

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204153Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 204153  
Product Name: Luzu (luliconazole) cream, 1%

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PMR/PMC Description: 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 these in vitro assessments.

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PMR/PMC Schedule Milestones:

Final Protocol Submission:	<u>06/30/2014</u>
Study/Trial Completion:	<u>10/31/2014</u>
Final Report Submission:	<u>03/31/2015</u>
Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The sponsor conducted in vitro inhibition potential assessment and the results showed that luliconazole may inhibit CYP2C19 and CYP3A4. The sponsor has not evaluated the inhibition potential of luliconazole for enzymes CYP2B6 and CYP2C8 or induction potential of luliconazole for enzymes CYP1A2, CYP2B6 and CYP3A as recommended in guidance for industry Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (draft, 2012).

This theoretical concern is not sufficient to preclude approving the drug product if it is otherwise approvable.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This study will evaluate the in vitro potential of luliconazole to inhibit CYP2B6 and CYP2C8 or induce CYP1A2, CYP2B6 and CYP3A. The results will be compared with the systemic luliconazole concentration expected from clinical use to determine whether there is a potential for in vivo drug interaction. Additional in vivo drug interaction trial may be needed based on in vitro results.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

In vitro CYP inhibition and induction studies.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other  
In vitro CYP inhibition and induction studies.
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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J P PHILLIPS  
11/13/2013

DAVID L KETTL  
11/13/2013

TATIANA OUSSOVA  
11/13/2013

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA/BLA # 204153  
Product Name: Luzu (luliconazole) cream, 1%

---

PMR/PMC Description: 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 interdigital tinea pedis. This trial may be omitted if the results from the trial with the CYP2C19 substrate indicate no significant interaction.

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PMR/PMC Schedule Milestones: Final Protocol Submission: 03/31/2016  
Study/Trial Completion: 04/30/2017  
Final Report Submission: 12/31/2017  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In vitro inhibition studies suggest a potential for in vivo drug interaction. Based on guidance for industry Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (draft, 2012), an in vivo drug interaction study should be conducted to determine whether there is an in vivo interaction.

This theoretical concern is not sufficient to preclude approving the drug product if it is otherwise approvable. The product label will include text to note the potential drug interaction. This language can be removed if the in vivo trial shows there is no interaction. If the in vivo trial results show that there is an interaction with CYP3A4 substrates, appropriate labeling (e.g., avoid concomitant use with CYP3A4 substrates) could be added.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In vitro inhibition studies suggest a potential for in vivo drug interaction. Concomitant administration with a substrate of CYP3A4 may increase the exposure of the concomitantly administered drug and lead to adverse effects.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Drug interaction trial with a substrate of CYP3A4.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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J P PHILLIPS  
11/13/2013

DAVID L KETTL  
11/13/2013

TATIANA OUSSOVA  
11/13/2013

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA/BLA # 204153  
Product Name: Luzu (luliconazole) cream, 1%

---

PMR/PMC Description: 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 interdigital tinea pedis.

---

PMR/PMC Schedule Milestones: Final Protocol Submission: 03/31/2014  
Study/Trial Completion: 04/30/2015  
Final Report Submission: 12/31/2015  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In vitro inhibition studies suggest a potential for in vivo drug interaction. Based on guidance for industry Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (draft, 2012), an in vivo drug interaction study should be conducted to determine whether there is an in vivo interaction.

This theoretical concern is not sufficient to preclude approving the drug product if it is otherwise approvable. The product label will include text to note the potential drug interaction. This language can be removed if the in vivo trial shows there is no interaction. If the in vivo trial results show that there is an interaction with CYP2C19 substrates, appropriate labeling (e.g., avoid concomitant use with CYP2C19 substrates) could be added.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In vitro inhibition studies suggest a potential for in vivo drug interaction. Concomitant administration with a substrate of CYP2C19 (e.g., diazepam) may increase the exposure of the concomitantly administered drug and lead to adverse effects. Concomitant administration with a prodrug that is converted to active metabolite by CYP2C19 (e.g., clopidogrel) may lead to decreased exposure of the active metabolite and lead to reduced efficacy of the concomitantly administered drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Drug interaction trial with a substrate of CYP2C19.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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TATIANA OUSSOVA  
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The goal of the maximal use pharmacokinetic study in pediatric subjects is to evaluate the safety of luliconazole in the pediatric population 12 years and older. Use of luliconazole cream, 1% maybe indicated in subjects 12 year or older for interdigital tinea pedis and tinea cruris.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A pharmacokinetic safety study in children and adolescents.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 204153  
Product Name: LUZU (luliconazole) Cream, 1%

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PMR/PMC Description: Conduct a multi-center, randomized, blinded, vehicle-controlled study, including pharmacokinetic assessments with luliconazole cream 1% for the treatment of tinea corporis in pediatric patients 2 years of age and older.

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PMR/PMC Schedule Milestones: Final Protocol Submission: 01/31/2014  
Study/Trial Completion: 11/30/2016  
Final Report Submission: 04/30/2017  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is insufficient safety database for adolescent populations down to the age of 2 years in the tinea corporis population. A complete vehicle-controlled study, including pharmacokinetic assessments, is being requested for treatment of tinea corporis subjects down to 2 years of age.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is to demonstrate safety, efficacy, and pharmacokinetic assessment of luliconazole cream, 1% in pediatric patients 2 years to 17 years, 11 months for the indication of tinea corporis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A multi-centered clinical trial for safety, efficacy, and pharmacokinetics in children

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
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- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
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- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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J P PHILLIPS  
11/13/2013

DAVID L KETTL  
11/13/2013

TATIANA OUSSOVA  
11/13/2013

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY ADDENDUM**

**DATE:** November 8, 2013

**TO:** Cristina Attinello, Regulatory Project Manager  
J. Paul Phillips, Regulatory Project Manager  
Gary Chiang, M.D., Medical Officer  
David Kettl, M.D., Medical Team Leader  
Division of Dermatologic and Dental Products

**FROM:** Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 204153

**APPLICANT:** Medicis Pharmaceutical Corporation

**DRUG:** 33525 Cream, Luliconazole Cream, 1% (Luzu<sup>®</sup>)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Treatment of interdigital tinea pedis, tinea cruris, and tinea corporis in male or female subjects, (b) (4) years of age or older.

CONSULTATION REQUEST DATE:	February 7, 2013
CLINICAL INSPECTION SUMMARY DATE:	August 9, 2013
DIVISION ACTION GOAL DATE:	November 27, 2013
PDUFA DATE:	December 11, 2013

## **I. BACKGROUND:**

The Applicant submitted this NDA to support the use of luliconazole cream for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis in male or female subjects, <sup>(b)</sup><sub>(4)</sub> years of age or older.

The pivotal studies (Protocols MP-1000-01 entitled “A Randomized, Multi-Center, Double-Blind, Vehicle-Controlled Study Evaluating the Efficacy and Safety of Product 33525 in Subjects with Tinea Cruris” and MP-1000-02 entitled “A Randomized, Multi-Center, Double-Blind, Vehicle-Controlled Study Evaluating the Efficacy and Safety of Product 33525 in Subjects with Tinea Pedis” were inspected in support of the indication. The clinical sites of Drs. Barba, Pollak, and Roman-Miranda were selected for inspection based on enrollment numbers, dates of previous inspections, and the sites’ contributions to the overall treatment effect.

This addendum is issued in follow up to the August 6, 2013, Clinical Inspection Summary (CIS) because a delay in the inspection of Dr. Roman-Miranda’s site did not permit for a review of the establishment inspection report (EIR) and a final classification of the inspection. This inspection has now been completed, the EIR has been reviewed, and the letter has been signed in DARRTS.

For ease of review, the RESULTS table from the original August 6, 2013, CIS is updated here with information relevant to the inspection of Dr. Roman-Miranda.

**II. RESULTS (by Site):**

Name of CI, Location	Protocol #/ Site #/ # of Subjects (mITT)	Inspection Dates	Final Classification
Alicia Barba, MD International Dermatology Research, Inc. 8370 W. Flagler, Suite 200 Miami, FL 33144	MP-1000-01/ Site #02/ 15	Jun 2013	NAI
Richard Pollak, DPM, MS Endeavor Clinical Trials, PA 8042 Wurzbach, Suite 420 San Antonio, TX 78229	MP-1000-02/ Site #11/ 19	11-13 Jun 2013	NAI
Amaury Roman-Miranda, MD Advanced Medical Concepts, PSC 4 Baldorioty Street Cidra, PR 00739	MP-1000-01/ Site #14/ 24	14-20 Aug 2013	NAI
Amaury Roman-Miranda, MD Advanced Medical Concepts, PSC 4 Baldorioty Street Cidra, PR 00739	MP-1000-02/ Site #10/ 36	14-20 Aug 2013.	NAI
Medicis Pharmaceutical Corp. 7720 N. Dobson Road Scottsdale, AZ 85256-2740	MP-1000-01 and MP-1000-02	13-17 May 2013	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

Amaury Roman-Miranda, MD  
Advanced Medical Concepts, PSC  
4 Baldorioty Street  
Cidra, PR 00739

**a. What was inspected:** At this site for Protocol MP-1000-01, 65 subjects were screened, 50 subjects were enrolled, and 43 subjects completed the study. For Protocol MP-1000-02, 75 subjects were screened, 66 subjects were enrolled, and 59 subjects completed the study. The records of all subjects in Protocol MP-1000-01 and 33 subjects in Protocol MP-1000-02 were audited. All subjects in Protocol MP-1000-01 signed informed consent forms prior to screening. The 33 subjects whose records were reviewed for Protocol MP-1000-02 also signed consent forms. Records reviewed for both protocols included, but were not limited to, source documents, case report forms (CRFs), eligibility criteria, screening and randomization procedures, laboratory data, concomitant medications, test article storage and accountability, adverse event reporting, protocol deviations, and IRB correspondence.

