CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205175Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 205175, Ecoza (econazole nitrate) topical foam, 1%
Date: 15-OCT-2013

Introduction

The Ecoza (econazole nitrate) topical foam is white to off-white foam packaged in pressurized (b) (4) canisters, which are available as 70g per canisters. (b) (4) The drug product was developed for the treatment of interdigital tinea pedis (b) (4)

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies. An overall acceptable recommendation from the Office of Compliance was issued on 21-July-2013. All labeling issues have been also satisfactorily resolved on 30-Sep-2013.

All CMC review issues have been resolved, and ONDQA recommends approval of this NDA.

Administrative

The original submission of this 505(b)(2) NDA was received on 26-DEC-2012 from AmDerma Pharmaceuticals, LLC. Eleven (11) CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (20-AUG-2013, Dr. Nina Ni), Addendum to Chemistry Review #1 (30-SEP-2013, Dr. Nina Ni), the Microbiology Review (25-JUN-2013, Dr. Erika Pfeiler), and the Biopharmaceutics Review (26-JUL-2013, Dr. Kelly Kitchens).

All DMFs were assessed for adequacy in the chemistry review.

Summary and Recommendation

Chemistry Review #1 (20-AUG-2013, Dr. Nina Ni) recommended a Complete Response due to incomplete resolution of CMC related labeling issues. The Addendum to Chemistry Review #1 (30-SEP-2013, Dr. Nina Ni) now recommends an Approval action as all the previously identified labeling issues have been resolved.

The 20-AUG-2013 Chemistry Review captures discussion of retaining the approved USAN name (econazole acetate) despite the fact that it contradicts the current salt name policy. The issue was brought to the attention of ONDQA's Precedence Committee on 20-AUG-2013, and, after taking into consideration the historical and medication error perspectives, the Committee decided to retain the salt name with corresponding strength.

I concur that there are no outstanding CMC deficiencies for this NDA, and I concur with the Reviewer's recommendation of approval for this application.

As per the 30-SEP-2013 Addendum to Chemistry Review #1, the 24-month of expiration dating period for the drug product can be granted.

Also, as per the Addendum, the applicant decided to market only the 70g canister configuration (b) (4)

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/s/

THOMAS F OLIVER
10/16/2013
signed for Dr. Sarah Pope Miksinski

M E M O R A N D U M

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

DATE: September 30, 2013
FROM: Nina Ni, Ph.D., Review Chemist, Branch IV, DNDQA II/ONDQA
THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, DNDQA II/ONDQA
TO: NDA 205175
SUBJECT: Addendum to CMC Review #1 for NDA 205175

In CMC Review #1, dated 08-20-2013, this NDA was not ready for "Approval" due to the following issue:

- Label/labeling issues were not satisfactorily resolved.

As of the date of this memorandum, label/labeling issues were satisfactorily resolved through amendment 0018, dated September 20, 2013 (labels) and amendment 0019 which was submitted through email, dated September 26, 2013 (package insert). The final version of labeling (**Attachment-1**) and carton/container labels (**Attachment-2**) agreed upon by the applicant and the Agency are attached to this memorandum.

Note that the applicant has decided to only market the 70 g canister for the initial launch of the drug product.

Final Recommendation:

From the ONDQA's perspective, this **NDA is now recommended for APPROVAL** with an expiration dating period of 24 months when store at controlled room temperature 20º - 25°C with excursions permitted between 15º and 30ºC.

Attachments:

Attachment-1: PI

Highlights of Prescribing Information

ECOZA (econazole nitrate) topical foam, 1%, for topical use
Initial U.S. Approval: 1982

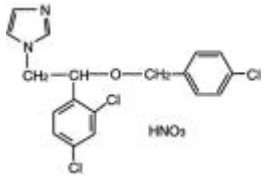
#3 Dosage Forms and Strengths

Foam, 1%. Each gram of Ecoza topical foam, 1%, contains 10 mg of econazole nitrate in a white to off-white foam.

#11 Description

Ecoza (econazole nitrate) topical foam, 1% contains the azole antifungal agent, econazole nitrate in an oil-in-water emulsion base consisting of the following inactive ingredients: dimethicone, glycerin, polysorbate 20, povidone, propylene glycol, stearic acid, trolamine, purified water and butane as a propellant. Each gram of Ecoza topical foam, 1% contains 10 mg of econazole nitrate, USP, in a white to off-white foam. Ecoza topical foam, 1% is alcohol (ethanol)-free and for topical use only.

