

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204153Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204153

SUPPL # 000

HFD # 540

Trade Name Luzu

Generic Name luliconazole

Applicant Name Medicis Pharmaceutical Corp.

Approval Date, If Known

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)(1)

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?

5 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).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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:

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 YES NO

Investigation #2 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 YES NO

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: J. Paul Phillips
Title: Regulatory Health Project Manager
Date: 11/12/2013

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

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/

J P PHILLIPS
11/12/2013

DAVID L KETTL
11/12/2013

SUSAN J WALKER
11/13/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 204153 Supplement Number: 000 NDA Supplement Type (e.g. SE5): n/a
Division Name: DDDP PDUFA Goal Date: Stamp Date: 12/11/2012
12/11/2013

Proprietary Name: Luzu

Established/Generic Name: Iuliconazole

Dosage Form: Cream

Applicant/Sponsor: Medicis Pharmaceuticals Corp.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 3
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Tinea corporis

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	1 yr. 11 mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.
 Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

- # Not feasible:
- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

^ Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	2 yr. __ mo.	17 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): <u>04/30/2017</u>							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: Adult studies are complete and ready for approval.

Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

ditional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

te: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Tinea pedis

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	11 yr. 11 mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	12 yr. __ mo.	17 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): <u>02/28/2017</u>							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: Adult studies are completed and ready for approval.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

ditional pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

ditional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

Indication #3: Tinea cruris

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)
 (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 Disease/condition does not exist in children
 Too few children with disease/condition to study
 Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	11 yr. 11 mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	12 yr. __ mo.	17 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): <u>02/28/2017</u>							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: Adult studies completed and ready for approval.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

1.3.3 Debarment Certification

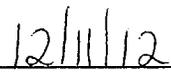
Pursuant to Sections 306(a) and (b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 335(a) and (b)), Medicis Pharmaceutical Corporation certifies that, in conjunction with NDA 204-153 for Luliconazole Cream 1% that:

1. we did not use in any capacity the services of any person debarred under subsection (a) or (b) of this section in connection with the development or submission of this application;
2. we will not use in any capacity the services of any person debarred under subsection (a) or (b) of this section in connection with this application; and
3. neither the applicant nor affiliated persons responsible for the development or submission of this application have been convicted within the past

List of convictions: none.



Diane Stroehmann
Executive Director, Regulatory Affairs



Date

CONFIDENTIAL AND PROPRIETARY INFORMATION

The information contained within this document may not be used, divulged, published, or otherwise disclosed without prior written consent of Medicis Pharmaceutical Corporation or any of its subsidiaries

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204153	NDA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: Luzu Established/Proper Name: Iuliconazole Dosage Form: Cream		Applicant: Medicis Pharmaceutical Corp. Agent for Applicant (if applicable): n/a
RPM: Cristina Attinello/ J. Paul Phillips		Division: Dermatology and Dental Products
<u>NDA and NDA Efficacy Supplements:</u> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 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.)		<u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s): Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain) <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> <input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 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		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 11, 2013</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> 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., new listed drug, patent certification revised).

<p>❖ 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 _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 1</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	<input checked="" type="checkbox"/> Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval; 11/14/2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	10/08/2013 (agreed on)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12/11/2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a

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

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	8/13/2013 (agreed on)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12/11/2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	09/10/2013 (agreed on)
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • 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. 	04/11/2013 (letter) 04/11/2013 (review)
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 02/06/2013 <input checked="" type="checkbox"/> DMPP/PLT 07/18/2013 <input checked="" type="checkbox"/> ODPD 07/18/2013 <input checked="" type="checkbox"/> DMEPA 08/01/2013 <input checked="" type="checkbox"/> SEALD 10/03/2013 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	02/06/2013 RPM filing review
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>01/09/2013</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included (DARRTS record unavailable so included Pediatric Page per PMHS recommendation)

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 (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	N=21
❖ Internal memoranda, telecons, etc.	n/a
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> n/a
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> 07/18/2012
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> 12/16/2009; 10/27/2010
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	n/a
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	n/a
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	n/a
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 11/14/2013
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 11/14/2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 09/17/2013
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> n=5
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	(see 09/17/2013 CDTL review)
• Clinical review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 01/30/2013 filing 06/05/2013 midcycle 09/17/2013 review
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	<input checked="" type="checkbox"/> pg. 15 Clinical Review/ 09/17/2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> 04/30/2013 QT-IRT review
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input checked="" type="checkbox"/> 08/08/2013 review 11/08/2013 addendum
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 02/01/2013 filing 07/24/2013 review
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 01/30/2013 filing 06/28/2013 review
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 01/30/2013 filing 07/26/2013 review 10/19/2013 addendum
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 08/07/2013
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> 07/30/2013
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input checked="" type="checkbox"/> 01/30/2013 filing 07/29/2013 review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> page 17 PharmTox review/ 07/29/2013
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 11/08/2013
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 01/31/2013 Biopharm filing 02/05/2013 CMC filing 07/16/2013 CMC review 07/17/2013 Biopharm review 09/27/2013 CMC addendum
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	<input checked="" type="checkbox"/> pg. 104 CMC review/ 07/16/2013
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	n/a
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	n/a
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(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 sites⁷)</i>	Date completed: 06/13/2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (pg. 90 CMC review/ 07/16/2013)

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.

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

/s/

J P PHILLIPS
11/15/2013

From: Phillips, J. Paul
Sent: Friday, October 04, 2013 4:15 PM
To: 'Humphrey, Sean'
Cc: Gould, Barbara
Subject: NDA 204153 Luzu

Mr. Humphrey,

See the attached draft labeling for NDA 204153 (Luzu).



Luzu PI_FDA
edits_10-4-13.doc ..

Please respond by Tuesday, October 8, 2013.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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

/s/

J P PHILLIPS
10/04/2013

From: Phillips, J. Paul
Sent: Tuesday, September 24, 2013 10:15 AM
To: 'Humphrey, Sean'
Cc: Gould, Barbara
Subject: NDA 204153 Luzu

Mr. Humphrey,

See the attached draft labeling for NDA 204153 (Luzu). A few additional edits in section 17 are included in track changes.



Luzu
raft_9-24-13.doc (1)

Please respond by Friday, 9/27/2013.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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

/s/

J P PHILLIPS
09/24/2013

From: Phillips, J. Paul
Sent: Friday, August 16, 2013 12:43 PM
To: 'Michael O'Beirne - C'
Cc: 'Diane Stroehmann'; Gould, Barbara
Subject: RE: NDA 204153 (Luzu)

Mr. O'Beirne,

As discussed with Mr. Sean Humphrey, we have added some additional edits to the draft labeling for NDA 204153 (Luzu). Please see the attached in track changes.



Luzu PI_FDA
I-16-13.doc (156 K..)

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: Phillips, J. Paul
Sent: Thursday, August 15, 2013 9:20 AM
To: 'Michael O'Beirne - C'
Cc: 'Diane Stroehmann'; Gould, Barbara
Subject: NDA 204153 (Luzu)

Mr. O'Beirne,

Please see the attached draft labeling for NDA 204153 (Luzu) with FDA edits in track changes. Please also share this with Mr. Humphrey. He currently does not have a secure email account with the FDA and I am therefore unable to send proprietary information to him via email.

<< File: Luzu PI_FDA 8-13-13.doc >>

We ask that you respond to the labeling edits by **August 20, 2013**.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189

10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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

/s/

J P PHILLIPS
08/16/2013

From: Phillips, J. Paul
Sent: Thursday, August 15, 2013 9:20 AM
To: 'Michael O'Beirne - C'
Cc: 'Diane Stroehmann'; Gould, Barbara
Subject: NDA 204153 (Luzu)

Mr. O'Beirne,

Please see the attached draft labeling for NDA 204153 (Luzu) with FDA edits in track changes. Please also share this with Mr. Humphrey. He currently does not have a secure email account with the FDA and I am therefore unable to send proprietary information to him via email.



Luzu PI_FDA
i-13-13.doc (151 K..)

We ask that you respond to the labeling edits by **August 20, 2013**.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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

/s/

J P PHILLIPS
08/15/2013

From: Phillips, J. Paul
Sent: Friday, August 02, 2013 10:05 AM
To: Humphrey, Sean
Cc: 'Michael O'Beirne - C'; 'Diane Stroehmann'; Gould, Barbara
Subject: NDA 204153 (Luzu)

Mr. Humphrey,

Below are comments regarding the proposed carton/container labels for NDA 204153 (Luzu).

- In all labeling (package insert, container labeling, carton labeling): insert a comma between the dosage form "cream" and the strength "1%" or move the strength to another line.
- Replace the (b) (4) statement on the container labels with the following statement: "Tamper Evident - Do not use if aluminum seal is broken"
- Replace the current storage temperature statement on the container and carton labels with the following: "Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room temperature]."
- Indicate clearly the location of the lot number and expiration date on the carton label of the physician sample (2 g).

A. Proposed Container Labels and Carton Labeling (all packaging sizes)

1. Revise the presentation of the proprietary name from all-caps (i.e. LUZU) to title case (i.e. Luzu) to improve readability of the name. Words set in title case are easier to read than the rectangular shape that is formed by words set in all capital letters.
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). As currently presented the typography used for proprietary name (all caps) versus the typography used for the established name (lower case and condensed font) we find they are not commensurate in prominence.
3. Relocate the strength statement, "1%" to appear below the established name to help increase the readability of this information.
4. Delete the round graphic or reduce the size and relocate the graphic away from the proprietary name, established name, and strength statement. As currently presented the round graphic may be mistaken as part of the proprietary name.
5. Consider decreasing the prominence of the large curved graphic. As currently presented the curved graphics appears to crowd and could be

considered more prominent than the proprietary name, established name, dosage form, strength, and route of administration. Ensure there is adequate white space around the most important information, and the graphic is not more prominent than this information.

B. Proposed Container Labels (all packaging sizes)

1. 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.
2. Include the statement “Keep Out of Reach of Children” on the principal display panel below and at the same prominence than the route of administration statement.
3. Relocate the NDC number to the upper right hand side of the principal display panel. Note: The 2 g container label is exempted from this comment.