**b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data submitted by this site appear acceptable in support of the respective indication.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Barba, Pollak, and Roman-Miranda as well as the sponsor, Medicis, were inspected in support of this NDA. These clinical investigators and the sponsor were not issued Form FDA 483s and the final classification for these inspections is No Action Indicated (NAI). Data generated by these three clinical sites and submitted by the sponsor appear adequate in support of the respective indication

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROY A BLAY  
11/08/2013

JANICE K POHLMAN  
11/08/2013

KASSA AYALEW  
11/08/2013

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

<b>Product Title</b>	<b>LUZU (Iuliconazole) Cream, 1% for topical use</b>
Applicant	Medics Pharmaceutical Corp
Application/Supplement Number	NDA 204153
Type of Application	Original Submission
Indication(s)	for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms <i>Trichophyton rubrum</i> and <i>Epidermophyton floccosum</i> , in patients 18 years of age and older
Established Pharmacologic Class <sup>1</sup>	azole antifungal
Office/Division	ODE III/DDDP
Division Project Manager	J. Paul Phillips
Date FDA Received Application	December 11, 2012
Goal Date	December 11, 2013
Date PI Received by SEALD	October 1, 2013
SEALD Review Date	October 3, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

# Selected Requirements of Prescribing Information

## Highlights (HL)

### GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:** Top margin is greater than 1/2 inch.

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*

## Selected Requirements of Prescribing Information

• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

**Comment:**

#### Highlights Limitation Statement

**NO**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: **"These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)."**

**Comment:** *In the HL Limitation Statement, insert the name of the drug product "LUZU" instead of "LUZU (luliconazole) Cream, 1%."*

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

**YES**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement **"Initial U.S. Approval:"** followed by the **4-digit year**.

**Comment:**

#### Boxed Warning

**N/A**

12. All text must be **bolded**.

**Comment:**

**N/A**

13. Must have a centered heading in UPPER-CASE, containing the word **"WARNING"** (even if more than one Warning, the term, **"WARNING"** and not **"WARNINGS"** should be used) and other words to identify the subject of the Warning (e.g., **"WARNING: SERIOUS INFECTIONS"**).

## Selected Requirements of Prescribing Information

### Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

### Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

### Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

### Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

### Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

### Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

### Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

### Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

### Comment:

**N/A**

## Selected Requirements of Prescribing Information

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *If approve in October, revision date must read "10/2013" not "XX/2013".*

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

## Selected Requirements of Prescribing Information

- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”  
Comment:

### Full Prescribing Information (FPI)

#### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>

## Selected Requirements of Prescribing Information

12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- NO** 39. 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 PI upon approval.

**Comment:** *The FDA-approved patient labeling (Patient Information) does not appear at the end of the PI. All patient labeling must appear at the end of the PI upon approval.*

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

**Comment:**

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

**Comment:**

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

## Selected Requirements of Prescribing Information

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### **Patient Counseling Information**

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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/s/  
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JEANNE M DELASKO  
10/03/2013

LAURIE B BURKE  
10/03/2013

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** August 6, 2013

**TO:** Cristina Attinello, Regulatory Project Manager  
J. Paul Phillips, Regulatory Project Manager  
Gary Chiang, M.D., Medical Officer  
David Kettl, M.D., Medical Team Leader  
Division of Dermatologic and Dental Products

**FROM:** Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
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Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 204153

**APPLICANT:** Medicis Pharmaceutical Corporation

**DRUG:** 33525 Cream, Luliconazole Cream, 1% (Luzu<sup>®</sup>)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Treatment of interdigital tinea pedis, tinea cruris, and tinea corporis in male or female subjects, (b) (4) years of age or older.

CONSULTATION REQUEST DATE:	February 7, 2013
CLINICAL INSPECTION SUMMARY DATE:	August 9, 2013
DIVISION ACTION GOAL DATE:	November 27, 2013
PDUFA DATE:	December 11, 2013

## **I. BACKGROUND:**

The Applicant submitted this NDA to support the use of luliconazole cream for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis in male or female subjects, <sup>(b)</sup><sub>(4)</sub> years of age or older.

The pivotal studies (Protocols MP-1000-01 entitled “A Randomized, Multi-Center, Double-Blind, Vehicle-Controlled Study Evaluating the Efficacy and Safety of Product 33525 in Subjects with Tinea Cruris” and MP-1000-02 entitled “A Randomized, Multi-Center, Double-Blind, Vehicle-Controlled Study Evaluating the Efficacy and Safety of Product 33525 in Subjects with Tinea Pedis” were inspected in support of the indication.

Protocol MP-1000-01 was a multi-center, double-blind, parallel-group, vehicle-controlled study of luliconazole in male and female subjects 12 years of age or older with tinea cruris treated with either luliconazole or vehicle cream for one week with both treatment groups followed through Day 28. The primary endpoint was the proportion of subjects who achieved complete clearance at Day 28.

Protocol MP-1000-02 was a multi-center, double-blind, parallel-group, vehicle-controlled study of luliconazole in male and female subjects 12 years or older with tinea pedis treated with either luliconazole cream 1% or vehicle cream for two weeks with both treatment groups followed for a 28-day post-treatment period. The primary endpoint was the proportion of subjects who achieved complete clearance at Day 42.

The clinical sites of Drs. Barba, Pollak, and Roman-Miranda were selected for inspection based on enrollment numbers, dates of previous inspections, and the sites’ contributions to the overall treatment effect.

**II. RESULTS (by Site):**

<b>Name of CI, Location</b>	<b>Protocol #/ Site #/ # of Subjects (mITT)</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Alicia Barba, MD International Dermatology Research, Inc. 8370 W. Flagler, Suite 200 Miami, FL 33144	MP-1000-01/ Site #02/ 15	Jun 2013	NAI Pending final classification.
Richard Pollak, DPM, MS Endeavor Clinical Trials, PA 8042 Wurzbach, Suite 420 San Antonio, TX 78229	MP-1000-02/ Site #11/ 19	11-13 Jun 2013	NAI Pending final classification.
Amaury Roman-Miranda, MD Advanced Medical Concepts, PSC 4 Baldorioty Street Cidra, PR 00739	MP-1000-01/ Site #14/ 24	Inspection pending. Investigator not available.	Pending final classification.
Amaury Roman-Miranda, MD Advanced Medical Concepts, PSC 4 Baldorioty Street Cidra, PR 00739	MP-1000-02/ Site #10/ 36	Inspection pending. Investigator not available.	Pending final classification.
Medicis Pharmaceutical Corp. 7720 N. Dobson Road Scottsdale, AZ 85256-2740	MP-1000-01 and MP-1000-02	13-17 May 2013	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

**1. Alicia Barba, MD**

International Dermatology Research, Inc.

8370 W. Flagler, Suite 200

Miami, FL 33144

- a. What was inspected:** At this site for Protocol MP-1000-01, 23 subjects were screened, 22 subjects were randomized, and 15 subjects completed the study. An audit of the study records for all 23 subjects was conducted. The primary endpoint was verified and no protocol deviations were observed.
- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

2. Richard Pollak, DPM, MS  
Endeavor Clinical Trials, PA  
8042 Wurzbach, Suite 420  
San Antonio, TX 78229

- a. **What was inspected:** At this site for Protocol MP-1000-02, 26 subjects were screened and enrolled, and 22 subjects completed the study. An audit of the study records of all subjects screened and/or randomized to the study was conducted. Informed consent forms were signed by all study subjects. Source documentation was compared with the line listings. Records reviewed included, but were not limited to, the primary endpoint, scoring assessments, adverse events, concomitant medications, test article accountability, and sponsor and monitor communications.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Amaury Roman-Miranda, MD  
Advanced Medical Concepts, PSC  
4 Baldorioty Street  
Cidra, PR 00739

**Inspection pending.**

4. Medicis Pharmaceutical Corp.  
7720 N. Dobson Road  
Scottsdale, AZ 85256-2740

- a. **What was inspected:** The inspection audited Protocols MP-1000-01 and MP-1000-02 and focused on Drs. Alicia Barba and Richard Pollak (The inspection of Dr. Amaury Roman-Miranda is pending.) The inspection reviewed, but was not limited to, the following: clinical site selection, protocol deviations, sponsor monitoring communications, investigator training, investigator's brochure, adverse event reporting, annual reports, record retention, and test article accountability.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Barba and Pollak were inspected in support of this NDA. These clinical investigators were not issued Form FDA 483s and the preliminary classifications are No Action Indicated (NAI). Data generated by these two clinical sites and submitted by the sponsor appear adequate in support of the respective indication. However, the final Establishment Inspection Reports (EIRs) have not been received by OSI. Should the classifications of these inspections change upon review of the EIRs, an inspection summary addendum will be issued to DDDP.

