for Agency review and comment.

Clinical/Biostatistics

Question 1:
Quinnova Pharmaceuticals accepts the Division's recommendation to include a small cream vehicle arm to promote blinding. The challenge for implementation is our inability to create a true vehicle without direct knowledge of the ratios of the ingredients in the marketed Econazole

Nitrate cream utilized in the study. However, since the intent will be to only use this for blinding purposes, we have identified a cream that approximates the look and feel of the marketed product. Additionally, we will over label the tube with a blank label and distribute the clinical supplies in plain, white cartons used to package the other test articles to be used in this study. The protocol has been modified to incorporate this change in a small sample of patients and the statistical analysis has been updated accordingly.

Does the Division agree that the study design is adequate to demonstrate safety between Econazole Nitrate Foam, 1% and Econazole Nitrate Cream, 1%?

Response:
The Agency agrees that adding 37 subjects as a placebo cream arm appears to address the blinding in Study 303 and permit a comparative safety evaluation between Econazole Nitrate Foam, 1% and Econazole Nitrate Cream, 1%. The demonstration of safety is a review issue. Please submit a sample and composition of the commercial grade placebo and the active cream product to the Agency for review.

Meeting Discussion:
The sponsor agreed to provide active and placebo cream samples and a list of ingredients.

Question 3:
The rationale for considering interdigital tinea pedis a non-chronic indication is presented in the Type A briefing book. Additionally, Econazole Nitrate has a well-defined and well-known safety profile. Over the last 28 years, the extensive population exposure has not identified any safety signals or new adverse events that would raise concerns regarding long-term safety for Spectazole Cream or Econazole Nitrate Cream, 1%. Successful completion of the clinical bridge will establish that the bioavailability of Econazole Nitrate Foam, 1% is comparable to Econazole Nitrate Cream, 1%, which provides for borrowing of FDA's finding on safety Econazole Nitrate Cream, 1%.

Does the Division agree that the long-term safety of Econazole Nitrate has been adequately established?

Response:
Assuming successful completion of the planned development program, long term safety will be adequately bridged to existing experience for the referenced econazole nitrate cream product.

Provided the Phase 3 studies (302 and 303), the four Phase 1 dermal safety studies and the 3-month nonclinical study in mini-pigs do not identify any new safety concerns, does the Division agree that there are no additional studies necessary for registration?

Response:
This is a review issue for the full NDA submission.

Additional Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

4. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

5. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details).

6. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-77523	GI-1	QUINNOVA PHARMACEUTICALS INC	ECONAZOLE NITRATE FOAM 1%

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

/s/

SUSAN J WALKER
04/21/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 77,523

Therapeutics, Inc.
Attention: Rebecca Tong, Director Regulatory Affairs
9025 Balboa Avenue
Suite #100
San Diego, California 92123

Dear Ms. Tong:

Please refer to your Investigational New Drug Application (IND) file for Econazole Nitrate 1% Foam.

We also refer to the meeting between representatives of your firm and the FDA on September 10, 2007. The purpose of the meeting was to seek the Agency's guidance on the development of your drug product and to obtain agreement on the required CMC, nonclinical, and microbiology studies to be conducted to support the proposed indication.

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

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 301-796-2311.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 15, 2009
TIME:	9:00 am
LOCATION:	White Oak, Room 1311
APPLICATION:	IND 77,523
DRUG NAME:	Econazole Nitrate Foam 1%
TYPE OF MEETING:	End of Phase 2 (Type B)
MEETING CHAIR:	Susan J. Walker, M.D., F.A.A.D., Director, Division of Dermatology and Dental Products (DDDP)
MEETING RECORDER:	Catherine Carr, M.S., Regulatory Health Project Manager, DDDP

FDA ATTENDEES: (Title and Office/Division)

Susan Walker, M.D., Director, DDDP
David Kettl, M.D., Clinical Team Leader, DDDP
Amy Woitach, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Carmen Booker, Ph.D., Pharmacology Reviewer, DDDP
Catherine Carr, M.S., Regulatory Health Project Manger, DDDP
Kerry Snow, Ph.D., Microbiology Reviewer, DAIODP
Tarun Mehta, Ph.D., Product Quality Reviewer, DPMA II, Branch III
Dennis Bashaw, PharmD., Director, DCP III
Seongeun Cho, Ph.D., Clinical Pharmacology Reviewer, DCP III
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DB III
Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DB III

EXTERNAL CONSTITUENT ATTENDEES: Quinnova Pharmaceutics

Christopher Hensby, Ph.D., Senior Vice President, Research & Development, Quinnova
Mats Silvander, Ph.D., Vice President, Product Development (CMC), Quinnova
David Miska, Ph.D., Senior Director, Clinical & Regulatory Affairs, Quinnova
Jay E. Birnbaum, Ph.D., Consultant, Clinical Affairs & Microbiology, Quinnova
Shahbaz Khan, M.D., Associate Director, Clinical & Regulatory Affairs, Quinnova
John Quiring, Ph.D., Consultant, Biostatistics and Data Management, Quinnova
Linda Mahoney, Senior Director, Project Management & CMC, Quinnova
Rebecca Tong, M.S., Regulatory Affairs Consultant, Therapeutics, Inc., US Agent for Quinnova

BACKGROUND:

The sponsor submitted a briefing document, dated March 12, 2009, which included background information and questions for discussion. Preliminary responses were sent to the sponsor on April 13, 2009.