Chemically, econazole nitrate is 1-[2-{(4-chloro-phenyl)methoxy}-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole mononitrate. Econazole nitrate has the molecular formula C18H15Cl3N2O.HNO3 and a molecular weight of 444.70. Its molecular structure is as follows:



#16 How Supplied

Ecoza topical foam, 1% is white to off-white foam supplied in 70 g (NDC 23710-100-70) aluminum pressurized canister.

Store at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F). Do not refrigerate or freeze.

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.

Attachment-2: Labels

Container label for 10 g physician sample:

Carton label for 10 g physician sample:

Container label for 70 g to-be-marketed drug product:

Carton label for 70 g to-be-marketed drug product:

(b) (4)

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/s/

NINA NI
09/30/2013

MOO JHONG RHEE
09/30/2013
Chief, Branch IV

NDA 205175

Ecoza (econazole nitrate) Foam
1%
AmDerma Pharmaceuticals, LLC.

Nina Ni, Ph. D.

Review Chemist

Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

CMC REVIEW
For the Division of Dermatology & Dental Products

Table of Contents

CMC Review Data Sheet

1. NDA 205175

2. REVIEW #: 1

3. REVIEW DATE: 08/20/2013

4. REVIEWER: Nina Ni, Ph. D.

5. PREVIOUS DOCUMENTS:

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission Correspondence (C)	12/26/2012
Amendment (BC): 0001	01/25/2013
Amendment (BC): 0003	02/07/2013
Amendment (BC): 0005	03/15/2013
Amendment (BC): 0006	02/15/2013
Amendment (BC): 0008	02/19/2013
Amendment (BC): 0009	03/25/2013
Amendment (BC): 0010	04/05/2013
Amendment (BC): 0013	06/24/2013
Amendment (BC): 0014	07/22/2013

7. NAME & ADDRESS OF APPLICANT:

Name:	AmDerma Pharmaceuticals, LLC
Address:	440 US Hwy 22 East. Suite 104 Bridgewater, NJ 08807
Representative:	Candis Edwards, Regulatory Affairs Consultant
Telephone:	631-656-7538

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ecoza (proposed)
b) Non-Proprietary Name (USAN): Econazole nitrate
c) Code Name/# (ONDQA only): NA
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3

- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: For the treatment of interdigital tinea pedis

(b) (4)

11. DOSAGE FORM: Foam

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __√__Rx ___OTC

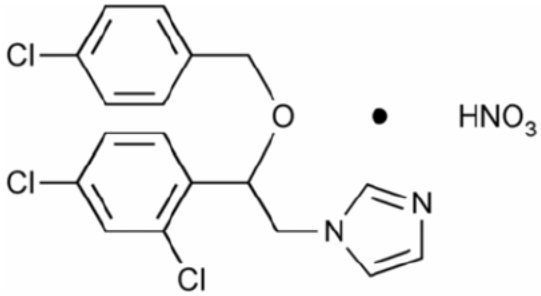
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Econazole nitrate
CHEMICAL NAME: 1H-Imidazole, 1-[2-[(4-chlorophenyl)methoxy-]2-(2,4-dichlorophenyl)[ethyl]-, mononitrate, (±)-, or (±)-1-[2,4-Dichloro-β-[(p-chlorobenzyl)oxy]phenethyl]-imidazole mononitrate

STRUCTURAL FORMULA:



MOLECURAL FORMULA: $C_{18}H_{15}Cl_3N_2O.HNO_3$

MOLECULAR WEIGHT: 444.70 g/mol
CAS NUMBER: [68797-31-9]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	08/12/2013	Reviewed by N. Ni, Ph. D.
	III			4 & 7	Adequate	08/20/2013	CFR citation was provided in the DMF for the referenced item.
	III			4 & 7	Adequate	08/20/2013	CFR citation was provided in the DMF for the referenced item.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77523	Econazole nitrate foam 1%

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	07/21/2013	
Pharm/Tox	NA		
Biopharm	Approval	07/26/2013	K. Kitchens, Ph. D.
LNC	NA		
Methods Validation	NA, according to the current ONDQA policy.		
DMEPA	NA		
EA	Claim for the categorical exclusion is granted	06/18/2013	R. Bloom, Ph. D.
Microbiology	Approval	06/25/2013	E. Pfeiler, Ph. D.