The inspection of Dr. Roman-Miranda has been delayed and is pending. This inspection is scheduled to be conducted in mid-August. An inspection summary addendum will be issued to DDDP as soon as the EIR can be reviewed.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.  
Team Leader  
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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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ROY A BLAY  
08/08/2013

JANICE K POHLMAN  
08/08/2013

KASSA AYALEW  
08/08/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: August 1, 2013

Reviewer: Carlos M Mena-Grillasca, RPh, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, MS, PharmD  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Luzu (Luliconazole) Cream, 1%

Application Type/Number: NDA 204153

Applicant/sponsor: Medicis Pharmaceuticals Corporation

OSE RCM #: 2013-132

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Luzu (Luliconazole) Cream NDA 204153 for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

Luzu (Luliconazole) Cream, 1% (NDA 204153) is currently under review. The proposed proprietary name Luzu was found conditionally acceptable in OSE review 2013-182.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the December 11, 2012 submission.

- Active Ingredient: Luliconazole
- Indication of Use: Treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum*, (b) (4), or *Epidermophyton Floccosum*, in patients 18 years of age and older.
- Route of Administration: Topical
- Dosage Form: Cream
- Strength: 1 %
- Dose and frequency:
  - Tinea pedis: Once daily application for 2 weeks
  - Tinea cruris and Tinea corporis: Once daily application for 1 week
- How Supplied: 2 gram tubes (physician samples), 30 and 60 gram tubes.
- Storage: 15-30°C (59-86°F)
- Container and Closure Systems: Aluminum tube and (b) (4) cap.

## 2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Luzu container labels, carton and package insert labeling submitted by the Applicant.

### 2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

---

<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels and Carton Labeling submitted December 12, 2012 (Appendix A and B)
- Insert Labeling submitted December 12, 2012

### **3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT**

Luzu (Luliconazole) is a new molecular entity (NME) of the azole class of antifungals. However, other drugs in the same class are available for the same indications. The Applicant is proposing to market Luzu in 30 g and 60 g tubes. The proposed packaging configurations are in line with other prescription medications approved for the treatment of tinea (e.g. Naftin cream is available in 45 g and 90 g tubes; Econazole nitrate cream is available in 15 g, 30 g, and 85 g tubes; Lotrisone cream is available in 15 g and 45 g tubes; Exelderm cream is available in 15 g, 30 g and 60 g tubes). We note that there have been post-marketing medication errors of accidental ingestion of topical products packaged in tubes due to patients mistaking the drug for toothpaste. Therefore we will provide comments to increase the prominence and relocate the route of administration statement to the principal display panel.

We reviewed the container labels and carton labeling and noted that the established name does not appear to be ½ the size of the proprietary name. In addition, the use of fanciful graphics is distracting and more prominent than more relevant information on the labels.

### **5 RECOMMENDATIONS**

#### **5.1 Comments to the Review Division**

DMEPA provides the following comments for consideration by the Review Division prior to approval of this NDA.

##### **A. Prescribing Information (PI) – Dosage and Administration Section Patient Information (PPI) – How should I use Luzu Cream Section**

The current presentation of the dosing information in a paragraph format makes it difficult to differentiate the 2 different dosing scenarios for the proposed indications. We recommend that the dosing be presented in bulleted format. For example:

- For Interdigital Tinea Pedis: Apply a thin film to the affected and immediate surrounding skin area(s) once a day for two weeks.
- For Tinea Cruris and Tinea Corporis: Apply a thin film to the affected and immediate surrounding skin area(s) once a day for one week.

#### **5.2 Comments to the Applicant**

DMEPA recommends the following be implemented prior to approval of this Application.

##### **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**

If you have further questions or need clarifications, please contact Janet Anderson, project manager, at 301-796-0675.

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CARLOS M MENA-GRILLASCA  
08/01/2013

LUBNA A MERCHANT  
08/01/2013

SCOTT M DALLAS  
08/01/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** July 18, 2013

**To:** J. Paul Phillips, MS, Regulatory Project Manager  
Division of Dermatology and Dental Products (DDDP)

**From:** Kemi Asante, PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 204153 – Luzu (Iuliconazole) Cream, 1%

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As requested in DDDP's consult dated February 11, 2013, OPDP has reviewed the Luzu Package Insert (PI), Carton and Container Labeling and Patient Package Insert (PPI).

Please note that comments on the PPI were provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP) on July 18, 2013.

OPDP has no comments on the substantially complete versions of the PI and Carton and Container Labeling provided to OPDP on July 10, 2013, via access to the DDDP eRoom.

Thank you for your consult. If you have any questions please contact me at 301-796-7425 or at [Kemi.Asante@fda.hhs.gov](mailto:Kemi.Asante@fda.hhs.gov).

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OLUWASEUN A ASANTE  
07/18/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: July 17, 2013

To: Susan Walker, MD  
Director  
**Division of Dermatology and Dental Products (DDDP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Karen Dowdy, RN, BSN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Kemi Asante, Pharm. D.  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): LUZU (luliconazole)

Dosage Form and Route: Cream, 1%, For topical use

Application Type/Number: NDA 204-153

Applicant: Medicis Pharmaceutical Corporation

## 1 INTRODUCTION

On December 11, 2012, Medicis Pharmaceutical Corporation submitted for the Agency's review a New Drug Application (NDA) 204-153 for LUZU (luliconazole) Cream, with the proposed indication for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum*, (b) (4) or *Epidermophyton floccosum*, in patients 18 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on February 11, 2013, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LUZU (luliconazole) Cream.

## 2 MATERIAL REVIEWED

- Draft LUZU (luliconazole) Cream PPI received on December 11, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on July 10, 2013.
- Draft LUZU (luliconazole) Cream PPI received on February 11, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on July 10, 2013.
- Draft LUZU (luliconazole) Cream Prescribing Information (PI) received on December 11, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on July 10, 2013.
- Draft LUZU (luliconazole) Cream Prescribing Information (PI) received on February 11, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on July 10, 2013.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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KAREN M DOWDY  
07/18/2013

OLUWASEUN A ASANTE  
07/18/2013

LASHAWN M GRIFFITHS  
07/18/2013

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>NDA</b>	204153
<b>Brand Name</b>	Luzu (luliconazole) Cream, 1%
<b>Sponsor</b>	Medicis Pharmaceutical Corp
<b>Indication</b>	Topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by <i>Trichophyton rubrum</i> , (b) (4) or <i>Epidermophyton floccosum</i> , in patients 18 years of age and older.
<b>Dosage Form</b>	Topical cream
<b>Drug Class</b>	imidazole antimycotic drug
<b>Therapeutic Dosing Regimen</b>	Luliconazole cream 1%
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Cream 1% 5 g
<b>Submission Number and Date</b>	SDN 001 11 Dec 2012
<b>Review Division</b>	DDDP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

## 1 SUMMARY

### 1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of luliconazole Cream 1% (2g and 10 g) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between luliconazole Cream 1% (2g and 10 g) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcI}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, double-blind, comparative, placebo and active controlled 4-way crossover thorough QT/QTc study, 51 healthy subjects received luliconazole Cream 1% 2 g, luliconazole Cream 1% 10 g, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Luliconazole Cream 1% (2g and 10 g) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
Luliconazole Cream 1% 2g	3.5	2.2	(-0.1, 4.4)
Luliconazole Cream 1% 10g	14	1.8	(-0.5, 4.1)
Moxifloxacin 400 mg*	3	12.8	(9.8, 15.9)

\* Multiple endpoint adjustment of 3 time points was applied.

The suprathereapeutic dose (luliconazole cream 1% 10 g) produces mean  $C_{max}$  values 4.0-fold higher than the mean  $C_{max}$  for the therapeutic dose (luliconazole cream 1% 2 g). At these concentrations there was no relationship between luliconazole concentration and QTc. The Applicant also conducted a maximal use pharmacokinetic trial (MP-1007) in patients with tinea pedis and tinea cruris. In this study, the  $C_{max}$  in patients with tinea cruris was approximately 4.6-fold that of suprathereapeutic dose in the TQT study (7.4 ng/mL vs. 1.61 ng/mL). Study MP-1007 included many components of a thorough QT assessment (triplicate ECGs, central reading, adequate ECG collection times) and therefore is useful to better characterize the potential QT effect of luliconazole at higher exposures. It did not include a placebo or positive control, however, and can not be used by itself to exclude small changes in QT of about 10 ms. The results of study MP-1007 are consistent with those of the TQT study (MP-1000-08) and suggest that luliconazole is not associated with QT prolongation.