MEETING OBJECTIVES:

The purpose of the meeting was to seek the Agency's guidance on the development of Econazole Nitrate 1% Foam and to obtain agreement on the required CMC, nonclinical, microbiology, and clinical studies to be conducted to support an indication of the topical treatment of interdigital tinea pedis (b) (4) in patients age twelve (12) and older.

DISCUSSION POINTS:

Regulatory:

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

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

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

CMC/Product:

Question 1:

Drug Substance
The proposed econazole nitrate drug substance test parameters and acceptance criteria are presented in Section 4.2.3 of this briefing package.

Does the Division agree that the proposed drug substance test parameters and acceptance criteria are acceptable for continued clinical development and NDA registration?

Response:

They are acceptable for continued clinical development and NDA filing. However, their adequacy for NDA approval is a review issue.

Question 2:

Drug Product
Quinnova has procured a source of butane propellant with an established limit of NMT (b) (4) impurity. The test parameters and acceptance criteria for the butane propellant are presented in Section 4.3.3.

Does the Division agree that the test parameters and acceptance criteria for the butane propellant are acceptable to support continued clinical development and NDA registration?

Response:

They are acceptable for continued clinical development and NDA filing. However, their adequacy for NDA approval is a review issue.

Question 3:

Drug Product
A summary of packaging qualification studies conducted on the primary packaging components is presented in Section 4.3.9. This section also includes a protocol synopsis for a proposed product/package interaction study.

Does the Division agree that the packaging component qualification program and proposed product/package interaction study are adequate to support the NDA registration?

Response:

Your proposed list of tests is adequate. However, we noticed that N/A is marked on Table 4-11 for the compliance of can and valve components with USP<661>. We want to advise you that any and all the components which may come in contact of drug product during the drug product life cycle should conform to USP <661> including the leachables test.

You should include a visual examination in the analysis for potential discoloration of any parts or materials tested in the special product/package interaction study (Table 4-12). The visual examination of packaging components and formulation should also be included in registration stability studies as a part of evidence to support the compatibility of packaging components with the formulation.

Meeting Discussion:

The Agency indicated that the portion of the packaging needs testing according to USP <661>. The Agency indicated that once additional information is received on the packaging, we will provide additional comments on what testing is required. The sponsor indicated that they will provide a rationale.

Question 4:

Drug Product
The proposed manufacturing plan for pivotal Phase 3 clinical trial materials and NDA registration batches is presented in Section 4.3.4. The proposed econazole nitrate drug product specifications are presented in Section 4.3.7. The protocol for stability is presented Section 4.3.8.

Does the Division agree that the proposed drug product specifications, manufacturing plan and stability protocol are adequate to support initiation of a Phase 3 clinical trial with econazole nitrate foam in patients with tinea pedis, and that the overall plans support submission of an NDA?

Response:

We do not agree that they are adequate to support the initiation of a Phase 3 trial and NDA submission. Below are our comments:

Specification:

1. Add an appearance test (b) (4)

Meeting Discussion:

(b) (4)

Meeting Discussion:

The Agency indicated that we need a baseline weight (b) (4)

4. Provide the results and analytical method used (b) (4)

Meeting Discussion:

The sponsor indicated that they will provide data [redacted]

Manufacturing plan:

1. The proposed batch sizes [redacted] for registration stability batches need to be at least [redacted] of the proposed commercial batch size.
2. The physician sample size should be studied in all three registration stability batches.

Meeting Discussion:

The sponsor indicated that they will provide the metrics on the packaging.

Stability Protocol:

1. Beside the upright container position, also perform the testing of the drug product stored in an inverted position for all three stability storage conditions.
2. Add the following three tests to Test Attributes: appearance test [redacted] and packaging-formulation interaction.

Additional CMC Comments:

1. Explain the stability results [redacted] for Batches M7035 and M7036, especially for 6 month and 12 month time points (pages 67 and 75 of 151 of briefing package).

2. Please clarify if the [redacted] formulation is [redacted] an emulsion.

Meeting Discussion:

The sponsor stated that their product is an emulsion. The sponsor indicated that they will provide the data and rationale for the dosage form of emulsion.

[redacted]

Pharmacology/Toxicology:

Question 5:

Econazole nitrate has a well established safety profile with multiple topical dosage forms marketed at concentrations equivalent to the proposed foam formulation, and supported by decades of safe use for the treatment of tinea pedis. Per previous Agency agreement, Quinnova has completed an array of nonclinical studies to support the Phase 3 studies as detailed in Section 5.2.2. In parallel with the pivotal study program, Quinnova will complete the Agency's requirements for nonclinical studies to support NDA submission per previous agreement by

conducting a 3-month topical minipig study and will report that study in the NDA. The study design for the 3-month topical minipig study is provided in Section 5.3.