C. Proposed Carton Labeling (all packaging sizes)

1. Relocate the route of administration statements “For Topical Use Only” and “Not for ophthalmic, oral or intravaginal use” to the upper right hand side of both principal display panels in two separate lines. Increase the prominence of the correct route of administration statement “For Topical Use Only” by increasing the font size, bolding, and/or using color.
2. Include the statement “Keep Out of Reach of Children” on both principal display panels below and at the same prominence than the route of administration statement. For example:

For Topical Use Only

Not for ophthalmic, oral or intravaginal use

Keep Out of Reach of Children

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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

/s/

J P PHILLIPS
08/02/2013

From: Phillips, J. Paul
Sent: Thursday, August 01, 2013 10:34 AM
To: Humphrey, Sean
Cc: 'Diane Stroehmann'; Gould, Barbara; Attinello, Cristina
Subject: NDA 204153 (Luzu)

Mr. Humphrey,

Please see the attached draft labeling with FDA edits in track changes for NDA 204153 (Luzu).
Please respond by **August 9, 2013**.



NDA 204153 (Luzu) NDA 201453
PI_draft_8-1... Luzu)_PPI_draft.do.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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

/s/

J P PHILLIPS
08/01/2013



Division of Dermatology and Dental Product
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel: 301 796-2110
Fax: 301 796-9894

MEMORANDUM OF TCON

Date of Teleconference: 06/26/2013

Time: 4:20 p.m. ET

Application: NDA 204153

Product: Luzu (luliconazole) Cream, 1%

Applicant: Medicis Pharmaceutical Corp.

FDA Participants:

David Kettl, MD, Clinical Team Leader, DDDP

J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP

Sponsor/Applicant Participants:

Sean Humphrey, Manager, Regulatory Affairs

Purpose:

Request that the applicant propose a section 6.2 for labeling, if warranted by postmarketing Adverse Reaction reports from ex-U.S. regions where the product is marketed.

Discussion Summary:

The FDA asked that the applicant propose language for section 6.2 of the draft labeling based on international postmarketing experience with the product. The FDA clarified that section 6.2 should include only those adverse reactions which were not observed in the pivotal U.S. trials and captured in section 6.1. If no adverse reactions were reported different from those seen in the U.S. clinical trials, then the applicant could indicate this and section 6.2 would not be needed.

The applicant agreed to this request with a target date of July 12, 2013 to provide updated labeling if warranted by ex-U.S. postmarketing adverse reaction reporting.

The phone call ended amicably.

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

/s/

J P PHILLIPS
06/26/2013



NDA 204153

INFORMATION REQUEST

Medicis Pharmaceutical Corporation
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

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

We also refer to your May 17, 2013, submission, containing a response to our May 1, 2013 information request.

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

You proposed to modify the pH specification to (b) (4) without supporting clinical information. The proposal is not acceptable, as the clinical performance of your product cannot be assured at the proposed pH level.

Tighten the pH specification to 5.0 – 7.0 and submit the revised drug product specification with the tightened pH specification to Module 3 of the NDA, or provide clinical information related to performance of your product with a pH value (b) (4) in subjects with tinea pedis, tinea cruris, and tinea corporis.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

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

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
06/13/2013



NDA 204153

MID-CYCLE COMMUNICATION

Medicis Pharmaceutical Corporation
Attention: Diane Stroehmann, MSRA, RAC
Executive Director, Regulatory Affairs
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Ms. Stroehmann:

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

We also refer to the teleconference between representatives of your firm and the FDA on May 8, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

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

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: May 8, 2013; 10:00 a.m. (EDT)

Application Number: NDA 204153
Product Name: Luzu (luliconazole) Cream, 1%
Proposed Indication: Treatment of interdigital tinea pedis, tinea cruris, tinea corporis
Applicant Name: Medicis Pharmaceutical Corporation

Meeting Chair: David Kettl, MD
Meeting Recorder: J. Paul Phillips

FDA ATTENDEES

David Kettl, M.D., Clinical Team Leader, DDDP
Julie Beitz, M.D., Director, ODE III
Victoria Kusiak, M.D., Deputy Director, ODE III
Gary Chiang, M.D., M.P.H., Clinical Reviewer, DDDP
Terry Ocheltree, Ph.D., Director, DNDQA II
Moo-Jhong Rhee, Ph.D., Branch Chief, DNDQA II, Branch IV
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II
Raymond Frankewich, Ph.D., Product Quality Reviewer, DNDQA II, Branch IV
Kelly Kitchens, Ph.D., Biopharmaceutics Reviewer, ONDQA
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP3
Chinmay Shukla, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Kim Taylor, Operations Research Analyst, OPA
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP
Maria R. Walsh, R.N., M.S., Associate Director for Regulatory Affairs, ODE III
Giuseppe Randazzo, M.S., Regulatory Scientist, ODE III
Strother D. Dixon, Regulatory Health Project Manager, DDDP
Matthew E. White, Regulatory Health Project Manager, DDDP
CDR Dawn Williams, R.N., B.S.N., U.S.P.H.S., Regulatory Health Project Manager, DDDP
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEE

(b) (4)

APPLICANT ATTENDEES

Susan Hall, Ph.D., Head, Global R&D
Steven Knapp, Vice President, Regulatory Affairs
Diane Stroehmann, MSRA, Executive Director, Regulatory Affairs
RK Pillai, Ph.D., Head of Dermatology Development

Sean Humphrey, MS, Manager, Regulatory Affairs
David Lust, Senior Director, Regulatory Affairs, CMC
Mandeep Kaur, M.D., Executive Director, Clinical Research
Bharat Warriar, Associate Director, Technical Services

(b) (4)

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Chemistry, Manufacturing and Controls

- Be advised a DMF Deficiency letter was sent to the holder of Drug Master File (DMF) (b) (4) luliconazole drug substance on April 19, 2013.
- Your response to the 74-day letter did not include the requested viscosity value for the representative sample of the commercial batches sold in Japan.
- Your proposal of broadening the pH acceptance criterion to (b) (4) is not acceptable.
- The current proposed expiration dating period of (b) (4) is not supported by stability data.

3.0 INFORMATION REQUESTS

Clinical Pharmacology

1. Luliconazole was produced by selectively synthesizing only the R-enantiomer of the (b) (4) (b) (4). Provide information to support whether or not there is inter-conversion from R to S-enantiomer *in-vivo*.

Meeting Discussion:

The Agency clarified that we are requesting data on *in-vivo* conversion potential in humans.

2. We note that luliconazole is a substrate of CYP2D6 and CYP3A4. Provide an assessment of the implications of luliconazole systemic safety in presence of other drugs that are strong CYP2D6 and CYP3A4 inhibitors.

ONDQA Biopharmaceutics

3. Clarify the purpose of the *ex-vivo* skin permeation study, and specify if the study is a supportive study of the in vitro release studies or a comparative study. If the study is comparative, explain why test articles from the (b) (4) and DPT manufacturing sites were not compared.
4. In the Formulation Development sections of your original submission (Module 2.3.P.2.2.1.7 and Module 3.2.P.2.2.1.3.5), it is indicated that one test article was maintained at 25°C for 3 months and the other test article was maintained at 40°C for 3 months for Study R11-1091 (skin permeation study). However, the study report does not provide details on the treatment of the test articles prior to application to the skin samples. Please clarify the storage conditions of the test articles prior to application to the skin sample.

Chemistry, Manufacturing and Controls/ Clinical

5. Your response to the 74-day letter did not include the requested viscosity value for the representative sample of the commercial batches sold in Japan. Provide the viscosity value requested in the 74-day letter.
6. Your proposal of broadening the pH acceptance criterion to (b) (4) is not acceptable. Revise the acceptance criterion in the drug product specification to pH 5.0 – 7.0 and submit the revised specification table to module 3, or provide clinical information related to the performance of your product with a pH value (b) (4) in subjects with tinea pedis, tinea cruris, and/or tinea corporis.
7. The current proposed expiration dating period of (b) (4) is not supported by stability data. Revise your proposal to 18 months or less.

Meeting Discussion:

The applicant inquired regarding whether or not they could submit additional stability data. The Agency responded that the applicant could submit such data but the Agency noted this is beyond the 30 day time frame allowed for additional submission as previously agreed upon, and the Agency may determine not to review the data in the current review cycle. The Agency may determine, upon review, that this data could represent a major amendment which would extend the PDUFA goal date by 3 months.

8. Regarding pH stability data reported in Section 3.2.P.8, indicate the specific pH method (neat or 10%) for each data point.
9. Your revised pediatric plan did not address subjects ages 0 to 1 year, 11 months old. Submit a complete pediatric plan that addresses subjects of all ages from 0 to 17 years, 11 months

old. Your pediatric plan should provide all the necessary information, including a proposed timeline for completion, as outlined in section 505B(a) of the Food, Drug, and Cosmetic Act (FD&C), to support your request for deferral and/or waiver of the required pediatric studies.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

No major safety concerns have been identified at this stage of review and therefore there was no discussion related to risk management plans.

5.0 ADVISORY COMMITTEE MEETING

This new azole antifungal presents no novel or complex regulatory issues which might warrant advisory committee discussion and therefore there was no discussion of this topic.

6.0 LATE-CYCLE MEETING

Late Cycle Meeting date(s) proposed: September 4, 2013 or September 11, 2013

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

/s/

DAVID L KETTL
06/05/2013



NDA 204153

INFORMATION REQUEST

Medicis Pharmaceutical Corporation
Attention: Diane Stroehmann, MSRA, RAC
Executive Director, Regulatory Affairs
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Ms. Stroehmann:

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

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by May 17, 2013 in order to continue our evaluation of your NDA.

Clinical Pharmacology

1. Luliconazole was produced by selectively synthesizing only the R-enantiomer of the (b) (4) Provide information to support whether or not there is inter-conversion from R to S-enantiomer *in-vivo*.
2. We note that luliconazole is a substrate of CYP2D6 and CYP3A4. Provide an assessment of the implications of luliconazole systemic safety in presence of other drugs that are strong CYP2D6 and CYP3A4 inhibitors.