## 2 PROPOSED LABEL

### 2.1 SPONSOR'S PROPOSED LABEL

#### 12.2 Pharmacodynamics

(b) (4)

### 2.2 QT-IRT'S PROPOSED LABEL

(b) (4)

At therapeutic doses, Luzu Cream does not prolong QTc to any clinically relevant extent.

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

Luliconazole is an antifungal agent.

### **3.2 MARKET APPROVAL STATUS**

Luliconazole is approved for marketing in Japan (and perhaps elsewhere).

### **3.3 PRECLINICAL INFORMATION**

There was no effect of luliconazole on hERG currents at concentrations >100-fold the expected human exposure. There were no effects on luliconazole on the ECG in anesthetized dogs.

### **3.4 PREVIOUS CLINICAL EXPERIENCE**

Among around 200 subjects exposed in clinical trials there were few adverse reactions of any kind, and nothing indicative of proarrhythmic risk.

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 7.1 summarizes the key features of luliconazole's clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND 76049. The sponsor submitted the TQT study report MP-1000-08 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

### **4.2 TQT STUDY**

#### **4.2.1 Title**

A Randomized, Double-Blinded, Placebo and Positive Controlled, Four-Group Crossover Study to Evaluate the Effect of 33525 Cream at a Projected Therapeutic and Supra-Therapeutic Dose on Cardiac Repolarization in Healthy Male and Female Subjects.

#### **4.2.2 Protocol Number**

MP-1000-08 (R12-0052)

#### **4.2.3 Study Dates**

22 April 2012 -- 19 June 2012

#### **4.2.4 Objectives**

The primary objectives of the study were:

- To assess the effect of two dose regimens of topical Luliconazole Cream 1% (therapeutic and supra-therapeutic) versus Vehicle Cream on QT interval duration corrected for heart rate (QTc), and electrocardiogram (ECG) morphology in healthy subjects.
- This comparison was made by evaluating the change from the period-specific predose baseline using the QT interval duration corrected for heart rate by the individual subject-specific correction formula (QTcI), and electrocardiographic morphology.

- To validate the study sensitivity by inclusion of a positive control treatment, Moxifloxacin.

The secondary objectives of this study were:

- To evaluate the pharmaco-dynamic (PD) relationship between the duration of the QT/QTc intervals and the plasma concentration of luliconazole.
- To evaluate the change from the period-specific pre-dose baseline of QT duration corrected by the Fridericia (QTcF) and the Bazett (QTcB) methods.
- To provide additional safety information.

## **4.2.5 Study Description**

### **4.2.5.1 Design**

This was a single center, randomized, double-blind, comparative, placebo and active controlled 4-way crossover thorough QT/QTc study. There were seven dosing days in each of the four crossover periods and a wash-out period of at least five days between treatment periods.

### **4.2.5.2 Controls**

The Sponsor used both placebo and positive (moxifloxacin) controls.

### **4.2.5.3 Blinding**

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were over-encapsulated.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

Group	Description
<b>A</b> <b>(Therapeutic Dose)</b>	2 grams of Luliconazole Cream 1% applied once daily for seven days (1 gram to the right back and 1 gram to the right groin), 8 grams of Vehicle Cream applied once daily for seven days (4 grams to the left back and 4 grams to the left groin) <b>plus</b> Oral Moxifloxacin placebo capsule once daily for seven days
<b>B</b> <b>(Supra-therapeutic Dose)</b>	10 grams of Luliconazole Cream 1% applied once daily for seven days (1 gram to the right back, 1 gram to the right groin, 4 grams to the left back, and 4 grams to the left groin) <b>plus</b> Oral Moxifloxacin placebo capsule once daily for seven days
<b>C</b> <b>(Positive Control Group)</b>	10 grams of Vehicle Cream applied once daily for seven days (1 gram to the right back, 1 gram to the right groin, 4 grams to the left back, and 4 grams to the left groin) <b>plus</b> Oral Moxifloxacin placebo capsule once daily for six days and over-encapsulated Moxifloxacin 400 mg oral tablet on the seventh day
<b>D</b> <b>(Placebo Group)</b>	10 grams of Vehicle Cream applied once daily for seven days (1 gram to the right back, 1 gram to the right groin, 4 grams to the left back, and 4 grams to the left groin) <b>plus</b> Oral Moxifloxacin placebo capsule once daily for seven days

### 4.2.6.2 Sponsor's Justification for Doses

Based upon the results of an open-label, repeated-dose, maximal use study MP-1007 in patients with either tinea pedis or tinea cruris, this TQT study evaluated a supra-therapeutic dose of Luliconazole Cream 1% by applying it to a large skin surface area on the back and to the groin where absorption was shown to be greatest. In MP-1007 the mean daily exposure was approximately 3.5 grams per day corresponding to at least three times the proposed clinical dose. Recognizing that absorption tends to be higher when applied to diseased skin, the supra-therapeutic dose consisted of a total of 10 grams per day with 5 grams applied to the back and 5 grams to the groin.

*Reviewer's Comment: The suprathematic dose was not adequate because the dose used in the maximal use study in patients (MP-1007) resulted in exposures that were roughly 4.6-fold higher.*

### 4.2.6.3 Instructions with Regard to Meals

All activities and meal times remained the same on Day -1 Period 1, and on study Day 7 of each treatment period. The subjects remained fasting and at supine rest (with limited ambulation) for five hours from one hour pre-dose to four hours post-dose. A lunch was served and completed in 30 minutes from 4 to 4.5 hours post-dose. At least 1.5 hours

must have elapsed between completing the meal and the next ECG nominal time point at six hours post-dose. Consumption of grapefruit products was prohibited during this study.

*Reviewer's Comment: Acceptable. When applied topically, drug exposure is unlikely to be affected by food.*

#### **4.2.6.4 ECG and PK Assessments**

**ECG Assessments:** On Day +7 of each treatment period, Holter recorders were used to acquire the ECGs that were extracted in triplicate. The ECG data was done at prior to dosing (0 hours) and after dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, and 22.5 hours.

**PK Assessments:** On day +7 of each period, blood samples were obtained prior to dosing (0 hour) and after dose at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, and 22.5 hours. The PK blood samples on Day +7 were obtained immediately following the 10-minute ECG extraction time windows

*Reviewer's Comment: The ECG and PK sampling schedule is acceptable. The chosen time points are matched and covered the  $T_{max}$  (~3 hours), the time when the maximum plasma concentration of luliconazole was reached.*

#### **4.2.6.5 Baseline**

Pre-dose ECG at Day 1 were used as baseline for each treatment period.

#### **4.2.7 ECG Collection**

Twelve-lead Holter monitoring was used to obtain digital ECGs. Subjects were supine around nominal time points for ECG samples.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

Fifty-six healthy, non-obese subjects (approximately half males) were enrolled and 48 completed all crossover periods.

##### **4.2.8.2 Statistical Analyses**

###### ***4.2.8.2.1 Primary Analysis***

No changes in QTcI were observed after seven days of topical application of the therapeutic dose (2 grams) or the supra-therapeutic dose (10 grams) of Luliconazole Cream 1% to healthy subjects. Table 11.4.1 is a summary of the results of the primary analysis and Figure 11.4.1 is a graphic representation of the same data. The largest 95% UCB on the mean differences from Vehicle Cream are 3.95 msec at 3.5 hours after the last application of the 2 gram dose and 3.87 msec at 14 hours after the last application of the 10 gram dose. Both values are below 10 msec and therefore, the primary hypothesis is rejected and the study is negative for QT interval prolongation.