Given the established safety profile of econazole nitrate per the literature and previous human use, the previously completed nonclinical studies on the econazole nitrate foam formulation, and the study design of the proposed 3-month minipig study on the econazole nitrate foam formulation, and, assuming a clinical bridge is established, does the Agency concur that all nonclinical study requirements as per pervious agreement with the Agency have been fulfilled and are adequate for NDA submission and registration and that no additional nonclinical studies are required?

Response:

The proposed study design for the 3 month minipig study appears adequate. If you are able to generate an appropriate clinical bridge to Fougera® Econazole Nitrate 1% Cream drug product, no additional nonclinical studies should be necessary provided the 3 month minipig study is well conducted and no unexpected toxicity is observed.

Clinical/Statistics:

Question 6:

Complete Clinical Study Report for the Phase 2 study was submitted to the Agency on February 27, 09 (S-008) and the results of this study are presented in Section 7.2 of this brochure.

Does the Division agree that the results of the study are adequate to a) allow reference to the Agency's findings on systemic safety of econazole nitrate, and b) establish a bridge for local and systemic safety under a 505(b)(2) application for the proposed indication and the intended patient population?

Response:

An adequate clinical bridge is generally built by demonstration of comparative bioavailability; for a topical product this is accomplished through conduct of well-controlled phase 3 trials with clinical endpoints.

The clinical bridge will be established by successful completion of your planned phase 3 trial which will compare your proposed product to the reference product and their respective vehicles.

Meeting Discussion:

The Agency acknowledged that the clinical pharmacology study overview as submitted appeared to follow the previous Agency guidance.

Question 7:

In Phase 3 clinical development, Quinnova plans to conduct two randomized, double-blind clinical studies in parallel. Study 1 (Protocol 079-2951-302; Section 7.5 Appendix H) and Study 2 (Protocol 079-2951-303; Section 7.5 Appendix I).

Does the Division agree that the proposed study designs and protocols of the two studies are adequate for Phase 3 development of Econazole Nitrate Foam for the proposed indication and the intended patient population?

Response:

Adequacy of the studies and the indication which they might support is a review issue. However, at this stage the plan to conduct two Phase 3 studies, one vehicle-controlled study and one vehicle and listed drug controlled study, appears to be appropriate. In Study 303 we recommend also including a small 'cream vehicle' arm to promote blinding.

In both trials (302 and 303) you have proposed the primary endpoint of complete cure which is defined as negative KOH, negative fungal culture, and no evidence of clinical disease as indicated by scores of 0 (none) for each sign and symptom (erythema, scaling, fissuring, maceration, vesiculation and pruritus). This endpoint is acceptable.

In addition we have the following comments on the Phase 3 studies.

1. A few subjects in the econazole foam arm of the phase 2 trials experienced hyperglycemia or an increase in their baseline glucose compared to none in the vehicle or comparator arm. You will need to address this safety issue prior to initiation of phase 3 trials. It may be acceptable to proceed with phase 3 trails if screening laboratory assessments are performed at baseline, weekly during treatment, and at follow-up visits.

Meeting Discussion:

The sponsor plans to submit a written assessment of the laboratory data and clinical follow up for these subjects. The Agency stated that the laboratory assessments may still be required for Phase 3 studies.

2. Provide a rationale for requiring contraception in your Phase 3 trials.

3. We recommend that your protocol more clearly define the extent of involvement of the foot permitted for inclusion in your phase 3 trials.

4. We encourage the use of clinical photography for documentation of treatment effect.

Meeting Discussion:

The sponsor acknowledged the request and the Agency agreed that a subset would be acceptable.

5. We recommend including in the protocol a few sensitivity analyses regarding the handling of missing data, to ensure that the results are not driven by the method of handling missing data.

6. We recommend incorporating a method of strong error control over the set of secondary endpoints that support efficacy claims.

Meeting Discussion:

The sponsor stated that they will include sensitivity analyses for handling missing data and will propose a sequential method for analyzing the secondary endpoints.

You should submit you final Phase 3 protocols to the IND. It would be helpful if the final protocols were marked with highlight/strikeout to identify any changes from the versions of the protocols submitted for review for today's meeting.

Question 8:

Four Phase 1 dermal safety studies (21 day primary irritation, repeat insult patch tests, phototoxicity, and photoallergenicity studies) will be conducted in healthy subjects. The respective protocol synopses are presented in Section 7.5 (Appendices J, K, L and M). In addition, Phase 2 and Phase 3 studies also include full assessment for dermal safety, including a comparative RLD arm in one of the Phase 3 studies.

Does the Division agree that a) the respective study designs for the Phase 1 studies are adequate and b) the proposed set of studies (Phase 1, 2 & 3 with results subject to Agency's review) is adequate to establish dermal safety of Econazole Nitrate Foam for registration for the proposed indication and the intended patient population?