ONDQA Biopharmaceutics

3. Clarify the purpose of the *ex-vivo* skin permeation study, and specify if the study is a supportive study of the in vitro release studies or a comparative study. If the study is comparative, explain why test articles from the (b) (4) and DPT manufacturing sites were not compared.
4. In the Formulation Development sections of your original submission (Module 2.3.P.2.2.1.7 and Module 3.2.P.2.2.1.3.5), it is indicated that one test article was maintained at 25°C for 3 months and the other test article was maintained at 40°C for 3 months for Study R11-1091 (skin permeation study). However, the study report does not provide details on the treatment of the test articles prior to application to the skin samples. Please clarify the storage conditions of the test articles prior to application to the skin sample.

Chemistry, Manufacturing and Controls/ Clinical

5. Be advised a DMF Deficiency letter was sent to the holder of Drug Master File (DMF) (b)(4) luliconazole drug substance on April 19, 2013.
6. Your response to the 74-day letter did not include the requested viscosity value for the representative sample of the commercial batches sold in Japan. Provide the viscosity value requested in the 74-day letter.
7. Your proposal of broadening the pH acceptance criterion to (b)(4) is not acceptable. Revise the acceptance criterion in the drug product specification to pH 5.0 – 7.0 and submit the revised specification table to module 3, or provide clinical information related to the performance of your product with a pH value (b)(4) in subjects with tinea pedis, tinea cruris, and/or tinea corporis.
8. The current proposed expiration dating period of (b)(4) is not supported by stability data. Revise your proposal to 18 months or less.
9. Regarding pH stability data reported in Section 3.2.P.8, indicate the specific pH method (neat or 10%) for each data point.
10. Your revised pediatric plan did not address subjects ages 0 to 1 year, 11 months old. Submit a complete pediatric plan that addresses subjects of all ages from 0 to 17 years, 11 months old. Your pediatric plan should provide all the necessary information, including a proposed timeline for completion, as outlined in section 505B(a) of the Food, Drug, and Cosmetic Act (FD&C), to support your request for deferral and/or waiver of the required pediatric studies.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

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

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

/s/

DAVID L KETTL
05/01/2013



Division of Dermatology and Dental Product
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel: 301 796-2110
Fax: 301 796-9894

MEMORANDUM OF TCON

Date of Teleconference: 04/26/2013

Time: 3:38 p.m.

Application: NDA 204153

Product: Luzu (luliconazole) Cream, 1%

Sponsor/Applicant: Medicis Pharmaceutical Corp.

FDA Participants: J. Paul Phillips, RPM, DDDP

Sponsor/Applicant Participants:

Diane Stroehmann, MSRA, RAC

Purpose:

Inform the applicant that the 4/24/2013 information request letter that was sent contained some errors. Set up date for midcycle communication teleconference between FDA and applicant.

Discussion Summary:

Ms. Stroehmann was informed that the 4/24/2013 information request letter she had received for NDA 204153 contained some errors. She was notified that a corrected version of the letter would be provided prior to the planned midcycle communication teleconference and would serve as the basis for the discussion at the teleconference.

May 8, 2013 at 10 a.m. was discussed as the tentative time for the midcycle communication teleconference to take place between the FDA and the applicant.

The call ended amicably.

NOTE: Ms. Stroehmann subsequently followed-up with an email (see attachment below) confirming the date and time of the midcycle communication teleconference.

From: Phillips, J. Paul
Sent: Friday, April 26, 2013 5:01 PM
To: 'Diane Stroehmann'
Cc: Humphrey, Sean; Gould, Barbara; Attinello, Cristina
Subject: RE: Luzu IR

Ms. Stroehmann,

Thank you. Also as discussed, we will provide the corrected IR letter prior to the May 8 teleconference.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: Diane Stroehmann [mailto:dstroehmann@medicis.com]
Sent: Friday, April 26, 2013 4:50 PM
To: Phillips, J. Paul
Cc: Humphrey, Sean; Gould, Barbara; Attinello, Cristina
Subject: RE: Luzu IR

Hi Paul,

I confirm the date and time of the midcycle review meeting: Wednesday, May 8 at 10:00am EDT.

Teleconference details:

Dial-in:  (b) (4)
Code: 

Best regards,
Diane Stroehmann, MSRA, RAC
Executive Director, Regulatory Affairs
Medicis Pharmaceutical Corp.
phone: 480-291-5611
fax: 480-291-8611

From: Phillips, J. Paul [mailto:Paul.Phillips@fda.hhs.gov]
Sent: Wednesday, April 24, 2013 2:00 PM
To: Diane Stroehmann

Cc: Humphrey, Sean; Gould, Barbara; Attinello, Cristina
Subject: RE: Luzu IR

Ms. Stroehmann,

As a follow-up to my voice message, I wanted to make you aware that the information request letter you received today for NDA 204153 (Iuliconazole) contained some errors. We will provide you with the corrected version of the letter as soon as it is signed.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: Diane Stroehmann [<mailto:dstroehmann@medicis.com>]
Sent: Wednesday, April 24, 2013 3:28 PM
To: Attinello, Cristina
Cc: Phillips, J. Paul; Humphrey, Sean
Subject: RE: Luzu IR

Hi Cristina,

I confirm receipt of this e-mail and attachment. [REDACTED] (b) (6)
[REDACTED] at which time Sean Humphrey will become the primary contact with FDA for this application. Going forward, please copy Sean on all correspondence related to this application. Sean may be reached via e-mail at shumphrey@dowpharmsci.com or via phone at (707) 796-7222.

Best regards,
Diane Stroehmann, MSRA, RAC
Executive Director, Regulatory Affairs
Medicis Pharmaceutical Corp.
phone: 480-291-5611
fax: 480-291-8611

From: Attinello, Cristina [<mailto:Cristina.Attinello@fda.hhs.gov>]
Sent: Wednesday, April 24, 2013 12:14 PM
To: Diane Stroehmann
Cc: Phillips, J. Paul
Subject: Luzu IR

Good Afternoon,

Please see the attached IR for Luzu. We are requesting a response by May 6. In addition, Paul Phillips will now become the lead RPM for this application. You are welcome to copy me on email correspondence for the next few weeks as we make the transition.

Please confirm receipt of this email and attachment.

Thank you,

Cristina Petruccelli Attinello, MPH
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology & Dental Products
White Oak, Bldg. 22, Room 5181
Phone: 301-796-3986
Fax: 301-796-9895

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

/s/

J P PHILLIPS
04/26/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204153

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Medicis Pharmaceutical Corporation
7720 North Dobson Road
Scottsdale, AZ 85256

ATTENTION: Diane Stroehmann, MSRA, RAC
Executive Director, Regulatory Affairs

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) dated December 11, 2012, received December 11, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Luliconazole Cream, 1%.

We also refer to your January 10, 2013, correspondence, received January 11, 2013, requesting review of your proposed proprietary name, Luzu. We have completed our review of the proposed proprietary name, Luzu and have concluded that it is acceptable.

The proposed proprietary name, Luzu, 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 10, 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 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

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

/s/

CAROL A HOLQUIST
04/11/2013



NDA 204153

FILING COMMUNICATION

Medicis Pharmaceutical Corporation
Attention: Diane Stroehmann, MSRA, RAC
Executive Director, Regulatory Affairs
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) dated December 11, 2012, received December 11, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (luliconazole) Cream, 1%.

We also refer to your amendments dated January 25 and February 1, 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**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is December 11, 2013.

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 August 9, 2013. In addition, the planned date for our internal mid-cycle review meeting is April 26, 2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

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 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.

Clinical Pharmacology

3. Provide storage stability information on internal standard Lanoconazole to support the period of analysis for trials MP-1007 and MP-1000-08.

Clinical

4. Your request for full deferral of pediatric studies did not include a pediatric plan. Submit a pediatric plan that identifies the pediatric studies for which a deferral and/or waiver is requested.

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

1. In Highlights, white space must be present before each major heading. Add white space between each major heading in Highlights.
2. 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 Warnings and Precautions.

3. In Highlights, the Highlights Limitation Statement must appear with the drug product name in upper case. Revise this statement to include the drug product name in upper case.
4. There is currently no initial U.S. approval for this drug product. In Highlights, revise the date for the Initial U.S. Approval to appear as “XXXX.”
5. In Highlights, the Adverse Reactions statement should include the name of the manufacturer. Remove [REDACTED] ^{(b) (4)} following the name of the manufacturer.
6. 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.
7. In the FPI, FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the FPI upon approval. Remove Section 17.1 Instructions for Use from the FPI.

We request that you resubmit labeling that addresses these issues by March 1, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. 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 full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral 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

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
02/12/2013



NDA 204153

INFORMATION REQUEST

Medicis Pharmaceutical Corporation
Attention: Diane Stroehmann, MSRA, RAC
Executive Director, Regulatory Affairs
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Ms. Stroehmann:

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

We are reviewing the Clinical Pharmacology and Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by February 1, 2013 (unless otherwise noted) in order to continue our evaluation of your NDA.

Clinical Pharmacology

1. Provide in a tabular format the Lot No./Batch No. and manufacturing site of the formulation used and also provide information if the formulation is the same as the to-be-marketed formulation for all 18 clinical trials (11 USA and 7 Japanese). Provide the response by COB January 25, 2013.