**Table 2: Mean Difference from Day 1 Pre-dose Baseline in QTcI for Each Luliconazole Cream 1% Dose and Vehicle Cream and 95% UCB on the Mean Difference from Vehicle Cream (ms) (Sponsor's Results)**

Hours Post Dose	Vehicle Cream (Treatment D)		Luliconazole Cream 1% 2 grams (Treatment A)		Luliconazole Cream 1% 10 grams (Treatment B)		2 grams minus Vehicle Cream Treatment A minus Treatment D)		10 grams minus Vehicle Cream (Treatment B minus Treatment D)	
	n	mean	n	mean	N	mean	mean	95% UCB	mean	95% UCB
0.5	51	- 6.35	49	- 4.81	51	- 5.49	1.54	3.79	0.86	3.09
1.0	51	- 3.55	49	- 3.20	51	- 3.27	0.35	2.60	0.28	2.51
1.5	51	- 1.89	49	- 1.58	51	- 1.89	0.30	2.55	- 0.00	2.23
2.0	51	- 0.40	50	- 0.52	51	- 1.45	- 0.12	2.11	- 1.05	1.17
3.0	51	- 1.69	49	- 1.30	51	- 0.58	0.40	2.65	1.11	3.34
3.5	51	- 1.41	49	0.30	51	0.01	1.70	3.95	1.41	3.64
6.0	51	- 3.18	49	- 3.63	51	- 3.18	- 0.45	1.80	0.00	2.23
8.0	51	- 5.02	50	- 4.43	51	- 4.43	0.59	2.83	0.59	2.81
12.0	51	- 2.33	50	- 2.73	51	- 2.42	- 0.40	1.84	- 0.09	2.14
14.0	50	- 1.58	50	- 0.16	51	0.05	1.42	3.67	1.63	3.87
22.5	50	- 4.64	49	- 4.73	49	- 5.04	- 0.08	2.18	- 0.40	1.86

Source: CSR Table 11.4.1

Reviewer's Comments: FDA reviewer's results are similar to the sponsor's; the reviewer's analysis is in section 5.2.

#### 4.2.8.2.2 Assay Sensitivity

The study was sufficiently sensitive to detect an effect of luliconazole. Lower confidence bounds at 2, 3, and 3.5 hours after 400 mg of Moxifloxacin exceeded 5 msec (see Table 11.4.5). Figure 11.4.2 shows the effect of Moxifloxacin over the complete time course of 22.5 hours with peak changes occurring between two and four hours which is the approximate time at which maximum concentrations of moxifloxacin are typically reached. To assess the impact of this potential carryover effect, three post hoc sensitivity analyses were performed.

**Table 3: Mean Differences from Day 1 Pre-dose Baseline in QTcI for Moxifloxacin and Vehicle Cream and 98.33% LCB on the Mean Differences from Vehicle Cream (ms) (Sponsor's Results)**

Hours post Dose	Vehicle Cream (Treatment D)		Moxifloxacin (Treatment C)		Moxifloxacin minus Vehicle Cream (Treatment C minus Treatment D)	
	n	mean	n	mean	mean	98.33% LCB
2	51	-0.40	50	11.31	11.7	8.81
3	51	-1.69	50	11.31	13.0	10.11
3.5	51	-1.41	50	10.20	11.6	8.71

Source: CSR Table 11.4.2

Reviewer's Comments: FDA reviewer's results are similar to the sponsor's; the reviewer's analysis is in section 5.2.

#### 4.2.8.2.3 Categorical Analysis

Categorical analysis of QTc intervals showed no adverse change in cardiac intervals. Tables 22-30, Section 10, of the Cardiac Safety Report show the number of subjects with QTc intervals >450, 480, and 500 msec. One subject on Vehicle Cream, two subjects on the 2 gram dose, and two subjects on the 10 gram dose had one or more QTcI intervals >450 msec. One subject in each of the treatments segments had one or more QTcF intervals >450 and three subjects in each of the treatment sequences had a QTcB interval >450 msec. No subject had a QTc interval >480 msec. Therefore, there were no treatment-related categorical changes of clinical significance induced by Luliconazole Cream 1%.

Tables 31-36 of the Cardiac Safety Report are summaries of the numbers of subjects with increases from Day 1 pre-dose baseline in QTc >30 and >60 msec. One subject on Vehicle Cream and two subjects on the 2 gram dose has a single increase in QTcI >30 msec. One subject on the 2 gram dose had a single increase in QTcF >30 msec. Three subjects on Vehicle Cream and three subjects on the 2 gram dose had a single increase in QTcB >30 msec. No subject had an increase in QTcI or QTcF > 60 msec. One subject, Subject 52, had an increase in QTcB of 76 msec 14 hours after the 2 gram dose but at no other time point and not at any time point after the 10 gram dose.

No subject sustained an increase in the QRS interval >110 msec or 200 msec that was also a 25% increase from Day 1 predose baseline.

#### **4.2.8.3 Safety Analysis**

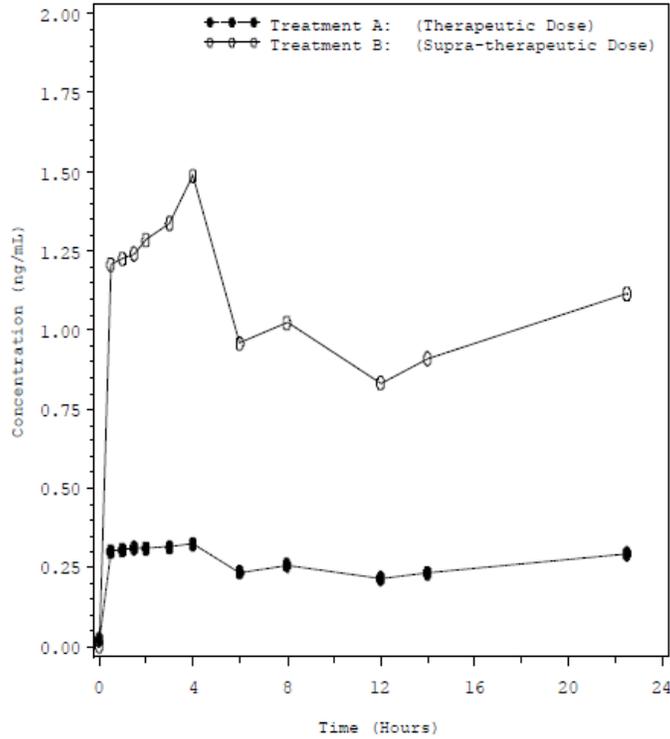
There were no cardiovascular adverse events of note.

#### **4.2.8.4 Clinical Pharmacology**

##### ***4.2.8.4.1 Pharmacokinetic Analysis***

The PK results are presented in Table 4 (luliconazole).  $C_{max}$  and AUC values in the thorough QT study were 4-fold higher following topical administration of luliconazole cream 1% 10 g compared with 2 g, the intended clinical dose.

**Figure 1: Mean Plasma Concentrations (0-24 hours) for Luliconazole**



Source: Figure 11.4.5 on page 60 of sponsor's report

**Table 4: Summary of Mean (%CV) Luliconazole Pharmacokinetic Parameters on Day 7**

Parameter	Treatment A: Therapeutic Dose Luliconazole Cream 1% (2 grams) (N=50)	Treatment B : Supra-therapeutic Dose Luliconazole Cream 1% (10 grams) (N=51)
AUC <sub>0-24</sub> (ng·h/mL)*	5.91 (62.8)	23.62 (68.9)
C <sub>max</sub> (ng/mL)	0.40 (62.0)	1.61 (73.9)
T <sub>max</sub> (h)**	3.17 (0.67 – 22.68)	3.67 (0.67 – 22.68)
C <sub>min</sub> (ng/mL)	0.18 (72.7)	0.77 (69.8)

\*As there was no 0 hr PK value collected on Day 7, the Day 1 Hour 0 values were used for the 0 hr PK.

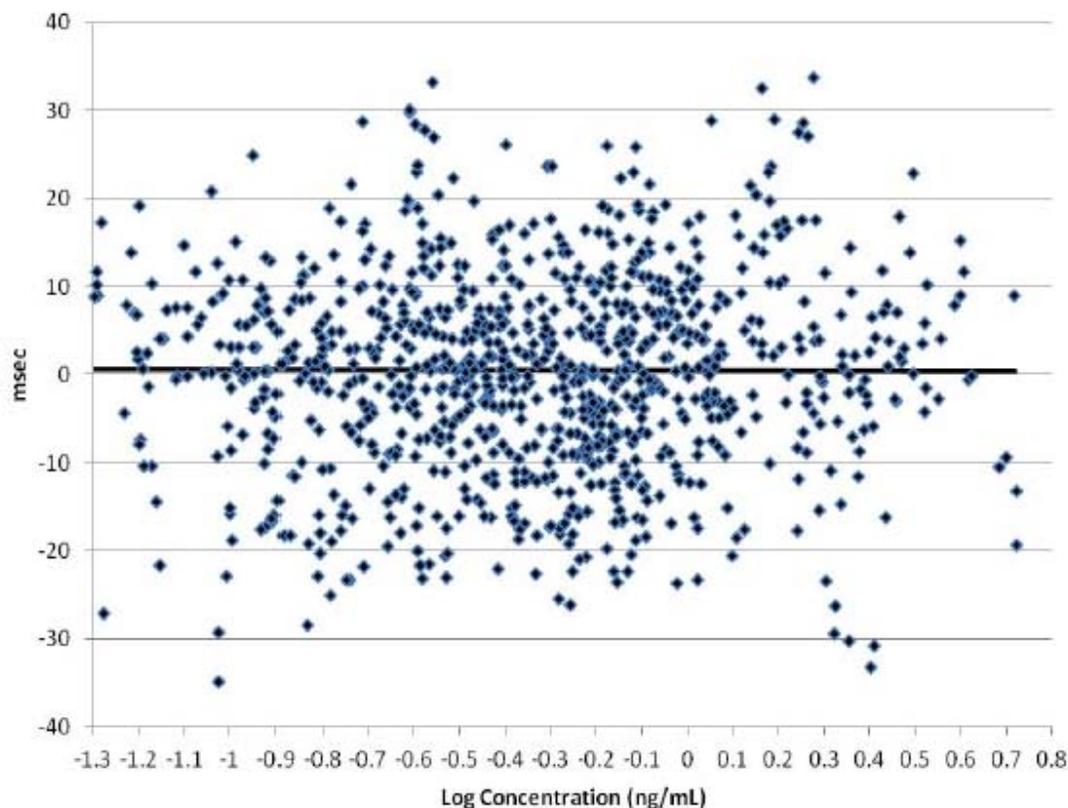
\*\*Median (range)

Source: Table 11.4.6 on page 60 of sponsor's report

#### 4.2.8.4.2 Exposure-Response Analysis

The relationship between  $\Delta\Delta\text{QTcI}$  and log luliconazole concentration is shown in Figure 2. No apparent trend was observed.