Response:

The design of your topical safety studies appears adequate. Additional assessment of dermal safety will be determined by your phase 3 trial safety assessments. You are reminded that these trials should be conducted with the final "to-be-marketed" formulation.

Question 9:

Components of the clinical development plan are provided in Table 7.1.1: List of Planned and Completed Clinical Studies (VoL. 2, Page 3 of this brochure).

Does the Division agree that the proposed clinical development plan (results subject to Agency's review) will be adequate to support registration of Econazole Nitrate Foam for the proposed indication and the intended patient population?

Response:

There is no information provided on additional dose ranging as recommended by the Agency in a previous communication dated May 30, 2008. Phase 2 dose-ranging studies that adequately explore the elements of dosing, duration and frequency of treatment are recommended to

establish the best performance of your product before proceeding with the pivotal Phase 3 studies.

Your phase 3 development plan of one vehicle controlled study and one vehicle and reference drug controlled study may be appropriate. However, the Agency recommends including a fourth study arm for the reference drug product vehicle. See response to Question 7.

(b) (4)

You are reminded that the indication in product labeling will reflect the indication in the population studied. Therefore, if your proposed studies are successful, your drug will be labeled for interdigital tinea pedis. (b) (4)

Your rationale for a waiver of pediatric studies for subjects less than 12 years of age appears reasonable at this time. A final determination regarding the waiver will be made at the time of NDA review.

Question 10:

The estimated total number of subjects exposed to Econazole Nitrate Foam 1 % throughout the development plan is presented in Table 7.1.2: Extent of Exposure to Econazole Nitrate Foam 1 % (Vol., Page 4 of this brochure).

Does the Division agree that the proposed extent of exposure is adequate to support registration of Econazole Nitrate Foam for the proposed indication and the intended patient population?

Response:

Adequacy of extent of exposure to the study drug to support registration is a review issue. Safety information regarding hyperglycemia (see response to Question #7) will need to be addressed before this determination can be made.

The sponsor is referred to the ICH E1a guidance in terms of numbers of patients needed on drug product for long-term safety and to the ICH E5 guidance concerning a good demographic balance of patients.

Meeting Discussion:

The sponsor should submit information to support their conclusion that this is not a chronic indication.

Question 11:

Reference is made to "Draft Guidance for Industry- Applications Covered by Section 505(b) (2). (October 1999)". The indication that sponsor will be seeking for Econazole Nitrate Foam is

(b) (4)

[redacted] (b) (4)

Does the Division agree that the safety and efficacy data generated through the proposed non-clinical and clinical development plan (subject to Agency's review), the data in the literature, and Agency's findings on econazole nitrate bridged through this development program, are adequate to support registration of Econazole Nitrate Foam under Section 505 (b)(2) for the proposed indication and the intended patient population?

Response:

The Agency recommends that you revise your development plan based on our comments above and provide additional safety information or implement monitoring requested before proceeding to phase 3 trials. The adequacy of your program to support registration will be reviewed as part of the eventual NDA submission.

Additional Clinical Microbiology Comments:

1. Please confirm that susceptibility testing will be performed on all fungal isolates confirmed as dermatophytes (all isolates of *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*), including all isolates from specimens collected at any visit listed in the proposed Phase 3 trial protocol (Day 1, Day 29, and Day 43).

Meeting Discussion:

The sponsor proposed performing susceptibility testing only on dermatophytes isolates collected from subjects defined as clinical failures.

Addendum to minutes:

The Agency requests receiving susceptibility data on all isolates collected at baseline, end of treatment, and end of study.

2. Susceptibility testing of fungal isolates should be done using the appropriate Clinical and Laboratory Standards (CLSI) method.

3. Please confirm that all isolates will be appropriately stored at the central testing facility for additional analysis, as needed, and include details in the protocol appendix (Appendix 4: Clinical Microbiology Methods) that state the minimum period that such isolates will be stored, and the storage conditions employed (media, incubation temperature, atmospheric conditions, etc.).

Project Management:

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

Meeting Discussion:

The Agency requested the sponsor to submit the QT/QTc and hyperglycemia reports for Agency review prior to submission of the Special Protocol Assessment.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

5. In response to a final rule published February 11, 1998, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this demographic analysis.

6. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.

7. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details).

8. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 77523	QUINNOVA PHARMACEUTICALS	ECONAZOLE NITRATE FOAM 1%

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

/s/

SUSAN J WALKER
04/27/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND 77,523

Therapeutics, Inc.
Attention: Rebecca Tong, Director Regulatory Affairs
9025 Balboa Avenue
Suite #100
San Diego, California 92123

Dear Ms. Tong:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Econazole Nitrate 1% Foam.

We also refer to the meeting between representatives of your firm and the FDA on September 10, 2007. The purpose of the meeting was to seek the Agency's guidance on the development of your drug product and to obtain agreement on the required CMC, nonclinical, and microbiology studies to be conducted to support the proposed Phase 1 study.

