

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204153Orig1s000**

**CHEMISTRY REVIEW(S)**

ONDQA Division Director's Memo  
NDA 204153, Luzu (luriconazol) cream, 1%  
Date: 08-NOV-2013

## **Introduction**

The Luzu (luriconazol) cream, 1%, is white cream available as 30g and 60g per an aluminum tube, and each gram of cream contains 10mg of luriconazol. The drug product was developed for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms trichophyton rubrum, or epidermophyton floccosum in patients 18 years of age and older.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation from the Office of Compliance was issued on 13-Jun-2013. All label and labeling issues have been also satisfactorily resolved on 10-SEP-2013 and 08-Oct-2013, respectively.

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

## **Administrative**

The original submission of this 505(b)(1) NME NDA was received on 11-DEC-2012 from Medicis Pharmaceutical Corp. Seven (7) CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (16-JUL-2013, Dr. Raymond Frankewich), Addendum to Chemistry Review #1 (27-SEP-2013, Dr. Raymond Frankewich), and the Biopharmaceutics Review (17-JUL-2013, Dr. Kelly Kitchens).

All DMFs were assessed for adequacy in the chemistry review.

## **Summary and Recommendation**

Chemistry Review #1 (16-JUL-2013, Dr. Raymond Frankewich) recommended a Complete Response due to incomplete resolution of CMC related labeling issues. The Addendum to Chemistry Review #1 (27-SEP-2013, Dr. Raymond Frankewich) now recommends an Approval action as all the previously identified labeling issues have been resolved.

*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 27-SEP-2013 Addendum to Chemistry Review #1, the 18-month of expiration dating period for the drug product can be granted.*

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/s/  
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MOO JHONG RHEE

11/08/2013

This document is checked in on behalf of Sarah Pope Miksinski

SARAH P MIKSINSKI

11/08/2013

MEMORANDUM

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

DATE: September 27, 2013

FROM: Raymond P. Frankewich, Ph.D., Review Chemist, Branch IV, DNDQA II/ONDQA

THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, DNDQA II/ONDQA

TO: CMC Review #1, NDA 204153

SUBJECT: Final Recommendation

The previous CMC Review #1, dated 7-16-2013, made a recommendation of not approval of this NDA because of the following unresolved issues:

- Issues concerning labels/labeling had not been satisfactorily resolved from the CMC perspective.

Labels/labeling are now satisfactorily revised according to our recommendations in the CMC Review #1 (see the **Attachment-1**).

One note: The recommended drug product title is Luzu (luliconazole) cream, 1%. The nomenclature of the dosage form, **cream**, conforms to the standardized format prescribed by USP<1121> Nomenclature, and the draft Guidance for Industry: Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products, March 2012. A description is provided in **Attachment-2** for the standardized format pertinent to dermatological dosage forms.

The CMC review team concurs with the conclusions of the Patient Labeling Review dated July 17, 2013, which evaluated the Patient Package Insert (PPI).

**Recommendation:**

Therefore, from the ONDQA's perspective, this NDA is now recommended for **APPROVAL** with an expiration dating period of 18 months.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## **Attachment-2: Product Title Format for Dermatological Dosage Forms**

The standardized format prescribed by USP<1121> for USP (or NF) monograph titles is [DRUG][ROUTE OF ADMINISTRATION][DOSAGE FORM]. USP<1121> instructs that the term for route of administration is omitted for those dosage forms for which the route of administration is understood. The general form then becomes simply [DRUG][DOSAGE FORM]. For dermatological dosage forms, USP<1121> lists creams, ointments, lotions, and pastes as dosage forms applied topically, unless otherwise indicated by the name.

The same recommendation is adopted by the draft guidance, but with a more expanded list of dermatological dosage forms in the category of "assumed to be topical". Below are the lists of dosage forms that are "assumed to be topical" and "not assumed to be topical" according to the draft guidance:

**Assumed to be topical:** cream, lotion, ointment, paste, plaster, shampoo, swab, and tape.

**Not assumed to be topical:** aerosol, film, foam, gel, implant, insert, powder, rinse, solution, spray, suspension, system

Those dosage forms **assumed** to be topical will have "route of administration" omitted from the product title whereas dosage forms **not assumed** to be topical will have the word "***topical***" inserted between the established name and dosage form.