**Figure 2: Time-Matched Difference from Vehicle Cream in Changes from Day 1 Pre-dose Baseline in QTcI versus Log Luliconazole Cream 1% Concentration**



*Source: Figure 11.4.3 on page 58 of sponsor's report*

*Reviewer's Analysis: An independent exposure-response analysis was conducted by the reviewer. A plot of  $\Delta\Delta QTcI$  vs. luliconazole concentrations is presented in Figure 5.*

## **5 REVIEWERS' ASSESSMENT**

### **5.1 EVALUATION OF THE QT/RR CORRECTION METHOD**

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 5, it appears that QTcI had smaller absolute slopes than QTcF. Therefore, QTcI is a better correction method for the study data.

**Table 5: Comparison of QTcF and QTcI Using the Mixed Model**

Treatment Groups	Slope of QTcF	Slope of QTcI	diff_p_value
All	0.01490	0.00093	0.00000
Luliconazole Cream 1% 10g	0.01192	-.00674	0.00001
Luliconazole Cream 1% 2g	0.01139	-.00643	0.00018
Moxifloxacin	0.02356	0.00648	0.00006
Placebo	0.00808	0.00012	0.05573

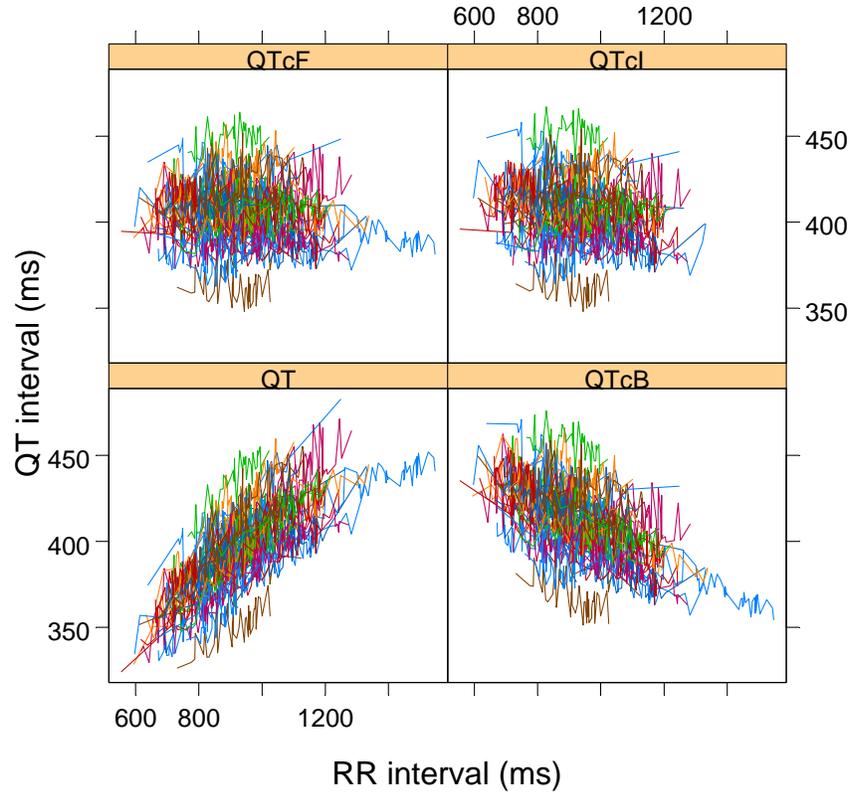
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it also appears that QTcI is the similar to QTcF. Since the sponsor chose QTcI, this statistical reviewer used QTcI for the primary statistical analysis.

**Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

method	Treatment									
	Luliconazole Cream 1% 10g		Luliconazole Cream 1% 2g		Moxifloxacin		Placebo		All	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	51	0.0047	50	0.0046	50	0.0042	51	0.0056	55	0.0047
QTcF	51	0.0012	50	0.0019	50	0.0038	51	0.0014	55	0.0012
QTcI	51	0.0014	50	0.0018	50	0.0025	51	0.0020	55	0.0013

The relationship between different correction methods and RR is presented in Figure 3:

**Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for Luliconazole

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcI effect. The model includes time point, sequence, and period as fixed effects and SUBJECT as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 7: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Treatment Group =  
Luliconazole 10g and 2g**

Time (hrs)	Luliconazole Cream 1% 10g				Luliconazole Cream 1% 2g			
	dQTcI	Placebo	ddQTcI		dQTcI	Placebo	ddQTcI	
	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-4.9	-5.8	0.9	(-1.3, 3.2)	-3.9	-5.8	1.9	(-0.4, 4.2)
1	-2.7	-3.0	0.3	(-2.0, 2.5)	-2.2	-3.0	0.8	(-1.5, 3.0)
1.5	-1.1	-1.2	0.1	(-2.3, 2.4)	-0.5	-1.2	0.7	(-1.7, 3.1)
2	-0.6	0.3	-0.9	(-3.2, 1.5)	0.7	0.3	0.4	(-1.9, 2.7)
3	0.2	-0.9	1.1	(-1.2, 3.5)	0.0	-0.9	1.0	(-1.4, 3.3)
3.5	0.9	-0.6	1.5	(-0.7, 3.7)	1.6	-0.6	2.2	(-0.1, 4.4)
6	-2.3	-2.4	0.1	(-2.4, 2.6)	-2.6	-2.4	-0.2	(-2.7, 2.3)
8	-3.5	-4.4	0.9	(-1.5, 3.4)	-3.1	-4.4	1.3	(-1.2, 3.7)
12	-1.6	-1.7	0.1	(-2.1, 2.4)	-1.8	-1.7	-0.1	(-2.3, 2.2)
14	0.7	-1.1	1.8	(-0.5, 4.1)	0.7	-1.1	1.7	(-0.5, 4.0)
22.5	-4.4	-4.3	-0.2	(-2.8, 2.5)	-4.1	-4.3	0.1	(-2.5, 2.8)

The largest upper bounds of the 2-sided 90% CI for the mean difference between Luliconazole 2g and placebo, and between Luliconazole 10g and placebo were 4.4 ms and 4.1 ms, respectively.

### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 8, The largest unadjusted 90% lower confidence interval is 9.8 ms after considering Bonferroni multiple endpoint adjustment of 3 time points, which indicates that an at least 5 ms QTcI effect of moxifloxacin can be detected from the study.