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

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 301-796-2311.

Sincerely,

{See appended electronic signature page}

Markham Luke, M.D.
Clinical Team Leader, Dermatology
Division of Dermatology and Dental Products (DDDP)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	September 10, 2007
TIME:	2:00 pm
LOCATION:	Teleconference
APPLICATION:	PIND 77,523
DRUG NAME:	Econazole Nitrate Foam 1%
TYPE OF MEETING:	Pre-IND (Type B)
MEETING CHAIR:	Markham Luke, M.D./Clinical Team Leader, Dermatology, Division of Dermatology and Dental Products (DDDP)
MEETING RECORDER:	Catherine Carr/Regulatory Health Project Manager, DDDP

FDA ATTENDEES: (Title and Office/Division)

Markham Luke, M.D./Clinical Team Leader, Dermatology, DDDP
David Kettl, M.D./Medical Officer, (DDDP)
Paul Brown, Ph.D./Pharmacology Toxicology Team Leader, DDDP
Jiaqin Yao, Ph.D./Pharmacology Reviewer, DDDP
Catherine Carr, M.S./Regulatory Health Project Manger, DDDP
Tamika White, M.PH./Regulatory Health Project Manger, DDDP
Harold Silver, Ph.D./Microbiologist, Division of Anti-Infective Drug Products
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment, Division of Pharmaceutical Assessment II (DPA-II)
Tapash Ghosh, Ph.D./Pharmacokinetics Reviewer, Office of Clinical Pharmacology, Division of Pharmaceutical Evaluation III (DPE-III)
Clara Kim, Ph.D./Biostatistian, Office of Biostatistics, Division of Biometrics III (DB-III)
Donald Hare, Ph.D./Special Assistant to the Director, Office of Generic Drugs
Wayne Mitchell/Regulatory Counsel, Office of Regulatory Policy

EXTERNAL CONSTITUENT ATTENDEES:

Christopher Brennan/EVP Operations, Quinnova Pharmaceutics
Mats Silvander, Ph.D./VP Scientific Affairs (CMC), Quinnova Pharmaceutics
David Miska, Ph.D./Sr. Director, Clinical & Regulatory Affairs, Quinnova Pharmaceutics
Jay E. Birnbaum, Ph.D./Clinical, Microbiology & Regulatory Affairs, Quinnova Pharmaceutics
Shahbaz Khan, MD/Project Manager-Scientific & Clinical Affairs, Quinnova Pharmaceutics
(b) (4) (Clinical & Human Pharmacology) (b) (4)
(b) (4)./Toxicology Consultant. (b) (4)
(b) (4) Project Management. (b) (4)
(b) (4) Regulatory Affairs (b) (4)

BACKGROUND:

The sponsor submitted a briefing document, dated August 8, 2007, which included background information and questions for discussion. Preliminary responses were sent to the sponsor on September 9, 2007.

MEETING OBJECTIVES:

The purpose of the meeting was to seek the Agency's guidance on the development of Econazole Nitrate 1% Foam and to obtain agreement on the required CMC, nonclinical, microbiology, and clinical studies to be conducted to support an indication of the topical treatment of tinea pedis [redacted] (b) (4)

In addition, the sponsor sought to obtain agreement from the Agency on the proposed development plan to support a 505(b)(2) NDA submission using a generic econazole nitrate 1% cream as the Reference Listed Drug.

DISCUSSION POINTS:

CHEMISTRY, MANUFACTURING AND CONTROLS:

Question 1:

Does the Agency agree that the proposed release Specifications and Acceptance Criteria are adequate for the API of a 505(b)(2) NDA using a generic econazole nitrate as Reference Listed Drug?

Response:

No, they are not adequate. The assay should be carried out using an HPLC method. As to the list of test parameters and acceptance criteria, they are acceptable for Phase 1 and Phase 2. We may reassess at the end of Phase 2 when you have data from multiple batches and have acquired a substantial amount of knowledge about the drug product.

Question 2:

Does the Agency agree that the inactive ingredients and their amounts listed in Section 3.3.4.1 (page 13) are acceptable?

Response:

Yes, they are acceptable. We note that five excipients used in the proposed formulation are EP grade rather than USP grade. Because they all have a USP/NF monograph, their quality should also comply with USP/NF.

Question 3:

Does the Agency agree that the proposed release specifications are acceptable?

Response:

No, they are not adequate for clinical supply release. Add an identity test for the active ingredient, and set appropriate acceptance criteria for USP<61> Microbial Limit Testing following the recommendation provided in USP<1111>.

Additional CMC Comments:

1. Include (b) (4) in the drug product stability specification for clinical supplies.

2. Reasonable acceptance criteria should be established for related substances by the end of Phase 2.

3. The following tests with appropriate acceptance criteria should be included in drug product specification when submitting the NDA: delivered amount, dispensing rate, pressure, (b) (4) product/packaging interaction, (b) (4) .