It is the intent of ONDQA to comply with USP<1121> and the draft guidance for Industry for the product title of package insert. Since July 2013, product titles approved for dermatological gels and foams have had the word "***topical***" inserted between the established name and dosage form. Despite being unprecedented for these two dosage forms, concurrence has been obtained from ONDQA Precedence Committee for Mirvaso (brimonidine) topical gel, 0.33% (NDA 204708) and Ecoza (econazole nitrate) topical foam, 1% (NDA 205175).

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/s/  
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RAYMOND P FRANKEWICH  
09/27/2013

MOO JHONG RHEE  
09/27/2013  
Chief, Branch IV

# **NDA 204153**

**Luzu<sup>®</sup> (Iuliconazole) Cream 1%**

**Medicis Pharmaceutical Corporation**

**Raymond P. Frankewich, Ph.D.**

**Review Chemist**

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

**CMC REVIEW  
For the Division of Dermatology and Dental Products  
(CDER/ODEIII/DDDP, HFD-540)**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 204153
2. REVIEW #: 1
3. REVIEW DATE: 16-July-2013
4. REVIEWER: Raymond P. Frankewich, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	December 11, 2012
Correspondence (C)	January 25, 2013
Amendment (BC)	February 1, 2013
Amendment (BC)	February 26, 2013
Amendment (labeling)	March 15, 2013
Amendment	May 17, 2013
Amendment	June 24, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Medicis Pharmaceutical Corporation  
Address: 7720 North Dobson Road  
Scottsdale, AZ 85256  
Representative: Diane Stroehmann, Executive Director,  
Regulatory Affairs  
Telephone: 480-291-5611

8. DRUG PRODUCT NAME/CODE/TYPE:

- |   |              |
|---|--------------|
| a) Proprietary Name:                            | Luzu         |
| b) Non-Proprietary Name:                        | luliconazole |
| c) Code Name/# (ONDQA only):                    | None         |
| d) Chem. Type/Submission Priority (ONDQA only): |              |

## CMC Review Data Sheet

- Chem. Type: 1
- Submission Priority: S (under PDUFA V Program)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antimycotic

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

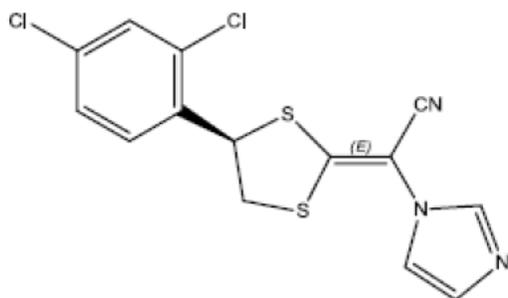
SPOTS product – Form Completed

Not a SPOTS product

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

Chemical name: (-)-(E)-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene](1H-imidazole-1-yl)acetonitrile

Structural formula:



Molecular formula: C<sub>14</sub>H<sub>9</sub>C<sub>12</sub>N<sub>3</sub>S<sub>2</sub>

## CMC Review Data Sheet

Molecular weight: 354.28 g/mol

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	July 11, 2013	
	III			1	Adequate	July 9, 2013	

<sup>1</sup> 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")

<sup>2</sup> 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	76049	IND for luliconazole cream, 1% held by NDA Applicant
NDA		

## CMC Review Data Sheet

## 18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	NA		
EES	Acceptable	June 13, 2013	
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	N/A (see review)		
DMETS	NA		
EA	Categorical exclusion (see review)	April 18, 2013	
Microbiology	NA		

## Executive Summary Section

# The CMC Review for NDA 204153

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has issued an overall "Acceptable" recommendation for the facilities involved.

However, issues concerning labels/labeling have *not* been satisfactorily resolved yet.

Therefore, from the ONDQA perspective, this NDA is not ready for approval per 21 CFR314.125(b)(6) in its present form until the above issues are satisfactorily resolved.

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

Not Applicable

### II. Summary of CMC Assessments

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

##### (1) Drug Substance

The drug substance is luliconazole, which is a New Molecular Entity (NME). Luliconazole is an antifungal drug. In the drug product labeling, luliconazole is described as an antifungal agent and is intended to be applied topically.

Luliconazole drug substance is a pale to light yellow crystalline powder. It possesses one chiral center. The active form of luliconazole is the *R* enantiomer. The acceptance specification for the drug substance and the release specification for drug product contain tests which limit the amount of *S* enantiomer to NMT (b) (4) in the drug substance.