The CMC Review for NDA 205175

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in this NDA.

However, issues on label/labeling have ***not*** been finalized as of this review.

Therefore, from the CMC perspective, this NDA is ***not*** ready for approval in its present form until label/labeling are satisfactorily resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of CMC Assessments

The microbial control information for the drug substance, excipients, and drug product was reviewed and found adequate by microbiologist, Erika Pfeiler, Ph. D. The in vitro release testing (IVRT) method and its validation was reviewed and found adequate by Kelly Kitchens, Ph. D. Please see their reviews on 06/25/13 and 07/26/13, respectively, for the detailed evaluation.

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance proposed under this NDA is econazole nitrate, USP, which has been widely used in different approved drug products. All information related to the chemistry, manufacturing, and controls are referenced to (b) (4) Drug Master File (DMF) (b) (4) The DMF was reviewed and found adequate to support this NDA by Nina Ni, Ph. D.

The applicant has proposed an in-house specification for econazole nitrate which meets and exceeds those requirements listed in the USP and EP monograph. It includes more controls on specific impurity and is also in accordance with ICH Q6A.

Certificate of analysis (CoA) from the DMF holder for the three batches of the drug substance used for manufacturing the drug product registration batches are included. The applicant also conducted in-house verification testing of the same lots. All test results met the proposed specification.

The established name for the drug substance retains the salt, even it is not in line with the CDER salt nomenclature policy (MAPP 5021.1). This was presented to ONDQA Precedence Committee meeting on 08/20/2013 based on a rationale that the RLD, Spectazole® Cream, referenced by this applicant, uses the same salt name with the strength, 1%, expressed based on the salt. The Precedence Committee concurred the proposed use of salt name for this product with the following four reasons:

- Historical reason: Four ANDAs of topical econazole nitrate cream, 1% have been approved for similar indication. All have a product name using the salt. Examples: ANDA 76005 Econazole Nitrate Cream 1% (Taro) and ANDA 76075 Econazole Nitrate Cream 1% (Fougera)
- DMEPA recommends the use of econazole nitrate as the established name to avoid market confusion.
- The proposed established name, econazole nitrate, matches the strength of 1% (i.e. no mismatch).
- USP has a monograph on econazole nitrate but no drug product monograph.

(2) Drug Product

The proposed drug product is a white to off-white foam packaged in pressurized aerosol cans. It is applied to a small skin area for the treatment of tinea pedis with a relatively short treatment duration. The filling weights are 70 g (b) (4) for trade and 10 g for physician sample. The inactive ingredients used to manufacture the econazole nitrate bulk are: stearic acid, povidone (b) (4) propylene glycol (PG), glycerin, dimethicone (b) (4), trolamine, polysorbate 20, and purified water. All excipients are compendial grade. (b) (4) Butane (b) (4) is used as propellant to dispense the drug.

(b) (4)

The manufacturing process appears to be straight forwarded and well defined (b) (4)

(b) (4)

The primary container/closure system for the drug product consists of a metal can, a valve, an actuator, and an over cap. All the components except for steel spring, comply with the pertinent 21CFR regulations for direct food contact. There is no safety concern for the container/closure system.

The proposed drug product specification which includes description, identity, pH, pressure, delivered amount, dispensing rate, appearance (b) (4) by both visual and microscopic observation, assay, (b) (4) packaging/product interactions, (b) (4) and microbiological testing, are supported by batch data and acceptable.

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches. Stability data submitted include 24 months of long term (25ºC/60% RH) and 6 months of accelerated temperature (40ºC/75% RH) data from 3 registration stability batches each for the fill sizes of 10 g (b) (4) The batch sizes of the registration stability batches are (b) (4) The production scale is (b) (4) Additionally, 24 months of long term and 6 months of accelerated temperature stability data are also provided for one 70 g fill size registration stability batch.

The stability data indicate that the drug product is physically and chemically stable with no significant change (b) (4) All tested attributes are within the specification. The stability data support the proposed expiration dating period of 24 months for econazole nitrate foam when stored at 20º - 25°C (excursions permitted to 15º - 30ºC).

In-use study appears to support the proposed in-use period (b) (4)

An IVRT study was conducted to bridge site change (b) (4) to (b) (4) U.S. and process changes. IVRT is reviewed and found satisfactory by the Biopharm reviewer, Kelly Kitchens, Ph. D.