Meeting Discussion:

The sponsor requested clarification on USP<601> requirements. The Agency stated that there are differences in product performance between topical foam vs. aerosol spray. Therefore, the sponsor is not expected to meet all requirements in USP<601>. However, the items provided in the list above should be met.

The Agency clarified that the expectation is to determine possible interaction between the formulation and the packaging material (e.g.,valve). This testing should be done at least for qualification of packaging. Continued testing will depend on the findings.

4. Evaluate the flammability of the proposed formulation in accordance with 16 CFR 1500.43. If necessary, an appropriate flammability warning should be included in the product labeling.

PHARMACOLOGY/TOXICOLOGY:

Question 4:

Quinnova has initiated a rabbit irritation study and a guinea pig sensitization study on the Econazole Nitrate 1% Foam, as well as a 28-day repeat-dose minipig dermal toxicity study on the foam vehicle, 1% and enhanced 4% foam formulations. In addition, Quinnova will summarize and refer to the econazole nitrate toxicity data supplied in the SPECTAZOLE® (econazole nitrate 1%) Cream NDA to address any potential systemic toxicity requirements. Does the Agency agree that this approach will be sufficient to support the initiation of the first human trial?

Response:

The approach is acceptable. We recommend that the sponsor submit complete reports and/or detailed literature references of the nonclinical studies. Although the adequacy of the studies will be assessed upon submission, it appears that the information may be sufficient in principle to support the proposed 28-day clinical study.

Question 5:

Since the safety of topical econazole nitrate has been well established and is supported by widely prescribed marketed econazole nitrate 1% topical generic products, and animal toxicity studies conducted (b) (4) for SPECTAZOLE® Cream, Quinnova is proposing to provide the in-life data and gross pathology data from the 28-day minipig study in the IND. Complete histopathology data will be provided when the final report is available. Does the Agency agree to this approach?

Response:

No. We recommend that at least a draft report of the 28-day minipig study, including the histopathology data, be submitted in the original IND submission.

Question 6:

For the NDA, Quinnova is proposing to conduct a 9-month dermal toxicity study in minipigs. Does the Agency agree that this chronic toxicity study along with the rabbit irritation, guinea pig sensitization and 28-day minipig studies will support a 505(b)(2) NDA submission?

Response:

The adequacy of the database will be a review issue under the IND and will depend on variety of factors, such as the clinical treatment duration, systemic exposure levels of the drug, and findings of the studies. Additional nonclinical information will be needed if a clinical bridge is not established, such as genotoxicty and reproductive toxicity of econazole. Submit copies of any literature references intended to support the application.

Additional Pharmacology/Toxicology Comments:

In the proposed chronic minipig dermal toxicity study, we recommend that at least 10% body area be treated with test articles and recovery groups be included.

CLINICAL AND CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS:

Question 7:

Does the Agency agree that the protocol design of the first clinical study is acceptable and that the proposed PK (including the specified time points and the analytic method sensitivity) and clinical assessments are adequate to support the clinical bridging requirement for a 505(b)(2)

NDA assuming the pivotal study is a three arm non-inferiority study comparing Econazole Nitrate Foam to the reference drug and the foam vehicle?

Response:

The proposed PK study may serve as a bridge PK study to demonstrate that systemic exposure from the proposed econazole nitrate 1% foam is comparable to the sponsor's proposed reference product in order to be able to fully reference the Agency's findings of systemic safety of econazole for the reference product in a 505(b)(2) application.

However, the proposed blood sampling scheme of only 1 hour sampling following application is not adequate to capture the PK profile of econazole following application of the drug product. Change the blood sampling scheme to include more sampling time points. Also, in order to use the proposed study as the pivotal PK study, the study should be conducted with the final to be marketed formulation in a suitable number of subjects with the dermatological disease(s) of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

a) Frequency of dosing
b) Duration of dosing
c) Use of highest proposed strength
d) Total involved surface area to be treated at one time
e) Amount applied per square centimeter
f) Method of application/site preparation

You should attempt to develop a LC/MS method to improve the sensitivity of the analytical method to measure econazole and its potential metabolites.

Sufficient nonclinical evaluations will need to be performed and reviewed prior to the conduct of the initial phase 2 trial. The primary endpoint, negative KOH and culture as well as the complete absence of signs and symptoms of tinea pedis, is acceptable to the Agency.

It is premature to provide comments on the proposed Phase 3 trial at this stage. You proposed one 3-arm Phase 2 study and one 3-arm non-inferiority pivotal trial to support a 505(b)(2) NDA submission. You are encouraged to first complete the Phase 2 trial and indicate how you intend to bridge to the safety and/or efficacy finding of the reference listed drug (RLD). The design of the future Phase 3 trials would be based on your proposed clinical bridge.

Meeting Discussion:

The Agency indicated that the sponsor's proposal may be acceptable upon review of the final protocol. Further discussion should take place during the End of Phase 2 meeting.

The sponsor agreed to take multiple blood samples at steady state.