(b) (4)  
The acceptance specification for the drug

## Executive Summary Section

substance and the release specification for drug product contain tests which limit the amount of the (b) (4) to NMT (b) (4) in the drug substance.

It is stated in the NDA that the drug substance does not exhibit a propensity for (b) (4). The dissociation constant ( $pK_a$ ) of luliconazole is (b) (4).

**(2) Drug Product**

The drug product is a white cream intended for topical use. The concentration of luliconazole in the drug product is 1% w/w. The drug product is considered an (b) (4).  
(b) (4)  
The container used for this drug product is a blind-end aluminum tube with a 2, 30, or 60 g fill volume and a white (b) (4) cap.

This drug product was first developed and approved for use in Japan and has been marketed there since 2005. The drug product formulation was not changed for the U. S. clinical development program or for the proposed U. S. commercial drug product except for the grade of excipients (NF or USP rather than JP).

The pH of the drug product (b) (4). The pH acceptance criterion in the drug product specification for the Japanese product and throughout clinical development in the U. S. has been 5.0 – 7.0.

One of the (b) (4) in the drug product formulation is polysorbate 60. The Japanese product is (and one of the clinical trial lots manufactured in the U. S. was) manufactured using polysorbate 60 (b) (4) (b) (4).

Because of the issues with pH, the applicant has requested that the pH acceptance criterion in the drug product specification be expanded to (b) (4). This was not agreed to since there has been no clinical or CMC experience with a product the pH of which is (b) (4). In addition, the applicant's proposed expiration date of (b) (4) was not considered acceptable (b) (4).  
(b) (4) The applicant has agreed to change the pH acceptance criterion in the drug product specification to 5.0 – 7.0. The applicant has also agreed to change the expiration dating period to 18 months.

## Executive Summary Section

Drug product marketed in Japan and manufactured in the U. S. exhibits (b) (4) when subjected to microscopic examination. It is stated in the NDA submission that the (b) (4)

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

The drug product is intended to be used as an antifungal. The drug product is indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum*, (b) (4) or *Epidermophyton floccosum*, in patients 18 years of age and older.

The drug product is applied topically. It is stated in the NDA submission (Amendment dated February 1, 2013) that the median total amount of product used per day in the Phase 3 study to assess the safety and efficacy of tinea cruris was 5.1 grams product per day.

**C. Basis for Not-Approval Recommendation**

21 CFR314.125(b)(6)

- Label / labeling are not finalized as of this review.

(see the **List of Deficiencies**, pg. 105)

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature:**

*(See appended electronic signature page)*

Raymond P. Frankewich, Ph.D., Branch IV, ONDQA / DNDQA II

**B. Endorsement Block:**

*(See appended electronic signature page)*

Moo Jhong Rhee, Ph.D., , Branch Chief, Branch IV, ONDQA / DNDQAII

**C. CC Block:** entered electronically in DFS

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/s/  
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RAYMOND P FRANKEWICH  
07/16/2013

MOO JHONG RHEE  
07/16/2013  
Chief, Branch IV

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

**OND Division:** Division of Dermatology and Dental Products  
**NDA:** 204-153  
**Applicant:** Medicis Pharmaceutical Corp.  
**Stamp Date:** Dec. 11, 2012  
**PDUFA Date:** Dec. 11, 2013  
**Trademark:** Luzu®  
**Established Name:** Luliconazole  
**Dosage Form:** Cream  
**Route of Administration:** Topical  
**Indication:** Treatment of interdigital tinea pedis, tinea cruris, tinea corporis

**CMC Lead:** Shulin Ding

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

**Summary and Critical Issues:**

A. Summary

Medicis Pharmaceuticals has submitted a 505(b)(1) New Drug Application (NDA) for the prescription use of Luzu® (luliconazole) cream, 1% for the topical treatment of interdigital tinea pedis, tinea cruris, tinea corporis. The same product has been approved by Japan since 2005.

Lliconazole is a new molecular entity in the U.S. The applicant references DMF (b)(4) held by (b)(4) for the CMC information of the proposed drug substance. A letter of authorization from (b)(4) is provided. The proposed drug substance manufacturing site is (b)(4). The DMF has not been reviewed for a NDA or ANDA. It has been reviewed once in October, 2012 for an IND.