Chemistry, Manufacturing and Controls

2. Provide method validation package to Section R3 of Module 3 per 314.50(e)(2). The information provided in Section R3 should be sufficient enough to be standalone (i.e. no need to go to other sections of Module 3).
3. You stated in Section 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. We are unable to locate photostability data in Section 3.2.P.8.1. Identify the location of the data in your submission.
4. You did not address the subject of extractables/leachables from the proposed container/closure system in Module 3. Calculate human daily exposure for each potential leachable based on the chemical composition of the formulation-contacting packaging

components (such as (b) (4) and cap) and assuming the worst case scenario (e.g. 100% leach-out and maximum use of the 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

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

/s/

DAVID L KETTL
01/24/2013



NDA 204153

NDA ACKNOWLEDGMENT

Medicis Pharmaceutical Corporation
Attention: Diane Stroehmann, MSRA, RAC
Executive Director, Regulatory Affairs
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Ms. Stroehmann:

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

Name of Drug Product: (luliconazole) Cream, 1%

Date of Application: December 11, 2012

Date of Receipt: December 11, 2012

Our Reference Number: NDA 204153

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 8, 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 Cristina Attinello, Regulatory Project Manager, 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

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

/s/

CRISTINA Petruccelli Attinello
01/11/2013



IND 076049

MEETING MINUTES

Tinea Pharmaceuticals
c/o Medicis Pharmaceutical Corporation
Attention: Diane Stroehmann, RAC
Executive Director, Regulatory Affairs
7720 N. Dobson Road
Scottsdale, AZ 85256

Dear Ms. Stroehmann:

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

We also refer to the meeting between representatives of your firm and the FDA on July 18, 2012. The purpose of the meeting was to discuss the development program for (luliconazole) Cream, 1% for the indications of tinea pedis, tinea cruris and tinea corporis.

A copy of the official minutes of the meeting 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}

Susan J. Walker, MD, FAAD
Director
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: B
Meeting Category: Pre-NDA

Meeting Date and Time: July 18, 2012, 9AM
Meeting Location: WO22, Rm 1311

Application Number: IND 076049
Product Name: (Iuliconazole) Cream, 1%
Proposed Indication: For the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis

Sponsor: Tinea Pharmaceuticals, Inc.

Meeting Chair: Susan Walker, MD
Meeting Recorder: Cristina Attinello, MPH

FDA ATTENDEES

Victoria Kusiak, MD, Deputy Director, ODE III
Susan Walker, MD, FAAD, Division Director, DDDP
David Kettl, MD, Clinical Team Lead, DDDP
Gary Chiang, MD, M.P.H., Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Kumar Mainigi, PhD, Pharmacology Reviewer, DDDP
Cristina Attinello, MPH, Regulatory Project Manager, DDDP
Strother D. Dixon, Regulatory Health Project Manager, DDDP
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DPA II, Branch III
Yichun Sun, PhD, Product Quality Reviewer, DPA II, Branch III
Mohamed Alosh, PhD, Biostatistics Team Lead, DB III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP 3
An-Chi Lu, PhD, Clinical Pharmacology Reviewer, DCP 3
Kerry Snow, M.S., Clinical Microbiology Reviewer, DAIOP
Lubna Merchant, MS, PharmD, Team Leader, OSE/DMEPA
Jessica Weintraub, PharmD, Safety Evaluator, OSE/DPV 1
Janet Anderson, PharmD, Safety Regulatory Project Manager, OSE
Jared Lantzy, Information Specialist, OBI
Roy Blay, Reviewer, OSI

SPONSOR ATTENDEES

Ira Lawrence, MD, Chief Medical Officer, Medicis
Steve Newhard, Sr. VP Quality and Technical Services, Medicis
Xiaoming Lin, VP Clinical Research and Development, Medicis

Diane Stroehmann, RAC, Executive Director, Regulatory Affairs, Medicis
Katy Morton, Consultant, Tinea Pharmaceuticals

(b) (4)

Mandeep Kaur, MD, Executive Director, Clinical R&D, Medicis

(b) (4)

Douglas Bakan, PhD, VP Product Development, Medicis

(b) (4)

Purpose of the Meeting:

The purpose of this meeting is to discuss the development program for (luliconazole) Cream, 1% for the indications of tinea pedis, tinea cruris and tinea corporis.

Regulatory Correspondence History

We have had the following meetings/teleconferences with you:

- October 27, 2010, End-of-Phase 2 Meeting (tinea cruris, tinea corporis)
- December 16, 2009, End-of-Phase 2 Meeting (tinea pedis)
- January 16, 2007, Pre-IND Meeting

We have sent the following correspondences:

- June 14, 2012, Advice/Information Request Letter
- April 3, 2012, Advice/Information Request Letter
- October 3, 2011, Advice/Information Request Letter
- March 3, 2011, Advice/Information Request Letter
- February 17, 2011, Special Protocol Agreement Letter (tinea cruris)
- July 20, 2010, Advice/Information Request Letter
- July 12, 2010, Advice/Information Request Letter
- July 7, 2010, Special Protocol Agreement Letter (tinea pedis)
- July 1, 2009, Advice/Information Request Letter
- May 8, 2009, Advice/Information Request Letter

Regulatory

Question 8:

Medicis proposes to submit safety and efficacy data, in CDISC format, for all individual US clinical studies listed in [Table 4](#) noted as Studies that Form Primary Basis of NDA. As previously agreed at the December 16, 2009, EOP2 meeting, Medicis will not provide datasets for the supportive Japanese studies listed in [Table 4](#) and intends to submit the available translated portions of the Japanese study reports as legacy studies. Does the Division concur?

Response:

Your proposal to submit data tabulations in SDTM format and analysis datasets in ADaM format for all U.S. clinical studies as SAS transport files is acceptable. 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.

Meeting Discussion:

The sponsor stated that the ADaM datasets will include observed data and LOCF data. They will include separate datasets to accommodate the multiple imputation analyses. The sponsor stated they will include all SAS programs and the seeds used in the analysis.

For ease of viewing and printing by the reviewer, if possible, submit corresponding define.pdf files in addition to the define.xml files. The analysis dataset documentation (define.xml file) should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

Statistical programs for any non-standard analyses should be submitted.

If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

For each U.S. clinical study 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 date of enrollment).

The Agency may have additional information requests related to the previously conducted Japanese studies as review of the application proceeds.

Question 9:

Medicis proposes to submit the Luliconazole Cream 1% NDA in eCTD format with a complete XML backbone. The proposed content for Modules 1-5 is provided in [Appendix 2](#). Does the Division concur with the content and format of the NDA?

Response:

Refer to 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>

References to contents of other applications should be included in Section 1.4.4 Cross Reference to Other Applications. Many Module 3 sections of your provided Table of Contents only indicate "DMF (b)(4)" and it is unclear what will be submitted in these sections in the actual application.

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

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Does the Division agree with the proposed finished product regulatory specification?

Response:

Generally, we can not agree with a regulatory specification without a comprehensive review of the information provided in the NDA submission. However, we have the following comments regarding the drug product specification and your proposed changes.

- We recommend that you add “no visually detectable signs of phase separation” to the acceptance criterion of “Description” test.
- Add tube content uniformity test to the drug product specification.

Meeting Discussion:

The sponsor agreed to add content uniformity to the drug product specification, but discussed challenges with providing this information for the physician sample size (2 g), due to the large sample size (1 g) for this test, which is not feasible for the 2 g physician sample size. The Agency indicated that this is a review issue, however; the Agency recommends that the sponsor make a good faith effort to investigate the possibility to take a smaller sample for physician sample size.

Corrigendum:

We encourage you to develop an *in-vitro* drug release method for your proposed product, and propose a specification for batch release and stability purposes. The same method and specification can be used to support post-approval changes.

- Your proposal of replacing the TLC method with a chiral HPLC method for identity test of luliconazole in the drug product appears to be reasonable, but the final decision will be made in the NDA review.
- We recommend that you keep the test of measuring (b) (4) of luliconazole in the drug product specification, and, if warranted, propose its elimination with acceptable justification in the NDA.
- The acceptable pH range for the drug product will be determined in the NDA review. A significant (b) (4) in the pH value of the drug product might affect its clinical performance (b) (4). State in the NDA if any (b) (4) pH batches of the drug product have been used in a clinical study. Additionally, provide certificates of analysis for the batches of (b) (4) that have been used in the clinical and registration stability studies in the NDA submission. (b) (4)

Pharmacology/Toxicology

Question 2:

Does the Division concur that there are no outstanding nonclinical questions/issues that would preclude the filing and acceptance of this CTD section?

Response:

Yes.

Question 3:

Does the Division concur that the compilation of the nonclinical studies according to the ICH CTD Written and Tabulated format is acceptable for filing?

Response:

Yes.

Clinical Pharmacology/Clinical/Biostatistics

There were no Clinical Pharmacology questions submitted in the briefing package, however; we have the following comments:

1. You are proposing an indication in subjects \geq (b) (4) years of age. We notice that your maximal use pharmacokinetic (PK) trial (MP-1007) included subjects 20 years of age and older with tinea pedis and 27 years and older with tinea cruris. We remind you of our comment sent July 20, 2010 to assess PK in subjects 12 - (b) (4) years of age and our comments sent on April 3, 2012 regarding lack of PK data in subjects 12 - (b) (4) years of age. To support an NDA for treatment in subjects \geq (b) (4) years of age, you should conduct a maximal use PK trial in subjects 12 - (b) (4) years of age with tinea pedis and tinea cruris.

In addition, the Pediatric Research Equity Act of 2007 (21 U.S.C. 355c) requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing required to contain an assessment of the safety and effectiveness of pediatric patients unless this requirement is waived or deferred. You will be required to conduct studies:

to demonstrate PK/safety/tolerability under maximal use conditions in subjects ages 12 years to 17 years, 11 months with tinea pedis and tinea cruris, and to demonstrate safety and efficacy of luliconazole in a pediatric population as young as 2 years of age for tinea corporis. In addition, pharmacokinetic information should be captured in this clinical trial to demonstrate the safety profile of your product in children as young as 2 years of age.

Meeting Discussion:

The sponsor stated that they plan to submit a Proposed Pediatric Study Request as part of the process to address the PREA requirements; they plan to submit a request for a deferral for certain pediatric studies. The Agency agreed that this plan seems reasonable.

2. You should address the potential for drug-drug interaction (both induction and inhibition) with your NDA submission. For further information, you are referred to "*Draft Guidance for Industry: Drug interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations - February 2012.*"
3. Submit raw PK data from trial MP-1007 in SAS transport (.xpt) format in your NDA submission.
4. Submit a bioanalytical method validation report and bioanalysis reports in your NDA submission.