CLINICAL:

Question 8:

This new drug product is composed of well known non-active ingredients and an API with established safety profile. The proposed proof-of-concept study in man will provide an assessment of tolerability of the new drug product and its vehicle in approximately 90 subjects. Given these features of the proposed development program, the Sponsor requests the need for a formal 21-day cumulative irritancy study be waived. Does the Agency agree? If not please provide an explanation.

Response:

Because this is a new formulation of econazole, irritancy assessment will be required. This study involves repeated application of a test product and controls to areas of healthy skin (usually on a subject's back) for 21 consecutive days and is conducted under occlusion. This test should be conducted in at least 35 evaluable subjects. Cumulative irritation studies may be waived in cases where the product formulation has already been shown to be significantly irritating in early phase clinical studies and will be identified as such in proposed labeling. Sensitization testing may be combined with cumulative irritation in a single study, with the induction phase (if of sufficient length) serving to detect cumulative irritation.

Question 9:

Does the Agency agree that the proposed Phase I, II and III clinical trials assuming favorable outcomes, subject to review, are adequate to support a 505(b)(2) NDA for the mentioned indication?

Response:

It is premature to agree that no other studies will be required and that the proposed development plan will be sufficient at the pre-IND stage. Safety assessments in the early phase trials may dictate the need for additional evaluations. Request and attend an End of Phase 2 meeting to discuss and obtain agreement on Phase 3 studies at the appropriate point in your development.

Meeting Discussion:

The Agency indicated that if the product changes from Phase 2 studies, it may require additional consideration.

Question 10:

Quinnova intends to include subjects 12 years of age and older in the Phase II pivotal trials and will request a waiver for the lower age groups (less than 12 years old) by providing scientific and medical rationale given the low incidence of the disease in these younger age groups. Does the Agency agree this is an acceptable approach to fulfill the Pediatric Rule?

Response:

You should submit a rationale supporting your request for a waiver or deferral. A decision will be made at that time. The currently labeling for Spectazole cream and its generic equivalents has no age exclusions. Tinea may be a disease that affects sufficient numbers of younger pediatric patients to not warrant exclusion.

Meeting Discussion:

The sponsor indicated that they will submit a pediatric waiver request for tinea pedis. The Agency requested a rationale to be submitted along with the data.

Question 11:

The Sponsor may consider expansion of the label for this product at a later date. To obtain broad labeling for other dermatophyte disease consistent with the current Spectazole and generic labeling, Quinnova proposes one additional well controlled pivotal study in a second disease state (e.g. tinea cruris). Subject to review, will this single additional study be adequate to obtain a broader labeling for common cutaneous dermatophyte based diseases?

Response:

Separate successful pivotal trials for tinea pedis and tinea cruris may gain an additional indication for tinea corporis. Cutaneous candidiasis and tinea versicolor will require separate study. Pharmacokinetic evaluations of applications to larger surface areas of skin may also be required for tinea versicolor.

Additional Clinical Comments:

1. Address product flammability and warnings required for IND labeling.

2. Outline in detail the standardized procedures used to obtain and transport fungal microscopy/culture samples.

3. Address blinding for the reference listed innovator product, which is substantially different in appearance from the proposed foam product.

Meeting Discussion:

The Agency indicated that the approach toward evaluator blinding appears reasonable. The blinding procedures should be included in the protocol.

MICROBIOLOGY:

Question 12:

The Sponsor recommends that the mycological outcome assessments from the clinical studies suffice as demonstration of the antifungal activity for this novel formulation of the established antifungal agent, econazole nitrate, in addition to specific in vitro testing of the study medication

for MIC and MLC as detailed in section 3.5. Does the Agency agree this meets the microbiology requirement for the NDA submission?

Response:

Please see "Additional Clinical Microbiology Comments" (below).

Question 13:

The Sponsor recommends that any outcome of studies to examine the induction of resistance to sub-inhibitory concentrations of econazole nitrate would be of minimal impact given the publicly available literature, and are not required for the submission of an NDA for Econazole Nitrate Foam, 1%. Does the Agency have any comment regarding this approach?

Response:

Provide the literature that you referenced "on the induction of resistance to sub-inhibitory concentrations of econazole nitrate" to the IND.

Any recent (i.e., 2003 to the present) fungal resistance data (literature, *in vitro* testing, clinical studies) on the proposed drug product would be beneficial for establishing data on current efficacy and safety.

Meeting Discussion:

The sponsor indicated that they will submit susceptibility testing and failures that occur during the clinical studies.

Additional Clinical Microbiology Comments:

For the Phase 2, Phase 3, and for Future Clinical/Microbiology Studies:

1. All relevant and targeted pathogenic dermatophytes causing tinea pedis are to be identified and speciated (genus, species).

2. All microscopic and cultural examination (e.g., using KOH/calcofluor white*), microbiology procedures/tests/methodologies, specimen collection, transportation, storage of specimens, and SOPs are to be identified.