The proposed drug product is a white, (b)(4) cream packaged in (b)(4) aluminum tubes with white (b)(4) caps. The proposed trade sizes are 30 g and 60 g. The physician sample size is 2 g. The propose formulation is shown in the table on the next page. Except for the grade of excipients (NF or USP grade versus JP grade), it is the same formulation approved for the Japanese marketing authorization. There are no novel excipients present in the formulation. Neither do any excipients originate from (b)(4)

The formulation of the proposed product is prepared by (b)(4)  
(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 (b) (4) at 20°-25°C (excursions permitted to 15°-30°C) include 12 months of long term (25°C//60%RH), 12 months of intermediate temperature (30°C/65%RH), and 6 months of accelerated temperature (40°C/75%RH) from 3 registration stability batches for each fill size. The batch size of the registration stability batches is (b) (4) which is approximately (b) (4). Additionally, 18 months of long term stability data are provided from one Phase 3 clinical batch (b) (4) for 30 g fill size.

Special stability studies such as in-use stability and freeze/thaw cycling studies are also included in the NDA to support storage/handling of the drug product.

Component	Function	Quality Standard	Quantity (% w/w)
Luliconazole	Active	In-house	1.0
Benzyl alcohol	(b) (4)	NF	(b) (4)
Butylated hydroxytoluene	(b) (4)	NF	(b) (4)
Cetostearyl alcohol	(b) (4)	NF	(b) (4)
Isopropyl myristate	(b) (4)	NF	(b) (4)
Medium-chain triglyceride	(b) (4)	NF	(b) (4)
Methylparaben	(b) (4)	NF	(b) (4)
Polysorbate 60	(b) (4)	NF	(b) (4)
Sorbitan monostearate	(b) (4)	NF	(b) (4)
Propylene glycol	(b) (4)	USP	(b) (4)
Purified water	(b) (4)	USP	(b) (4)

qs = quantity sufficient

USP = United States Pharmacopeia

NF = National Formulary

## B. Critical Issues for review

### 1. (b) (4) in Drug Product

The drug substance (b) (4). The applicant states (p.18 of 18 Section 3.2.P.5.6.3) that the presence of luliconazole (b) (4) does not impact product performance, and proposes no (b) (4) test in Drug Product specification. The applicant also concludes that the drug substance has only (b) (4) therefore, there is no need of routine monitoring of (b) (4) in drug product. The study reports on the investigation of the (b) (4) and dissolution comparisons will need a critical review.

### 2. Batch Equivalence between Japan-made and U.S.-made batches

The applicant includes safety/efficacy data established with the Japanese product in this NDA to support the safety/efficacy of the proposed U.S. product. To demonstrate that Japan-made batches are equivalent to U.S.-made batches, the results of two IVRT studies

using in-vitro enhancer cell and one Franz cell percutaneous absorption study using human skin are included in the NDA. The study reports need a critical review by the Biopharm reviewer to establish the batch equivalence.

The IVTR studies are used to support the site change from (b) (4) to DPT, and the technical grade change for excipients including the change in the (b) (4). The human skin study compared percutaneous absorption of fresh sample (25°C 3 months) with stressed sample (40°C 3 months).

It is noted that all Japan-made batches are not provided with viscosity data. This is a hole in the establishment of batch equivalence. A request should be made for the viscosity data of Japanese batches.

Certificates of analysis for the Japanese batches used in the IVRT and percutaneous absorption human skin studies can not be found either. Reviewers should request the certificates once confirming the omissions.



When reviewing and comparing pH data, please note that pH method changed during the course of stability studies without explanation. Comparison of pH values from batch to batch, and from time point to time point will need to be conducted with a grain of salt. The two OOS observations made at later time points of 30°C and 40°C studies should also be examined for the possibility of being outliers.

4. Drug Product Specification

The proposed drug product specification is noted for the following:

- Related substances spec does not include a limit for individual unspecified.
- Broadening of pH acceptance criterion to (b) (4) is proposed.
- Waiver of the test on content uniformity is proposed for the 2 g size.
- Viscosity acceptance criterion is not supported by the stability data.
- Identity test is by HPLC retention time only. A second technology such as UV by diodarray detector is not included.