B. Description of How the Drug Product is Intended to be Used

Sufficient econazole nitrate foam, 1% should be applied to cover affected areas once daily in patients with tinea pedis.

C. Basis for Not-Approval Recommendation

21 CFR 314.125(b)(6)

- Issues on labels and labeling have not been satisfactorily resolved.

(see the **List of Deficiencies** on p. 110)

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Nina Ni, Ph. D., CMC Reviewer, Branch IV, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph. D., Branch Chief, Branch IV, ONDQA

C. CC Block: entered electronically in DFS

Shulin Ding, Ph.D., CMC Lead, Branch IV, ONDQA

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/s/

NINA NI
08/20/2013

MOO JHONG RHEE
08/20/2013
Chief, Branch IV

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205175	**Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	December 21, 2012		
Division:	Division of Dermatology and Dental Products	**Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	AmDerma Pharmaceuticals, LLC	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Ecoza	**Date Assigned:**	February, 2013
Established Name:	Econazole Nitrate Foam, 1%	**Date of Review:**	April 16, 2013
Indication:	(b) (4)	**Type of Submission:** 505(b)(2)	
Formulation/ strengths	Foam/1%		
Route of Administration	Topical		
Type of Review:	New Drug Application		

SUMMARY:

Background: Econazole Nitrate Foam, 1%, is a topical antifungal agent that is currently indicated for a variety of fungal diseases, including tinea pedis, tinea crusis, tinea corporis, and cutaneous candidiasis, as well as for the treatment of tinea versicolor. The drug product was initially manufactured by (b) (4) In 2010, Quinnova Pharmaceuticals, Inc., the supplier for the excipients used in the formulation, initiated a technology site transfer to (b) (4) United States (b) (4)

Submission: In response to the August 29, 2012 pre-NDA meeting comments, the Applicant conducted in vitro release testing (IVRT) to qualify a (b) (4) manufacturing site change (b) (4) to (b) (4) USA (b) (4) The applicant submitted the IVRT method development report, and the validation reports for the IVRT and HPLC analytical assay.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the submitted IVRT data supporting the approval of the manufacturing site change.

RECOMMENDATION:
The in vitro drug release rate comparison data support the approval of the proposed drug product manufacturing site change [redacted] (b) (4) to [redacted] (b) (4) USA. From the Biopharmaceutics perspective, NDA 205175 for Econazole Nitrate Foam, 1% is recommended for approval.

Signature
Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. RLostritto.

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Recommendation:

The in vitro drug release rate comparison data support the approval of the proposed drug product manufacturing site change (b) (4) to (b) (4) USA. From the Biopharmaceutics perspective, NDA 205175 for Econazole Nitrate Foam, 1% is recommended for approval.

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/s/

KELLY M KITCHENS
07/26/2013

TAPASH K GHOSH
07/26/2013

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division:	Division of Dermatology and Dental Products
NDA:	205175
Applicant:	AmDerma Pharmaceuticals, LLC.
Stamp Date:	Dec. 21, 2012
PDUFA Date	Oct. 24, 2013
Trademark:	Not proposed
Established Name:	Econazole nitrate
Dosage Form:	Foam
Route of Administration:	Topical
Indication:	Treatment of interdigital tinea pedis
CMC Lead:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

AmDerma Pharmaceuticals has submitted a 505(b)(2) New Drug Application (NDA) for the prescription use of Tradename (econazole nitrate) foam, 1% for the topical treatment of interdigital tinea pedis [redacted (b) (4)]

Econazole is a racemic mixture. Its structure contains one chiral center. The applicant references to DMF [redacted (b) (4)] for the CMC information of the proposed drug substance. A letter of authorization [redacted (b) (4)] is provided. The proposed drug substance manufacturing site is located [redacted (b) (4)] The last DMF review was conducted in November, 2003 for an econazole nitrate cream, 1% ANDA. The DMF was deemed adequate to support the ANDA.

The proposed drug product is a white to off-white foam packaged in pressurized canisters. The proposed trade sizes are 70 g [redacted (b) (4)] The physician sample size is 10 g. The proposed formulation (shown in the table on the next page) contains [redacted (b) (4)] a propellant, butane. There are no novel excipients present in the formulation.