   * The Sponsor may consider using the "calcofluor white stain." It is useful for direct microscopic examination of specimens, as the fungal elements are seen more easily than the KOH preparation.

   These data should be included in an "APPENDIX" to each protocol.

   We strongly recommend that this information be submitted to the Agency for review and evaluation prior to initiating any study.

3. If a "clinical and/or microbiological" failure is determined at any scheduled clinical visit, specimens are to be collected for culture microbiology and susceptibility testing is to be performed on the organism(s) recovered. *In vitro* susceptibility testing is to be done by Clinical and Laboratory Standards Institute (CLSI) methods.

   Place the aforementioned clinical/microbiology statement to this effect in each of your clinical study protocols.

4. Methods of the Clinical and Laboratory Standards Institute (CLSI) for performing susceptibility (MICs) testing are the methods recognized by the FDA for generating susceptibility data. Data referenced to CLSI methods need not be accompanied by the details of the methodology. However, if susceptibility data are obtained by modifying the CLSI methods, or by other methods, a detailed description of the method, including the justification for the modification of the method and the impact on susceptibility results, should be included.

5. All susceptibility data are to be accompanied by quality control testing data. In order for any susceptibility data on target pathogens to be considered valid, the test results for the target pathogens tested against econazole need to be accompanied by quality control data. If QC parameters do not exist they will need to be established. Refer to the Clinical and Laboratory Standards Institute (CLSI) document M23 for a description of a method for establishing *in vitro* susceptibility test quality control parameters.

6. Isolates used in the clinical studies, especially in failure cases, should be saved for future reference and plans should be in place to conduct typing in cases where it becomes important to differentiate strains of the same organism.

Note: Refer to the CLSI document and use the most recent "Molecular Methods for Bacterial Strain Typing" (MM11), e.g., "pulse-field gel electrophoresis" (PFGE) procedure.

7. Provide econazole susceptibility data on recent (i.e., 2003 to present) isolates of each relevant and targeted pathogenic dermatophyte causing tinea pedis.

   For the common targeted dermatophytes, we recommend that you provide at least 50 isolates derived from broad geographic regions of the United States. For the fastidious or less frequent dermatophyte isolates, a case-by-case assessment of the number required will be done. These data will be used to monitor changes in the susceptibility profile if the drug is approved. Susceptibility testing is to be performed using CLSI susceptibility (MICs) procedures.

Note: Recent surveillance data and data from published literature can be submitted. However, susceptibility data are to be recent (i.e., 2003 to present).

Meeting Discussion:

The Agency indicated that susceptibility data should be submitted by the end of Phase 2. The sponsor requested clarification regarding reference to the active entity (i.e., drug substance). The Agency clarified that this data does not have to be in final product form.

8. Identify the all the multicenter sites and the central mycology laboratory used for the clinical studies.

9. All clinical microbiology references and "reports" are to be submitted to the IND.

Meeting Discussion:

The Agency clarified that all references or reports cited in the IND should be submitted.

REGULATORY AFFAIRS:

Question 14:
Since SPECTAZOLE® (econazole nitrate 1%) Cream is no longer marketed in the United States, Quinnova is proposing to use a generic econazole nitrate 1% cream (ANDA equivalent to Spectazole) as the Reference Listed Drug (RLD). Does the Agency agree that this approach is acceptable?

Response:
Spectazole cream 1% is still listed in the Orange Book and is still commercially marketed in the US. The RLD would typically be this innovator product for econazole applications. If you are aware of information to support your assertion that Spectazole is no longer marketed, please submit that information to the Agency.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54 and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at *http://www.fda.gov/cder/guidance/guidance.htm* for further information.

Identify those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference (for example, for reproductive toxicity studies).

Meeting Discussion:

The Agency indicated that Spectazole is still listed in the Orange Book. The sponsor indicated that the product is not available through the pharmacy. The Agency requested that the sponsor submit such information/verification. In addition, the Agency is confirming availability with the innovator company.

If the product is confirmed discontinued by the innovator company, it will be listed as discontinued in the Orange Book. The sponsor may refer to an ANDA drug if Spectazole is indeed discontinued.

In the event that Spectazole is discontinued, the Agency indicated that the RLD will be selected by FDA.

PROJECT MANAGEMENT:

1. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or information requests.

2. Your pre-IND has been assigned #77,523. Please reference this number on all submissions and correspondence. Please note, studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312).

3. Please submit copies of all references cited in the IND, including translations of any foreign articles.

4. The Sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

5. The sponsor is encouraged to request an End-of-Phase II and a Pre-NDA Meeting at the appropriate time.

6. 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.

7. The sponsor is reminded that all new NDAs/BLAs and efficacy supplements submitted on or after June 30, 2006 must include content and format of prescribing information based on the new Physicians Labeling Rule at the time of submission (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details)

ACTION ITEMS:

1. The sponsor will submit information/verification regarding the discontinuation of Spectazole.
2. The Agency will confirm availability of Spectazole with the innovator company.
3. The sponsor will submit IND application.

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/s/

Markham Luke
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