**Table 8: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Moxifloxacin**

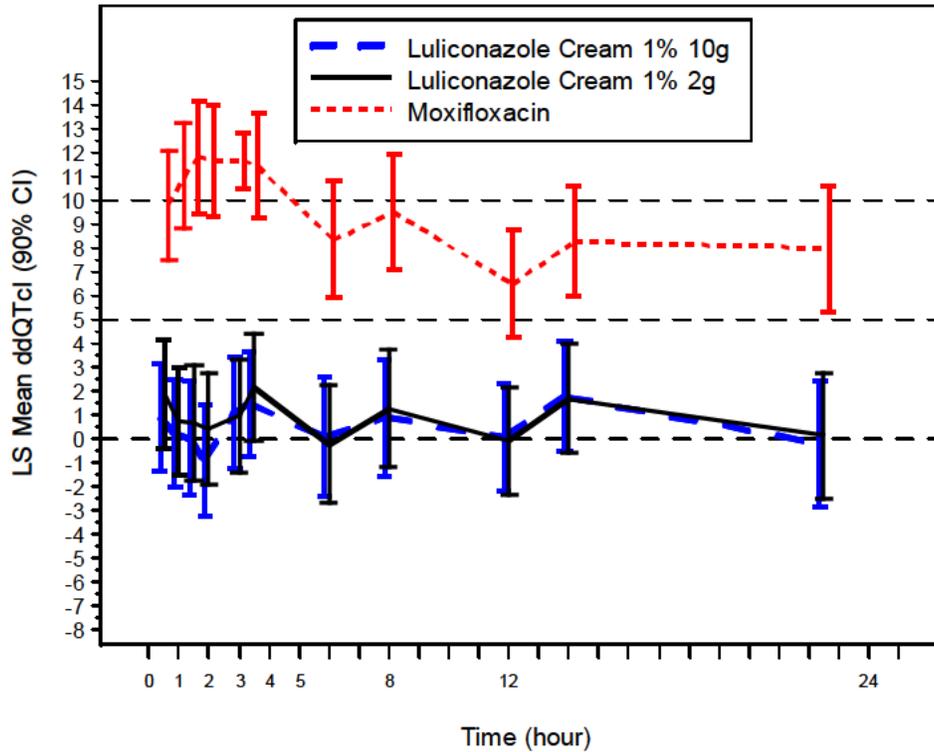
Time (hrs)	Moxifloxacin			
	dQTcI	Placebo	ddQTcI	
	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)*
0.5	4.0	-5.8	9.8	(6.9, 12.8)
1	8.1	-3.0	11.0	(8.2, 13.9)
1.5	10.6	-1.2	11.8	(8.7, 14.9)
2	12.0	0.3	11.7	(8.7, 14.7)
3	11.9	-0.9	12.8	(9.8, 15.9)
3.5	10.9	-0.6	11.5	(8.6, 14.3)
6	6.0	-2.4	8.4	(5.2, 11.6)
8	5.1	-4.4	9.5	(6.3, 12.7)
12	4.8	-1.7	6.5	(3.6, 9.4)
14	7.2	-1.1	8.3	(5.4, 11.3)
22.5	3.7	-4.3	8.0	(4.6, 11.4)

\* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcI for different treatment groups.

**Figure 4: Mean and 90% CI  $\Delta\Delta$ QTcI Timecourse**



(Note: CIs are all unadjusted including moxifloxacin)

#### 5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcI values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

**Table 9: Categorical Analysis for QTcI**

Treatment Group	Total N		Value $\leq 450$ ms		450 ms < Value $\leq 480$ ms		Value > 480	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Luliconazole Cream 1% 10g	51	559	49 (96.1%)	547 (97.9%)	2 (3.9%)	12 (2.1%)	0 (.%)	0 (0.0%)
Luliconazole Cream 1% 2g	50	543	48 (96.0%)	534 (98.3%)	2 (4.0%)	9 (1.7%)	0 (.%)	0 (0.0%)
Moxifloxacin	50	549	44 (88.0%)	519 (94.5%)	6 (12.0%)	30 (5.5%)	0 (.%)	0 (0.0%)
Placebo	51	559	50 (98.0%)	550 (98.4%)	1 (2.0%)	9 (1.6%)	0 (.%)	0 (0.0%)

Table 10 lists the categorical analysis results for  $\Delta$ QTcI. No subject's change from baseline was above 60 ms.

**Table 10: Categorical Analysis of  $\Delta$ QTcI**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms < Value $\leq$ 60 ms		Value > 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Luliconazole Cream 1% 10g	51	559	51 (100%)	559 (100%)	0 (0.0%)	0 (0.0%)	0 (.)	0 (0.0%)
Luliconazole Cream 1% 2g	50	543	48 (96.0%)	541 (99.6%)	2 (4.0%)	2 (0.4%)	0 (.)	0 (0.0%)
Moxifloxacin	50	549	47 (94.0%)	541 (98.5%)	3 (6.0%)	8 (1.5%)	0 (.)	0 (0.0%)
Placebo	51	559	50 (98.0%)	558 (99.8%)	1 (2.0%)	1 (0.2%)	0 (.)	0 (0.0%)

### 5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 11. The largest upper limits of 90% CI for the HR mean differences between luliconazole 2 g and placebo and luliconazole 10 g and placebo are both 2.3 bpm. No subject had HR > 100 bpm under either treatment.

**Table 11: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Treatment Group = Luliconazole**

Time (hrs)	Treatment Group							
	Luliconazole Cream 1% 10g				Luliconazole Cream 1% 2g			
	dHR	Placebo	ddHR		dHR	Placebo	ddHR	
LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)	
0.5	3.0	2.3	0.6	(-0.8, 2.1)	1.3	2.3	-1.1	(-2.5, 0.4)
1	1.9	2.1	-0.2	(-1.7, 1.3)	1.7	2.1	-0.5	(-2.0, 1.0)
1.5	1.6	0.9	0.8	(-0.7, 2.2)	1.5	0.9	0.7	(-0.8, 2.1)
2	1.7	1.3	0.4	(-1.2, 2.0)	1.7	1.3	0.3	(-1.2, 1.9)
3	2.2	1.7	0.5	(-1.1, 2.1)	2.3	1.7	0.6	(-1.1, 2.2)
3.5	3.0	2.7	0.3	(-1.4, 2.0)	2.5	2.7	-0.2	(-1.9, 1.5)
6	12.3	11.7	0.6	(-1.1, 2.3)	12.3	11.7	0.6	(-1.2, 2.3)
8	8.0	7.5	0.5	(-1.2, 2.2)	7.4	7.5	-0.0	(-1.7, 1.7)
12	8.0	9.1	-1.1	(-2.5, 0.2)	8.2	9.1	-0.9	(-2.2, 0.4)
14	3.7	4.7	-1.1	(-2.5, 0.3)	3.7	4.7	-1.0	(-2.4, 0.4)
22.5	4.7	6.6	-1.9	(-3.7, -0.1)	5.1	6.6	-1.5	(-3.3, 0.3)

**Table 12: Outliers of HR**

Treatment Group	Total N		Value $\leq$ 100 bpm		Value $>$ 100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Luliconazole Cream 1% 10g	51	559	51 (100%)	559 (100%)	0 (0.0%)	0 (0.0%)
Luliconazole Cream 1% 2g	50	543	50 (100%)	543 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin	50	549	50 (100%)	549 (100%)	0 (0.0%)	0 (0.0%)
Placebo	51	559	49 (96.1%)	557 (99.6%)	2 (3.9%)	2 (0.4%)

### 5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 13. The largest upper limits of 90% CI for the PR mean differences between luliconazole 2 g and placebo and luliconazole 10 g and placebo are 1.6 ms and 4.8 ms, respectively. There is one subject had PR  $>$ 200 ms in Luliconazole Cream 1% 2g group.

**Table 13: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Luliconazole**

	Treatment Group							
	Luliconazole Cream 1% 10g				Luliconazole Cream 1% 2g			
	dPR	Placebo	ddPR		dPR	Placebo	ddPR	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	1.9	1.9	0.0	(-1.9, 2.0)	0.0	1.9	-1.8	(-3.8, 0.1)
1	2.6	3.0	-0.5	(-2.6, 1.7)	0.2	3.0	-2.8	(-5.0, -0.7)
1.5	3.4	2.7	0.7	(-1.5, 2.9)	0.4	2.7	-2.4	(-4.6, -0.1)
2	1.8	2.5	-0.7	(-3.1, 1.7)	1.4	2.5	-1.1	(-3.6, 1.3)
3	1.0	2.4	-1.4	(-4.0, 1.1)	0.8	2.4	-1.6	(-4.1, 1.0)
3.5	2.5	1.1	1.4	(-0.9, 3.6)	0.5	1.1	-0.6	(-2.8, 1.6)
6	-2.7	-1.7	-1.0	(-3.2, 1.1)	-3.8	-1.7	-2.1	(-4.2, 0.1)
8	-4.1	-2.6	-1.6	(-4.1, 0.9)	-4.8	-2.6	-2.2	(-4.7, 0.3)
12	-0.4	-0.9	0.5	(-1.8, 2.9)	-2.3	-0.9	-1.4	(-3.8, 0.9)
14	3.3	0.7	2.6	(0.3, 4.8)	-0.2	0.7	-1.0	(-3.3, 1.3)
22.5	-0.5	0.4	-0.9	(-3.3, 1.6)	-1.0	0.4	-1.4	(-3.8, 1.0)

**Table 14: Outliers of PR**

Treatment Group	Total		Value $\leq$ 200 ms		Value $>$ 200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Luliconazole Cream 1% 10g	51	559	51 (100%)	559 (100%)	0 (0.0%)	0 (0.0%)
Luliconazole Cream 1% 2g	50	543	49 (98.0%)	541 (99.6%)	1 (2.0%)	2 (0.4%)
Moxifloxacin	50	549	50 (100%)	549 (100%)	0 (0.0%)	0 (0.0%)
Placebo	51	559	51 (100%)	559 (100%)	0 (0.0%)	0 (0.0%)

#### 5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 15. The largest upper limits of 90% CI for the QRS mean differences between luliconazole 2 g and placebo and luliconazole 10 g and placebo are 1.4 ms and 1.7 ms, respectively. There is one subject who experienced QRS interval greater than 110 ms in both luliconazole 2 g and luliconazole 10 g group.