Question 4:

Reference is made to the Protocol Amendment (S-0042) submitted November 14, 2011 in which Medicis revised the long-term safety protocol (MP-1005) to follow 100 new subjects for one year and approximately 400 subjects for six (6) months. In accordance with the E1A Guideline for Industry, "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions", the initial NDA submission will include at least 100 subjects exposed to Luliconazole Cream 1% for a minimum of one year and 400 subjects exposed to Luliconazole Cream 1% for six months.

Does the Division concur with this approach?

Response:

It appears that sufficient exposure to (luliconazole) Cream, 1% will be established to satisfy the ICH E1A guidelines. The adequacy of the safety data will be determined during the NDA review, and supplementary safety information may be requested should safety issues be identified.

Question 5:

For the U.S. clinical studies, Medicis intends to submit case report forms for subjects who died, discontinued because of an adverse event, or experienced a serious adverse event during any of the studies. Does the Division concur?

Response:

Case Report Forms (CRFs) should be submitted for all studies and electronic links for:

- a) all Serious AEs
- b) all Severe AEs
- c) all patients who discontinued for whatever the reason (not just because of adverse events)

Meeting Discussion:

The sponsor will submit requested CRFs for U.S. Phase 2 and Phase 3 studies.

Question 6:

In the Integrated Summary of Efficacy, Medicis plans to pool the efficacy results from the two Phase 3 tinea pedis studies (MP-1000-02 and MP-1000-03) and present the efficacy results from the Phase 3 tinea cruris study (MP-1000-01) separately. Does the Division concur?

Response:

Your approach appears reasonable.

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.
- a rationale for why the data presented represents a demonstration of substantial evidence of effectiveness for the proposed indication.

Meeting Discussion:

The sponsor agreed to submit a detailed analysis for age subgroups over 65 and under 18, in addition to above and below the median age.

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.

According to the efficacy results presented in Table 5 (pg. 24 of your June 1, 2012 briefing package), the treatment effect in Study MP-1000-02 was twice the size of the treatment effect in Study MP-1000-03. The ISE should include a thorough discussion of the apparent efficacy differences in the two studies.

Question 7:

In the Integrated Summary of Safety, Medicis plans to pool the safety data from the three Phase 3 studies (MP-1000-02, MP-1000-03, and MP-1000-01). Safety data from all other clinical studies, including the long-term safety study (MP-1005), will be presented separately. Does the Division concur?

Response:

Your approach appears reasonable.

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.

Meeting Discussion:

The sponsor agreed to submit shift tables for normal ranges and those that were deemed abnormal and clinically significant. The sponsor will provide information in the submission regarding the basis for determining patients to be a screening failure.

“The Program” Agreements

The Agency agreed that 18-month stability data could be updated no later than 30 days after the submission of the original application.

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. 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.
4. You should provide the Agency with SAS transport files in electronic form. The sponsor might refer to the Analysis Data model (ADaM) Examples in Commonly Used Statistical Analysis Methods for guidance:
http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf. The FDA prefers that the sponsor arrange a test submission, prior to actual submission. Please refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<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.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: 18-month stability data.

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).

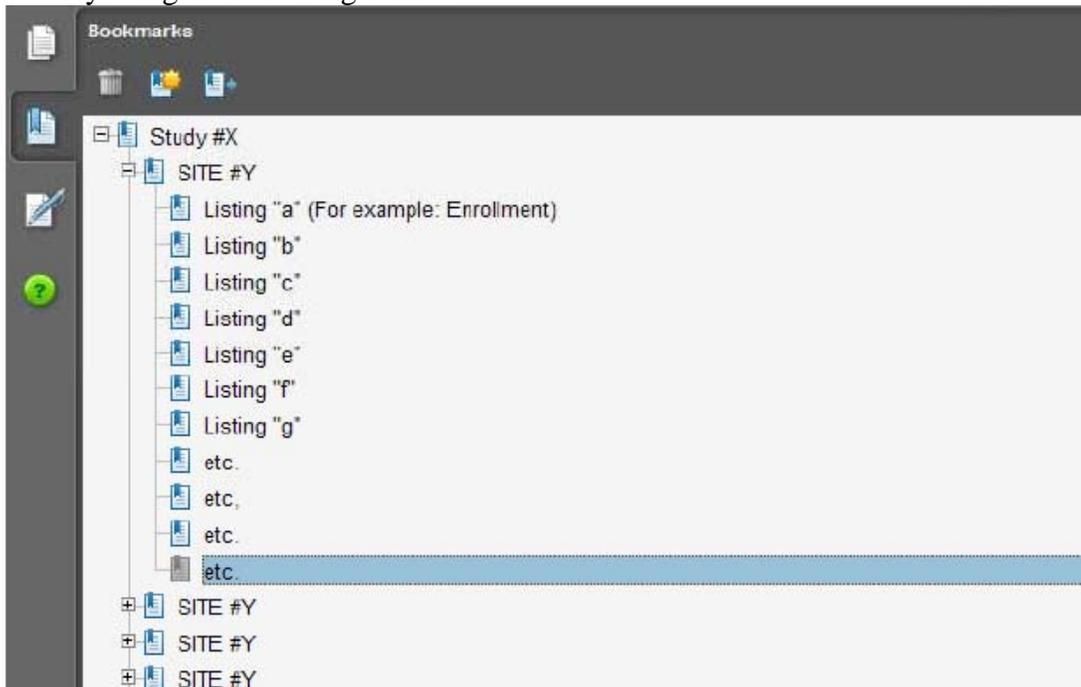
I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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 descr be 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., <u>not limited to</u> 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 parties. 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

MINITAL	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

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
08/07/2012



IND 076049

MEETING MINUTES

Tinea Pharmaceuticals, Inc.
c/o Medicis Pharmaceutical Corp.
Attention: Diane Stroehmann, RAC
Director, Regulatory Affairs
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Ms. Stroehmann:

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

We also refer to the teleconference between representatives of your firm and the FDA on October 27, 2010. The purpose of the meeting was to discuss the development program for the indications of tinea cruris and tinea corporis.

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 B Meeting
Meeting Category: End-of-Phase 2

Meeting Date and Time: October 27, 2010, 9AM
Meeting Location: Teleconference

Application Number: IND 076049
Product Name: luliconazole cream, 1%
Indication: treatment of tinea cruris and tinea corporis
Sponsor/Applicant Name: Tinea Pharmaceuticals, Inc. (Medicis, Regulatory Authority)

Meeting Chair: Susan Walker
Meeting Recorder: Cristina Attinello

FDA ATTENDEES

Susan Walker, MD, FAAD, Division Director, DDDP
David Kettl, MD, Clinical Team Lead, DDDP
Gary Chiang, MD, MPH, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Kumar Mainigi, PhD, Pharmacology Reviewer, DDDP
Cristina Petruccelli Attinello, MPH, Regulatory Project Manager, DDDP
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DPA II, Branch III
Minerva Hughes, Product Quality Reviewer, DPA II, Branch III
Mohamed Alosch, PhD, Biostatistics Team Lead, DB III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Abimbola Adebowale, PhD, Clinical Pharmacology Reviewer, DCP 3
Kerry Snow, MS, Clinical Microbiology Reviewer, DAIOP

SPONSOR ATTENDEES

Ira Lawrence, MD, Chief Medical Officer and Sr. VP Research and Development, Medicis
Steve Newhard, Sr. VP Quality and Technical Services, Medicis
Xiaoming Lin, VP Clinical Research and Development, Medicis
Diane Stroehmann, RAC, Director, Regulatory Affairs, Medicis
Katy Morton, VP, Regulatory Affairs and Quality Assurance, Tinea
Mark Davis, VP, Clinical Development, Tinea

(b) (4)

Purpose of the Meeting:

The purpose of this meeting is to discuss the development program for the indications of tinea cruris and tinea corporis.

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Does the Agency agree that the proposed analytical methods and specifications listed in Table 5 are suitable and adequate to support the initiation of Phase 3 clinical studies to assess the safety and efficacy of Luliconazole Cream, 1%?

Response:

No, the proposed drug product specification is not adequate. Include homogeneity testing of the finished product for API throughout the tube (top, middle, bottom) at release and during stability. In addition, the identity, quantity, morphology and (b) (4) in the cream formulation should be monitored for each Phase 3 clinical lot and in registration stability studies, and the information must be included in the NDA for marketing approval.

Additional CMC Comments

We acknowledge your commitment to provide a comprehensive pharmaceutical development section in the NDA regarding the presence of (b) (4) in the drug product and would like to remind you of the following CMC issues which should be adequately addressed in any future NDA for luliconazole cream:

1. Data included in your briefing package are inconclusive regarding the identity of the (b) (4). Comparative HPLC data should be included in support of the FTIR and XRD data for the identification of (b) (4). In addition, once the (b) (4) are confirmed to be luliconazole, you should clarify whether the (b) (4) found in the cream are a different (b) (4) from that of the drug substance.
2. An analysis of (b) (4) in previous lots of luliconazole cream, 1 % used in the Phase 2 clinical studies supporting IND 076049, as well as commercial lots marketed in Japan, is strongly recommended. If (b) (4) data were not collected in the past for these lots, a retrospective (b) (4) analysis on representative samples of these lots is requested. Comparisons should be made between these lots and U.S. Phase 3 clinical/registration stability lots regarding the (b) (4) present in the formulation with regards to identity, quantity, particle size distribution, morphology, and (b) (4).
3. Assuming the (b) (4) found in the cream are the (b) (4) luliconazole, you need to address the impact of (b) (4) formation on product performance due to batch-to-batch variations and potential changes upon storage. The in-vitro-release testing can be helpful in assessing the impact.
4. Conditions leading to the formation of the (b) (4) should be described, and the potential for formation of these related substances in the drug product discussed.
5. Antimicrobial effectiveness (i.e. USP<51>) should be demonstrated at the proposed lower limit of preservatives. In addition, compliance with USP <51> should be demonstrated on stability for at least one registration batch, in lieu of routine USP <51> testing.

Clarify whether the formulation composition of Japan-approved Lulicon Cream, 1% is identical to that of the to-be-marketed luliconazole cream, 1% formulation in the U.S.