[redacted (b) (4)]

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches. Stability data provided in the initial submission to support an expiration dating period of 24 months at 20°-25°C (excursions permitted to 15°-30°C) include18 months of long term (25°C//60%RH), and 6 months of accelerated temperature (40°C/75%RH) from 3 registration stability batches for the fill sizes of 10 g (b) (4) The batch size of the registration stability batches (b) (4) Additionally, 18 months of long term and 6 months of accelerated temperature (40°C/75%RH) stability data are provided form one of the registration stability batches for the 70 g fill size.

Special stability studies such as (b) (4) freeze/thaw studies are also included in the NDA to support storage/handling of the drug product. An IVRT study was conducted to bridge site change (b) (4) to (b) (4) U.S. and process changes. The pivotal PK study was conducted using a (b) (4) batch.

Ingredients	mg / g	% w/w
Econazole Nitrate, USP	10.000	1.00
Purified Water, USP	(b) (4)	
Stearic Acid, NF		
Povidone		
Propylene Glycol, USP		
Glycerin		
Dimethicone		
Trolamine		
Polysorbate 20, USP		
Total		
Butane, USP		

Fill Weights

	10 g	70 g	(b) (4)
Econazole Nitrate 1% Bulk			
Propellant (Butane, USP)			
Total Fill Weight			

B. Critical Issues for review

1. Drug Substance Starting Material
   The proposed starting material is (b) (4)

2. Function of Inactive Ingredients in Formulation
   The function of dimethicone (b) (4) in the formulation has not been assigned. The functions of propylene glycol and glycerin are assigned (b) (4)

(b) (4)

3. Drug Product Master Batch Records
There is a general lacking of information for operational parameters (b) (4) in the Master Batch Records. The applicant provides information regarding critical process steps and parameters in Pharmaceutical Development (Table 32 of Section 3.2.P.2.3.6), but none of the operational ranges have been incorporated into the Master Batch Records. Neither do the Master Batch Records include the information regarding (b) (4) testing points and acceptance criteria (b) (4)

4. IVRT Bridging Studies
The IVTR studies are used to support the site change (b) (4) to (b) (4) (U.S.) and also the process changes (b) (4)

5. Physical State of the Active Ingredient
(b) (4) More information will be needed in order to agree with the applicant's statement.

(b) (4)

A t-con with the applicant took place on Feb. 6 on this issue. (b) (4) The applicant agreed to submit an amendment by Feb. 15, 2013 to address the issue.

6. Drug Product Specification
The proposed drug product specification is noted for the following omissions:

- Identity for the active ingredient.
- (b) (4)
- Package integrity.
- (b) (4)

The above tests should be carefully reviewed to determine if the omissions are acceptable.

(b) (4) The current proposed acceptance criterion for the test on appearance (b) (4) is unacceptable.

7. Extractables/Leachables

(b) (4)

C. Other Review Issues

1. Solubility Information for Drug Substance
The applicant does not provide adequate information on this subject. As a result, it is difficult to understand the formulation characteristics of the proposed product. It is would be helpful if pH-solubility profile and solubilities of econazole nitrate (b) (4) can be provided.

2. Batch Release and Stability Data
Data from multiple batches are not presented side-by-side in one table in the section on Batch Analysis. Registration stability data from multiple time points are not presented side-y-side in one table in Section P.8.3 Stability Data. It is difficult to assess and compare the data with the current format.

3. (b) (4)
The safety of this ingredient needs a careful review.

D. Comments for 74-Day Letter:

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) The current proposed acceptance criterion of Report Results is unacceptable. (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)

E. Comments/Recommendation:

The application is acceptable for filing from CMC perspective.

Drug substance manufacturing site is located (b) (4) Drug product manufacturing site is located in U.S. GMP inspection requests have been submitted.

The in-vitro studies conducted for bridging will be reviewed by ONDQA Biopharm reviewer, Kelly Kitchens. CMC reviewer assigned to this NDA is Nina Ni.

Shulin Ding, Ph.D.
CMC Lead

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV

NDA Number:	Supplement Number and Type:	Established/Proper Name:
205175	0000	Econazole nitrate foam, 1%
Applicant: AmDerma	Letter Date: Dec 21, 2012	Stamp Date: Dec. 21, 2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		The (b) (4) facility is missing from Form 356h in the initial submission. The complete information is submitted in 2/7/13 amendment.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			n/a

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		The (b) (4) facility is missing from Form 356h in the initial submission. The complete information with the statement of readiness for inspection is submitted in 2/7/13 amendment.