A critical review needs to be performed on the specification. The proposed pH acceptance criterion deserves special attention because it implicates batch equivalence claimed by the applicant (see Critical Review Issue #2 above) as explained below:

Because pH impacts (b) (4) one can not assume that a pH (b) (4) cream would be bioequivalent to a pH

(b) (4) cream. (b) (4) It is noted that the two IVRT and one human skin studies (conducted with an intention to bridge between Japanese and U.S. batches) covered only a small pH difference (b) (4). Clinical experience with batches that are different in pH is also limited. To-date only the batches made of (b) (4) (b) (4) have been tested clinically, and no batches with a pH value (b) (4) have been used by study subjects. To agree that pH (b) (4) and pH (b) (4) batches would have comparable clinical performance, stability data along are not sufficient.

### C. Other Review Issues

#### 1. Photostability Studies

Data can not be found in Section 3.2.P.8.1 despite the statement given in 3.2.P.2.4.2 that the drug product is photosensitive but the container/closure system can provide adequate protection from light as summarized in Section 3.2.P.8.1. Upon request the applicant identified Section 3.2.P.8.3 Table C-14 as the location of the data in the amendment dated Feb. 1, 2013.

#### 2. Extractables/Leachables Studies

The applicant does not provide information on this subject. Although the components of the proposed container/closure system have been used in approved topical products (N17556/ (b) (4) Halog cream, N17824 (b) (4) Halog ointment, ANDA 78645 (b) (4) and (b) (4) the applicant should address this subject in the NDA because extractables/leachables is product specific. One possible resolution is an assessment based on the chemical composition of formulation-contacting component such as the (b) (4) and assuming the worst case scenario (100% leach-out and maximum dosing). Upon request the applicant provided calculations for maximum anticipated human daily exposure for potential extractables in the amendment dated Feb. 1, 2013.

#### 3. Conformance to USP<661>

Data showing the conformance of packaging components to USP<661> can not be found in the NDA. The data likely exist in the DMF of the container/closure system. The reviewer should look for this information when reviewing the Type III DMF.

#### 5. In-Process Controls for Drug Product Manufacture

The in-process controls described in the manufacturing section is highly inadequate. Most notably is the absence of pH and viscosity tests for (b) (4)

#### 6. Process Comparison between (b) (4) and DPT

The comparison of the process is highly inadequate. Most notably is the absence of a specific description/comparison for the (b) (4). Judging from the particle size data (Table 4 Section 3.2.P.2.2), the two processes may not be comparable but the difference may not be large enough to result in a difference in dissolution rate. (Comparable dissolution rate has been shown in the IVRT studies.)

D. Comments for 74-Day Letter:

1. Submit the following samples for evaluation of dosage form and equivalence of DPT made batches to (b) (4) made batches:
  - A representative sample of U.S. registration stability batches for each packaging configuration
  - A representative sample of Batch 1009051
  - A representative sample of the commercial batches sold in Japan
  - A sample with a viscosity near the proposed lower limit (b) (4) of viscosity specification
  - A sample with a viscosity near the proposed upper limit (b) (4) of viscosity specification

Each sample should be accompanied with corresponding certificate of analysis which should include viscosity and pH data with testing date information.

2. Provide certificates of analysis for all batches used in the in-vitro enhancer cell and the Franz cell percutaneous absorption study using human skin. The certificates of Analysis should include viscosity data if available.

E. Comments/Recommendation:

The application is acceptable for filing from CMC perspective.

Drug substance manufacturing site is located in (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 Raymond Frankewich.

Shulin Ding, Ph.D.  
CMC Lead

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

**NDA Number:** 204153      **Supplement Number and Type:** 0000      **Established/Proper Name:** Luliconazole cream, (b) (4)  
**Applicant:** Medicis      **Letter Date:** Dec 11, 2012      **Stamp Date:** Dec. 11, 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		
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? <b>This question is not applicable for synthesized API.</b>			n/a

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

9.	<p>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:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>			n/a
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		Provided in Module 1 of the initial submission for the facilities listed in the attachment to Form 356h.

\* 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>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?		x	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		
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

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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		Provided in 2/1/13 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)	Luliconazole	6/4/2012	
	III		(b) (4)	8/3/2011	

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 <b>filing</b> comments to be sent to the Applicant.			n/a
36.	Are there any <b>potential review</b> 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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHULIN DING  
02/04/2013

MOO JHONG RHEE  
02/05/2013  
Chief, Branch IV