Meeting Discussion:

The sponsor clarified that the formulations are the same and committed to providing supporting information to the IND. The sponsor commits to provide information requested by the Agency related to the CMC comments in advance of NDA submission.

Pharmacology/Toxicology

There were no Pharmacology/Toxicology questions submitted in the briefing package.

Clinical Pharmacology/Biopharmaceutics

There were no Clinical Pharmacology/Biopharmaceutics questions submitted in the briefing package, however; we have the following comments:

We acknowledge your proposal to conduct a maximal use PK study (Protocol # TP-1007) in patients with either tinea pedis or tinea cruris. We also acknowledge that Protocol TP-1007 was submitted to the Agency on May 5, 2010. However, the protocol that was submitted was for a maximal use PK study in patients with tinea pedis. This protocol was reviewed by the Agency and comments, recommendations and requests for information were sent to you on July 20, 2010. We note that you have included a draft amendment of this protocol in the briefing package to include patients with tinea cruris in the study for a total number of 30 subjects (15 with tinea pedis and 15 with tinea cruris). We have the following comments for this amended draft protocol for the maximal use human PK study (TP-1007):

It is not clear whether the proposed PK sampling times are adequate to ensure that the maximum concentration (C_{max}) can be adequately characterized. We recommend that you include a PK sampling time between 6 and 12 hours. This is based on the range of T_{max} reported (4-24 hours after a single dose and 4-8 hours after multiple dosing) in your previous studies conducted in healthy volunteers with luliconazole cream.

Meeting Discussion:

The sponsor committed to add a 9-hour PK sampling time on Days 1, 8, and 15, and also to collect EKGs at the 9-hour PK timepoint.

Clinical/Biostatistics

Question 2:

Does the Agency agree with the Sponsor's approach to addressing ICH E14?

Response:

A decision is pending the outcome of your maximal use study. If the maximal use study demonstrates that systemic exposure is higher than expected, the thorough QT issue will need to be reconsidered.

Meeting Discussion:

The sponsor will provide the results of the maximal use PK study to the IND as soon as it becomes available.

Question 3:

Does the Agency agree that further ECG monitoring of every patient is not needed during Phase 3 Clinical Development if a waiver has been granted for a Thorough QT/QTc (TQT) study?

Response:

No. The Agency recommends continued ECG monitoring during clinical trials to exclude other large ECG effects of your drug product. The Agency recommends that ECG evaluations include baseline, T_{max} at steady state, and periodically during the treatment.

Meeting Discussion:

The sponsor will provide a proposal including a rationale for timing of ECG monitoring in their Phase 3 clinical trials.

Question 4:

The Sponsor believes that the Phase 2 efficacy and safety data are sufficient to support the initiation of the Phase 3 clinical study to assess the safety and efficacy of the Luliconazole Cream, 1% in patients with tinea cruris. Does the Agency concur?

Response:

The late Phase 2 study data from PR2699-P2-01 provided in the briefing package describes only a small population treated with 1% luliconazole for tinea cruris. The doses explored in this study were 1%, 0.5%, and 0.1% luliconazole cream. Only a small subset of subjects (35) were enrolled with tinea corporis/cruris and received 1% luliconazole cream. Most subjects were male, and all were of Japanese ancestry.

Your primary endpoint was not the Agency recommended endpoint of complete clearance, defined by negative KOH and culture with no clinical evidence of disease. Clinical assessment described rates of improvement of skin symptoms. Mycologic cure was the antimycotic effect by direct microscopy, as opposed to fungal culture.

The purpose of Phase 2 dose ranging studies is to explore appropriate dose, duration, and frequency of your drug product for the indication you seek. Appropriate primary endpoints should be explored in Phase 2 studies to allow adequate estimates to properly power Phase 3 clinical trials. Additional Phase 2 explorations will be helpful in planning and powering the proposed Phase 3 trial for tinea cruris.

You should also consider how the results of this foreign study could be extrapolated to the U.S. population. The Agency recommends that you consult Guidance for Industry: ICH E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data.

Question 5:

Does the Agency agree that the overall study design and the primary efficacy endpoint for Study MP-1000-01 will support a labeled indication for the treatment of tinea cruris? The primary endpoint is the proportion of subjects who achieve “complete clearance” at Day 28 (3 weeks post-treatment). Complete clearance is defined as achieving both:

- Clinical cure - absence of the signs or symptoms of tinea cruris, i.e., score of 0 for each of the individual signs of tinea cruris (erythema, scaling, pruritus); and
- Mycological cure - negative potassium hydroxide (KOH) examination and negative fungal culture

Response:

Yes. Your proposed primary efficacy endpoint of “complete clearance” at Day 28 for Study MP-1000-01 is appropriate.

Generally, if you seek the indications of tinea pedis, tinea cruris, and tinea corporis, you may demonstrate safety and efficacy in two successful, adequate and well-controlled clinical trials in tinea pedis and one safety and efficacy clinical trial in tinea cruris, to achieve all three indications.

Question 6:

Does the Agency agree with the statistical approach proposed for the Phase 3 study for tinea cruris?

Response:

In general, the statistical analysis plan for the primary and secondary endpoints appears to be appropriate; however we have the following comments:

- The list of secondary endpoints should be limited in number, clinically relevant, and the analysis should appropriately adjust for multiplicity. Although you have proposed a sequential plan to account for multiplicity, you still have proposed a relatively large number of secondary endpoints (6 endpoints at various timepoints).
- You have proposed using LOCF as the primary way of handling missing data with two sensitivity analyses (imputing all missing as failures and imputing all missing as successes). In addition to these proposals, the Agency recommends including an additional method as a sensitivity analysis that uses a different framework and assumptions, such as multiple imputation.

Meeting Discussion:

The sponsor proposed adding a sensitivity analysis using multiple imputation on the derived primary endpoint (not the individual components). The Agency stated this would be acceptable.

Question 7:

Does the Agency agree that the proposed clinical program is adequate to support a Luliconazole Cream, 1% marketing application for treatment of tinea pedis, tinea corporis and tinea cruris?

The proposed clinical program for Luliconazole Cream, 1% includes:

- One maximal use PK study in patients with either tinea pedis or tinea cruris (MP-1007) (formerly submitted as TP-1007) (planned)
- One Phase 2 efficacy and safety study in subjects with tinea Pedis (TP-0801) (completed)
- Two Phase 3 efficacy and safety studies in subjects with tinea Pedis (MP-1000-02 and MP-1000-03) [formerly, TP-1003-01 and TP-1003-02, respectively] (planned)
- One Phase 3 efficacy and safety study in subjects with tinea cruris (MP-1000-01) (planned)
- One long-term safety study in subjects who have either tinea pedis, tinea corporis, or tinea cruris (MP-1005) (planned)
- Provocative safety studies to assess irritation, sensitization, phototoxicity and photosensitization (Protocol numbers TBD).
- Supportive efficacy and safety studies from Japanese Luliconazole Cream, 1% (completed)

Response:

Additional Phase 2 safety and efficacy data is recommended for the indication of tinea cruris, as described above. To claim safety and efficacy for all three indications (tinea pedis, tinea corporis, and tinea cruris), the proposed two Phase 3 efficacy and safety trials for tinea pedis and one Phase 3 efficacy and safety trial in tinea cruris would be acceptable.

Provocative studies to evaluate local safety of topical drug products should be conducted with the final to-be-marketed formulation. As the to-be-marketed formulation may not be finalized until late in development, topical safety studies may be conducted in parallel with Phase 3 clinical trials.

Clarify the necessity of two forms of contraception in your Phase 3 trials, as this will affect eventual product labeling should your product be approved.

Submit a copy of the prescribing information from Japan, translated into English.

Meeting Discussion:

There was discussion regarding the need for contraception. The sponsor will provide a submission to the IND.

Question 8:

Does the Agency agree with the proposed long-term study design?

Response:

The protocol proposed for study MP-1005 appears adequate. The adequacy of the study outcome is a review issue.

Question 9:

Does the Agency agree that the total number of subjects to be included in the US clinical studies (N≈ 1500) in combination with the Japanese clinical trial safety database (N=1035) established for Luliconazole Cream, 1%, provide an adequate basis for assessing the safety of Luliconazole Cream, 1% for the treatment of tinea pedis, tinea corporis and tinea cruris?

Response:

Yes. The adequacy of the safety database is a review issue.

Question 10:

Because of the relatively low prevalence of tinea corporis/cruris in the 12 year old and under pediatric populations, a request for a waiver for pediatric testing is planned. Is the Division in agreement with this strategy?

Response:

Submit your waiver request along with your rationale to the NDA.

Clinical Microbiology

1. Submit complete study reports for investigations of luliconazole, as summarized in Tables 1, 2, 3 and 4 of Appendix 3 in the November 13, 2009 briefing package submitted for the December 16, 2009 End-of-Phase 2 Meeting, including in vitro studies of luliconazole antifungal activity, in vivo studies of luliconazole antifungal activity, studies on skin retention, and mechanism of action studies. Study reports should include complete descriptions of methods employed, results for all comparators, statements concerning the standardization of these methods (e.g. methods for antifungal susceptibility approved by Clinical Laboratory and Standards Institute), geographic origin and phenotypic description of tested isolates, and quality control data.
2. Submit sufficient data from in vitro studies of antifungal activity, to permit evaluation of the antifungal spectrum of activity of luliconazole against species of interest. Study data should include at least 100 isolates of each species, with the majority of isolates collected in the U.S. In vitro investigations should include comparisons to currently approved topical antifungals and other appropriate comparators. Study reports should include descriptions of methods employed, descriptions of tested isolates (including geographic origin, specimen source, and phenotype/genotype information) and quality control performed during the course of the study. Susceptibility testing techniques should be based on standardized methods such as those approved by CLSI (CLSI Document M38-A2).
3. Submit information from investigations designed to investigate the development of resistance to luliconazole, in species of dermatophytes.
4. Ensure that all isolates collected in clinical trials are tested for susceptibility to luliconazole and appropriate comparators, and that susceptibility test methods conform to standardized methods (including appropriate quality control).
5. Ensure that all isolates collected in clinical trials are appropriately labeled and preserved for additional testing, as required.
6. Ensure that the central mycology testing facility is appropriately accredited.