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)			n/a
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		The complete information with the statement of readiness for inspection is submitted in 2/7/13 amendment.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		(b) (4) [redacted]

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	x		Also referenced to DMF (b) (4) for details.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	x		Also referenced to DMF (b) (4) for details.
15.	Does the section contain controls for the DS?	x		Also referenced to DMF (b) (4) for details.
16.	Has stability data and analysis been provided for the drug substance?	x		Also referenced to DMF (b) (4) for details.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	n/a
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		Submitted in 2/7/13 amendment

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	5/16/2012	
	III			7/2/2012	
	III			7/18/2012	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			n/a
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		

{See appended electronic signature page}

Shulin Ding, Ph.D.
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

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

/s/

SHULIN DING
02/08/2013

MOO JHONG RHEE
02/08/2013
Chief, Branch IV

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	205175
Submission Date	December 21, 2012
Product name, generic name of the active	Econazole Nitrate Foam, 1%
Dosage form and strength	Foam
Route of Administration	Topical
Applicant	AmDerma Pharmaceuticals, LLC
Clinical Division	Division of Dermatological and Dental Products
Type of Submission	505 (b)(2) NDA
Biopharmaceutics Reviewer	Kelly M. Kitchens, Ph.D.
Acting Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		X	Dissolution testing is not applicable for topical dosage forms. The application does contain **in vitro release testing (IVRT)** data. The remaining checklist parameters pertain to IVRT.
2.	Is the IVRT part of the DP specifications?		X	
3.	Does the application contain data to support the proposed IVRT acceptance criteria		X	
4.	Does the application contain the IVRT method development report?	X		Module 5.3.1.3.3 Method-Development, Development of Analytical Procedure for *In-Vitro* Release (b) (4) Study, Report no. (b) (4)
5.	Does the application contain data on the discriminating ability of the IVRT method	X		
6.	Is there a validation package for the analytical method and IVRT methodology?	X		Module 5.3.1.3.3 Method-Validation, Validation of Analytical Procedure for *In-Vitro* Release Test (b) (4) Report No. (b) (4)
7.	Does the application include a biowaiver request?		X	
8.	Does the application include an IVIVC model?		X	

9.	Is information such as BCS classification mentioned, and supportive data provided?		X	
10.	Is information on mixing the product with foods or liquids included?		X	Not applicable for topical dosage form
11.	Is there any in *vivo* BA or BE information in the submission?		X	
12.	Does the application include in *vitro* alcohol interaction studies?		X	Not applicable for topical dosage form

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
13.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
14.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	Not applicable
15.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	Not applicable
16.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		See the following comments

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

BIOPHARMACEUTICS INITIAL ASSESSMENT

GENERAL SUMMARY:

Econazole Nitrate Foam, 1%, is a topical antifungal agent that is currently indicated for a variety of fungal diseases, including tinea pedis, tinea crusis, tinea corporis, and cutaneous candidiasis, as well as for the treatment of tinea versicolor. The applicant conducted in vitro release testing (IVRT) to qualify a (b) (4) manufacturing site change (b) (4) The applicant submitted the IVRT method development report, and the validation reports for the IVRT and HPLC analytical assay.

The Biopharmaceutics review will be focused on the evaluation and acceptability of the submitted IVRT data supporting the approval of the manufacturing site change.

Reviewer notes:

- The applicant used the confidence interval computation method per the SUPAC-SS guidance. The 90% confidence intervals (b) (4) fall within the limits (b) (4) The test product passes (b) (4) However, validity of the results is a review issue.
- The applicant evaluated the in vitro release of econazole (b) (4)

Potential review issues to be forwarded to the Applicant for the 74-day letter:

1. 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)

(b) (4)

(b) (4) The applicant may consult ONDQA for specific guidelines in this respect.

2. Please explain precisely how the foam was applied (b) (4)

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 205175 is fileable. The ONDQA Biopharmaceutics team will further evaluate the IVRT method development, validation and results.

{See appended electronic signature page}
Kelly M. Kitchens, Ph.D. 02/08/13
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Tapash Ghosh, Ph.D. 02/08/13
Acting Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

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

/s/

KELLY M KITCHENS
02/08/2013

TAPASH K GHOSH
02/08/2013