Meeting Discussion:

The sponsor commits to provide information requested by the Agency and to perform susceptibility testing on all dermatophytes recovered during clinical trials.

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.

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
11/02/2010



IND 76049

MEETING MINUTES

Topica Pharmaceuticals, Inc.
Attention: Katy Morton
VP Regulatory Affairs & Quality Assurance
435 Tasso Street, Suite 325
Palo Alto, CA 94301

Dear Ms. Morton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for luliconazole cream, 1% for the treatment of tinea pedis.

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2009. The purpose of the meeting was to discuss the development plan for luliconazole cream, 1%.

A copy of the official minutes of the meeting 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 Petruccelli 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 B
Meeting Category: End of Phase 2

Meeting Date and Time: December 16, 2009, 9 AM
Meeting Location: White Oak 22, Room 1313

Application Number: IND 76049
Product Name: luliconazole cream, 1%
Indication: treatment of tinea pedis
Sponsor/Applicant Name: Topica Pharmaceuticals, Inc.

Meeting Chair: Susan Walker
Meeting Recorder: Cristina Petruccelli Attinello

FDA ATTENDEES

Susan Walker, MD, FAAD, Division Director, DDDP
David Kettl, MD, Clinical Team Lead, DDDP
Gary Chiang, MD, MPH, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Kumar Mainigi, PhD, Pharmacology Reviewer, DDDP
Barbara Gould, MBAHCM, Chief Project Management Staff, DDDP
Cristina Petruccelli Attinello, MPH, Regulatory Project Manager, DDDP
Jeannine Helm, BS, Regulatory Project Manager, DDDP
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DPA II, Branch III
Christopher Hough, Product Quality Reviewer, DPA II, Branch III
Mohamed Alish, PhD, Biostatistics Team Lead, DB III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Abimbola Adebawale, PhD, Clinical Pharmacology Reviewer, DCP 3
Kerry Snow, MS, Clinical Microbiology Reviewer, DAIOP

SPONSOR ATTENDEES

Greg Vontz, President/CEO
Norifumi Nakamura, PhD, Senior VP Corporate Development
Katy Morton, VP Regulatory Affairs & Quality Assurance

(b) (4)

Kazuo Kanai, Executive Officer
Makoto Goto, Chief Manager

Purpose of the Meeting:

The purpose of the meeting is to discuss the development plan for luliconazole cream, 1%.

Regulatory

There are no Regulatory questions presented by the sponsor in this briefing package, however, the Agency would like to remind Topica of the following correspondences:

- Advice Letter containing comments for Protocol TP-0801 (July 1, 2009)
- Advice Letter granting waiver from carcinogenicity studies (May 8, 2009)
- Pre-IND Meeting Minutes (January 26, 2007)

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Are the proposed specifications for luliconazole drug substance acceptable for the planned Phase 3 studies and future commercialization?

Response:

The drug substance specification is acceptable for Phase 3 studies. The adequacy of a specification for NDA approval is a review issue.

Question 2:

In accordance with the principles of SUPAC for Nonsterile Semisolid Dosage Forms, does the Division agree with the sponsor's proposed comparability studies for the qualification of new suppliers for luliconazole bulk drug substance and luliconazole cream, 1% drug product?

Response:

We agree that your proposal to qualify the new drug substance supplier, (b)(4) is acceptable, provided that the impurity profile of the bulk drug substances from the two manufacturing sites can be shown to be equivalent. A side by side analysis of the drug substance manufactured at the two sites using the proposed analytical methods is recommended.

Regarding the drug product manufacturer, we agree that your proposal to qualify the new manufacturer, DPT Laboratories, is acceptable, provided that the in-vitro release study shows comparable drug release results from the product made at these two manufacturing sites.

Question 3:

Does the Division agree with Topica's comparability protocol strategy for the introduction of the 30 gram tube and sample tube post approval?

Response:

We agree that you can utilize a comparability protocol in the NDA to facilitate the approval and implementation of a new container size post NDA approval. However, the adequacy of the protocol and reporting category is a review issue.

Question 4:

Are the proposed drug product specifications for luliconazole cream, 1% acceptable for the planned Phase 3 studies and commercialization?

Response:

The drug product specification is acceptable for the Phase 3 studies. The adequacy of a specification for NDA approval is a review issue.

Question 5:

Does the Division concur that Topica may claim a categorical exclusion based on the expected levels of luliconazole projected to enter the waste stream?

Response:

You may claim a categorical exclusion on the basis of levels of luliconazole expected to enter the aquatic environment as per 21 CFR 25.31(b), but whether you are granted with that claim for commercialization is a review issue.

Additional CMC Comments from FDA:

Provide a single representative sample of the proposed product to the IND for dosage form evaluation.

Conduct a special study to demonstrate that the proposed product can pass USP<51> Antimicrobial Effectiveness Testing in the presence of the lowest acceptable levels of preservatives

Pharmacology/Toxicology

Question 6:

For the NDA, Topica plans to summarize nonclinical pharmacological, pharmacokinetic and toxicology data for luliconazole in Module 2 and submit English translations of the Japanese study reports in Module 4, does the Division agree with this approach?

Response:

Yes, this plan is acceptable. You should include proper documentation to support the accuracy of the English translation.

Question 7:

Does the Division agree that the existing nonclinical safety data base is adequate to support the approval of luliconazole cream, 1% for the 14 day treatment of tinea pedis?

Response:

The nonclinical data appear acceptable. The final decision will be made during the NDA review. The adequacy of the nonclinical data will be partially dependent on if any new safety signals of concern emerge during the conduct of Phase 3 clinical studies which may trigger the need for additional nonclinical studies.

Clinical Pharmacology/Biopharmaceutics

There are no Clinical Pharmacology/Biopharmaceutics questions presented by the sponsor in this briefing package, however, the Agency has the following comment:

We acknowledge the summary information provided on the metabolism and drug–drug interaction potential of your drug in the nonclinical section of the briefing document. However, we did not find any information on the maximal usage PK study that the Agency requested at the Pre-IND meeting held on January 16, 2007. Therefore, we are reiterating our previous comment that the sponsor would need to conduct a maximal usage pharmacokinetic study with the final-to-be-marketed formulation, in a suitable number of patients with the target disease of interest at the upper range of severity, as anticipated in both your clinical trials and proposed labeling, during their clinical development program.

Meeting Discussion:

The Agency agreed to review and provide comments on the sponsor's PK protocol to be submitted to the IND.

Clinical/Biostatistics

Question 8:

Topica will provide supportive efficacy and safety information from Japanese luliconazole cream, 1% clinical studies as translated clinical study reports with selected elements of Appendix 16 of ICH E3. Safety information derived from the Japanese clinical studies will be discussed separately in the ISS but will not be integrated into the US safety database. Is this acceptable to the Division?

Response:

It is acceptable that the safety information from the Japanese clinical studies be separately discussed in the ISS. The sponsor is referred to ICH E5 Guidance: Ethnic Factors in the Acceptability of Foreign Clinical Data, regarding the completeness of the clinical data submitted and the ability to extrapolate that data to the US marketplace.

Question 9:

Does the Division agree with the patient population (as defined by inclusion and exclusion criteria), 14-day dosing regimen and overall design of the proposed Phase 3 studies of luliconazole cream, 1% for the treatment of tinea pedis to support registration?

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, in parallel, appears to be appropriate.

Comments on the inclusion criteria:

- The incidence and severity of tinea pedis may have a geographical component. Studies should ideally include investigators in warmer climates as well as the cooler ones. Additionally, every effort should be made to enroll adequate numbers of subjects in the various demographic groups to whom inferences will be made.
- The Agency recommends urine pregnancy tests to have a minimum analytical sensitivity of 25mIU/ml.
- Luliconazole's nonclinical findings suggest potential embryotoxic effects for this New Molecular Entity (NME). If subjects are required to use contraception in Phase 3 trials, the final product labeling will reflect this limitation.

Comments on the exclusion criteria:

- Exclusion of topical or systemic antibiotics should also be considered.
- Washout periods from previous medications should be consistent with the pharmacokinetics of that drug.

Your inclusion and exclusion criteria appear to limit your product's indication to interdigital tinea pedis and the (b) (4)

A Special Protocol Assessment can be considered for your revised Phase 3 study protocols. The sponsor should include information to assess the role of the study in the overall development of the drug, information supporting the proposed trial, and descriptions of any anticipated regulatory outcomes and proposed labeling that would be supported by the results of the study. The Agency refers you to Guidance for Industry: Special Protocol Assessment, for further details.

Question 10:

Does the Division agree with the described Day 42 efficacy endpoints and proposed statistical analysis plan for the proposed Phase 3 studies in support of the proposed indication?

Response:

The efficacy endpoints and statistical analysis plan appear to be appropriate in general. It is acceptable to define the primary endpoint as complete clearance at day 42, where complete clearance is defined as achieving both (1) clinical cure - absence of the signs or symptoms of tinea pedis, i.e., score of 0 for each of the individual signs of tinea pedis (erythema, scaling, pruritus) and (2) mycological cure - negative KOH examination and negative fungal culture.

We recommend proposing a framework for addressing multiplicity among the secondary endpoint analyses. Among the sensitivity analyses for handling missing data, we recommend including an additional method that uses a different framework and assumptions, such as multiple imputation.

Question 11:

Does the Division agree with Topica's approach to the conduct of a long-term safety study as a Phase 4 commitment?

Response:

No, we do not agree. Please see the response to Question 12 below.

Question 12:

Does the Division consider the projected body of efficacy and safety data (estimated 660 patients) to be sufficient for approval of luliconazole cream, 1% for the treatment of tinea pedis?

Response:

The Agency considers tinea pedis to be a chronic indication and therefore the duration of drug exposure and its relationship to both time and magnitude of occurrence of adverse events are important considerations in determining the size of the database necessary to achieve an adequate safety data base. Your proposed Phase 3 trials with an estimated 660 patients may be sufficient; however, the Agency refers you to ICH-E1A Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions. Specifically, reference to #6 of that guideline states: "It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1,500." It may be more prudent to conduct the long-term safety study that you propose in conjunction with your Phase 3 studies to comprise a sufficient safety population for NDA submission.

Question 13:

Because of the low prevalence of tinea pedis in the 12 year old and under pediatric populations, Topica plans to request a waiver for pediatric testing. Does the Division find this acceptable?

Response:

Yes. You may submit a request to waive studies of 12 year old and under pediatric population along with appropriate reasoning for that request when the NDA is submitted.

Additional Clinical Comments from FDA:

As this is a new molecular entity and an imidazole antifungal, the sponsor must address the product's potential as a proarrhythmic and address possible prolongation of QT/QTc intervals. The Agency refers you to Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

Provocative studies to evaluate local safety of topical drug products are needed prior to marketing and should be conducted with the final to-be-marketed formulation. While the protocols were not submitted for Agency comment, the numbers of evaluable subjects described in the briefing document are in line with Agency recommendations.

The sponsor should submit their Phase 3 protocols to the IND. Alternatively, a Special Protocol Assessment can be considered with the revisions to your protocol. It would be helpful if the final

protocols were marked with highlight/strikeout to elucidate any changes from the versions of the protocols submitted for review for today's meeting.

Clinical Microbiology

There are no Clinical Microbiology questions presented by the sponsor in this briefing package, however, the Agency has the following comments:

1. Submit complete study reports for investigations of luliconazole, as summarized in Tables 1, 2, 3 and 4 of Appendix 3 of the briefing package, including in vitro studies of luliconazole antifungal activity, in vivo studies of luliconazole antifungal activity, studies on skin retention, and mechanism of action studies. Study reports should include complete descriptions of methods employed, results for all comparators, statements concerning the standardization of these methods (e.g. methods for antifungal susceptibility approved by Clinical Laboratory and Standards Institute (CLSI)), geographic origin and phenotypic description of tested isolates, and quality control data.
2. Submit sufficient data from in vitro studies of antifungal activity, to permit evaluation of the antifungal spectrum of activity of luliconazole against species of interest. Study data should include at least 100 isolates of each species, with the majority of isolates collected in the U.S. In vitro investigations should include comparisons to currently approved topical antifungals and other appropriate comparators. Study reports should include descriptions of methods employed, descriptions of tested isolates (including geographic origin, specimen source, and phenotype/genotype information) and quality control performed during the course of the study. Susceptibility testing techniques should be based on standardized methods such as those approved by CLSI (CLSI Document M38-A2).
3. Submit information from studies designed to investigate the development of resistance in species of interest to luliconazole.

Meeting Discussion:

The sponsor agreed to submit a study of luliconazole resistance in dermatophytes performed in Japan.

4. Ensure that all isolates collected in clinical trials are tested for susceptibility to luliconazole and appropriate comparators, and that susceptibility test methods conform to standardized methods (including appropriate quality control).
5. Ensure that all isolates collected in clinical trials are appropriately labeled and preserved for additional testing, as required.
6. Ensure that the central mycology testing facility is appropriately accredited.

References:

Clinical and Laboratory Standards Institute (CLSI). Reference Methods for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi; Approved Standard-Second Edition. CLSI document M38-A2. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2008.

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. 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 or carcinogenicity) 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.
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. 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.
6. 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.

7. 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.
8. 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).
9. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-76049	GI-1	JANUS PHARMACEUTICA LS INC	NND502(LULICONAZOLE) CREAM 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
12/18/2009

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 204153

LATE-CYCLE MEETING MINUTES

Medicis Pharmaceutical Corporation
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your New Drug Application (NDA) dated December 11, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Luzu (luliconazole) Cream, 1%.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 11, 2013.

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

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

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

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 11, 2013; 11:00 a.m. (ET)
Meeting Location: Teleconference

Application Number: NDA 204153
Product Name: Luzu (luliconazole) Cream, 1%
Applicant Name: Medicis Pharmaceutical Corp.

Meeting Chair: David Kettl, MD
Meeting Recorder: Paul Phillips

FDA ATTENDEES

Susan J. Walker, MD, FAAD, Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Amy Woitach, DO, MS, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Kumar Mainigi, PhD, Pharmacology Reviewer, DDDP
Dennis Bashaw, PharmD, Director, DCP 3
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP 3
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Raymond Frankewich, PhD, Product Quality Reviewer, DNDQA II, Branch IV
Kelly Kitchens, PhD, Pharmacologist, ONDQA
Yuqing Tang, PhD, Biostatistician, DB III
Roy Blay, PhD, Reviewer, DGCP
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
Giuseppe Randazzo, MS, Regulatory Scientist, ODE III
J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

(b) (4)

APPLICANT ATTENDEES

Tage Ramakrishna, Chief Medical Officer
Phil Sturno, Vice President, Product Development
Sharon Tonetta, Vice President, Global Regulatory Affairs, Pharma
Steven Knapp, Vice President, Regulatory Affairs Dermatology and Aesthetics
RK Pillai, Head Dermatology Development
William Jo, Toxicologist III
Sean Humphrey, Manager, Regulatory Affairs

1.0 BACKGROUND

NDA 204153 was submitted on December 11, 2012 for Luzu (luliconazole) Cream, 1%.

Proposed indication: Topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older.

PDUFA goal date: December 11, 2013

FDA issued a Background Package in preparation for this meeting on August 30, 2013.

2.0 DISCUSSION

1. Introductory Comments
2. Objectives of the meeting
3. Postmarketing Requirements/Postmarketing Commitments
 - Discuss language and milestones (see appendix):
 - a. PREA PMR-1
 - b. PREA PMR-2
 - c. Clinpharm PMR-1
 - d. Clinpharm PMR-2
 - e. Clinpharm PMC

Meeting Discussion:

The applicant accepted PREA PMR-1 and the proposed timelines.

There was discussion related to PREA PMR-2 and anticipated difficulties in subject enrollment. The applicant would like to propose an open label study design. The FDA replied that the primary objective of this trial is safety and that the trial ideally should be blinded and vehicle controlled, but did not need to be powered for efficacy or statistical significance. A subject distribution with more active subjects compared to the vehicle arm would be acceptable. The FDA will provide comments on the protocol upon submission, which is anticipated in early 2014.

There was general discussion regarding the Clinical Pharmacology PMR-1 and PMR-2 drug interaction trials. The FDA acknowledged that these are new requests of applicants for topical products, but the FDA considers the information necessary as a PMR. The FDA indicated a willingness to provide feedback on protocol design to achieve the desired objectives.

The applicant accepted the Clinical Pharmacology PMC-1 and will submit proposed milestone dates to the NDA.

4. Review Plans

- At this time there are no significant review issues.
- The Office of Compliance has given an overall recommendation of acceptable for the manufacturing sites.
- The Office of Scientific Investigation (OSI) inspection results are pending.

Meeting Discussion:

The FDA stated that at this time there are no unresolved substantive review issues to discuss with the applicant, no advisory committee meeting is planned, and no issues related to risk management have been identified to date.

5. Wrap-up and Action Items

Meeting Discussion:

The applicant will provide a formal response regarding postmarketing requirements and commitments to the NDA. There were no additional action items.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

DAVID L KETTL
09/20/2013



NDA 204153

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Medicis Pharmaceutical Corporation
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luzu (Iuliconazole) Cream, 1%

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 11, 2013.
Attached is our background package with our agenda, for this meeting.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 11, 2013; 11:00 a.m. (ET)
Meeting Location: FDA W.O. Bldg. 22

Application Number: NDA 204153
Product Name: Luzu (luliconazole) Cream, 1%
Proposed Indication: Topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older.

Applicant Name: Medicis Pharmaceutical Corp.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

- No Discipline Review letters have been issued to date.

2. Substantive Review Issues

- At this time there are no unresolved substantive review issues.

ADVISORY COMMITTEE MEETING

- An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

- No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments
2. Objectives of the meeting
3. Postmarketing Requirements/Postmarketing Commitments
 - Discuss language and milestones for (see appendix):
 - a. PREA PMR-1
 - b. PREA PMR-2
 - c. Clinpharm PMR-1
 - d. Clinpharm PMR-2
 - e. Clinpharm PMC
4. Review Plans
 - At this time there are no significant review issues.
 - The Office of Compliance has given an overall recommendation of acceptable for the manufacturing sites.
 - The Office of Scientific Investigation (OSI) inspection results are pending.
5. Wrap-up and Action Items

Appendix

PREA PMR-1

Conduct a maximum use pharmacokinetic safety study in pediatric subjects 12 years to 17 years, 11 months of age with tinea pedis and tinea cruris.

Final Protocol Submission:	<u>01/31/2014</u>
Study/Trial Completion:	<u>10/31/2016</u>
Final Report Submission:	<u>02/28/2017</u>

PREA PMR-2

Conduct a multi-center, randomized, blinded, vehicle-controlled study, including PK assessments with luliconazole cream 1% for the treatment of tinea corporis in pediatric patients \geq 2 years of age.

Final Protocol Submission:	<u>01/31/2014</u>
Study/Trial Completion:	<u>11/30/2016</u>
Final Report Submission:	<u>04/30/2017</u>

Clinical Pharmacology PMR-1

Conduct in-vivo drug interaction trial using appropriate probe substrate to evaluate the inhibition potential of luliconazole for CYP2C19 under maximal use conditions in subjects with tinea cruris and tinea pedis.

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>MM/DD/YYYY</u>

Clinical Pharmacology PMR-2

Conduct in-vivo drug interaction trial using appropriate probe substrate to evaluate the inhibition potential of luliconazole for CYP3A4 under maximal use conditions in subjects with tinea cruris and tinea pedis. This trial may be omitted if the results from trial with CYP2C19 substrate indicate no significant interaction.

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>MM/DD/YYYY</u>

Clinical Pharmacology PMC-1

Conduct in-vitro assessments to evaluate the following:

- Inhibition potential of luliconazole for enzymes CYP2B6 and CYP2C8.
- Induction potential of luliconazole for enzymes CYP1A2, CYP2B6 and CYP3A.

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

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>MM/DD/YYYY</u>

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
08/30/2013