**Table 15: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Luliconazole**

	Treatment Group							
	Luliconazole Cream 1% 10g				Luliconazole Cream 1% 2g			
	dQRS	Placebo	ddQRS		dQRS	Placebo	ddQRS	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	0.3	0.4	-0.1	(-1.1, 0.8)	0.8	0.4	0.3	(-0.6, 1.3)
1	0.5	0.3	0.2	(-0.8, 1.1)	0.2	0.3	-0.1	(-1.1, 0.9)
1.5	0.2	0.6	-0.4	(-1.4, 0.6)	0.2	0.6	-0.4	(-1.4, 0.5)
2	0.1	0.5	-0.4	(-1.3, 0.6)	0.3	0.5	-0.1	(-1.1, 0.8)
3	0.7	-0.0	0.8	(-0.2, 1.7)	-0.0	-0.0	-0.0	(-0.9, 0.9)
3.5	-0.3	-0.1	-0.1	(-1.1, 0.8)	-0.3	-0.1	-0.2	(-1.2, 0.8)
6	0.2	0.3	-0.1	(-1.1, 1.0)	0.5	0.3	0.1	(-0.9, 1.2)
8	-0.4	-0.6	0.2	(-0.8, 1.2)	-1.0	-0.6	-0.3	(-1.4, 0.7)
12	0.3	0.2	0.1	(-0.9, 1.1)	-0.5	0.2	-0.7	(-1.7, 0.3)
14	0.8	0.4	0.4	(-0.5, 1.3)	0.2	0.4	-0.2	(-1.1, 0.7)
22.5	0.7	0.1	0.6	(-0.5, 1.7)	0.5	0.1	0.4	(-0.7, 1.4)

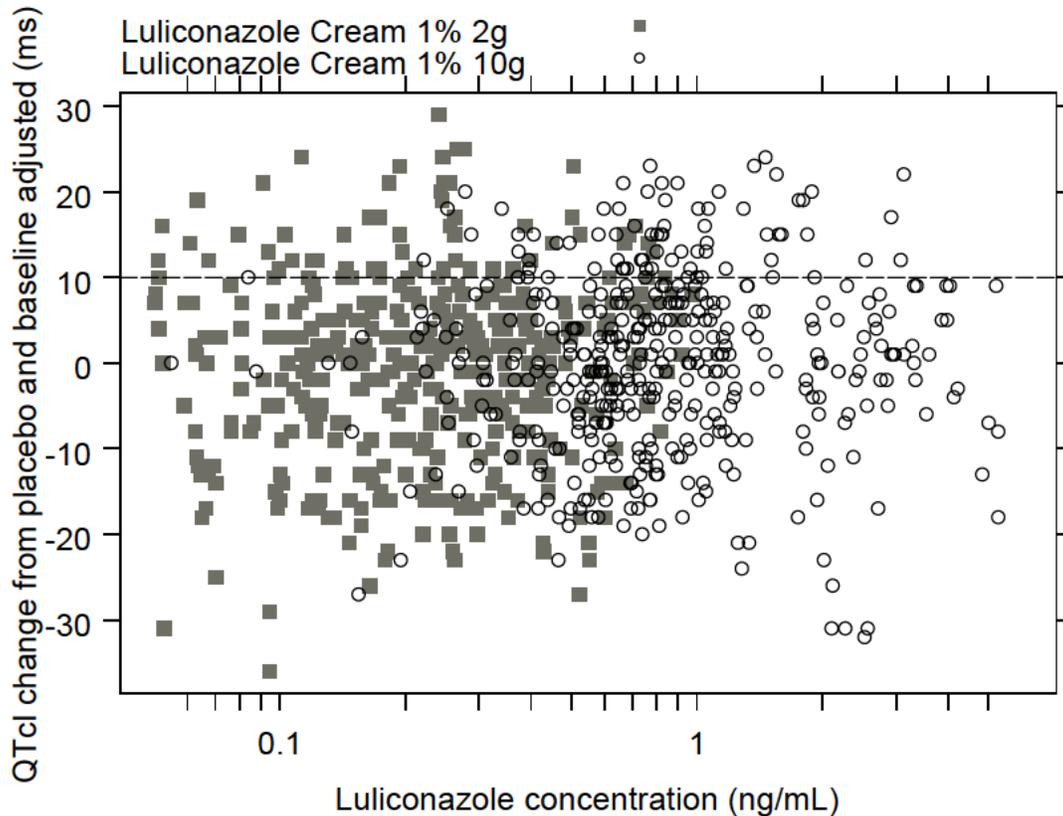
**Table 16: Outliers of QRS**

Treatment Group	Total		Value $\leq$ 100 ms		100 ms<Value $\leq$ 110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Luliconazole Cream 1% 10g	51	559	35 (68.6%)	434 (77.6%)	15 (29.4%)	114 (20.4%)	1 (2.0%)	11 (2.0%)
Luliconazole Cream 1% 2g	50	543	34 (68.0%)	437 (80.5%)	15 (30.0%)	97 (17.9%)	1 (2.0%)	9 (1.7%)
Moxifloxacin	50	549	36 (72.0%)	435 (79.2%)	13 (26.0%)	103 (18.8%)	1 (2.0%)	11 (2.0%)
Placebo	51	559	38 (74.5%)	451 (80.7%)	12 (23.5%)	97 (17.4%)	1 (2.0%)	11 (2.0%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between  $\Delta\Delta\text{QTcI}$  and luliconazole concentrations is visualized in Figure 5 with no evident exposure-response relationship.

**Figure 5:  $\Delta\Delta\text{QTcI}$  vs. Luliconazole Concentration**



### 5.4 CLINICAL ASSESSMENTS

#### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

#### 5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

#### 5.4.3 PR and QRS Interval

No clinically relevant effects were seen on PR or QRS.

## **6 ADDITIONAL INFORMATION (STUDY MP-1007)**

During the course of the review of the TQT Study (MP-1000-08), the Division alerted IRT that there was a maximal use study (MP-1007) in patients in which exposures of luliconazole exceeded those observed in the TQT study. Therefore, the results of this study were also taken into consideration and are presented below in an abbreviated study report review.

### **6.1 TITLE**

An Open-Label Study to Assess the Pharmacokinetics with Maximal Use of Luliconazole Cream, 1% in Patients with Moderate to Severe Tinea Pedis or Tinea Cruris

### **6.2 PROTOCOL NUMBER**

MP-1007

### **6.3 STUDY DATES**

Date of first enrollment: December 7, 2010

Date of completion: March 17, 2011

### **6.4 OBJECTIVES**

To evaluate the pharmacokinetics with maximal use of Luliconazole Cream, 1% as measured by circulating plasma levels of luliconazole in subjects with moderate to severe interdigital tinea pedis or tinea cruris

### **6.5 STUDY DESCRIPTION**

#### **6.5.1 Design**

This study was an open-label, non-randomized, single-treatment group, repeated-dose, maximal use study. Subjects received luliconazole cream, 1%, once daily for 15 days. The dose was approximately 3 g per application, which is 3 times the proposed daily clinical dose.

#### **6.5.2 ECG and PK Assessments**

Blood samples for measurement of luliconazole concentration were obtained at pre-dose on Days 1, 8 and 15 and at 1, 3, 6, 9, 12 and 24 hours post-dose on Days 1, 8 and 15. ECGs were extracted from Holter flashcards pre-dose on Day 1 and at 1, 3, 6, 9 and 12 hours post-dose on Days 1, 8 and 15.

#### **6.5.3 Baseline**

Baseline was determined from the mean of triplicate ECGs taken at three pre-dose time points.

#### **6.5.4 ECG Collection**

The electrocardiograms were measured and interpreted centrally by subject-specific cardiovascular physicians at (b) (4). All the ECGs whether transmitted directly by modem from the ELI-150 digital electrocardiograph for confirmation over-read

(screening,) or those that were subsequently extracted from the H-12 Plus ambulatory electrocardiograph recorder (pharmacodynamic electrocardiograms) were analyzed manually utilizing the same validated digital techniques of E-Scribe™ and the Veritas™ algorithm (Mortara Instruments, Milwaukee, WI). The QT intervals are measured using a high-resolution, manual, on-screen caliper method in compliance with the suggested standards set forth in The ICH Guidance for Industry E-14 Clinical Evaluation of QT/QTc Interval Prolongation, October 2005. All measurements were made adjusting the electronic calipers on the 12-lead global display. The measurements were either confirmed or re-adjusted by the cardiologist. The extractions were made in tracings void of artifact, wandering, lead reversal, or insufficient T wave amplitude and where the heart rate was stabilized.

## 6.6 SPONSOR'S RESULTS

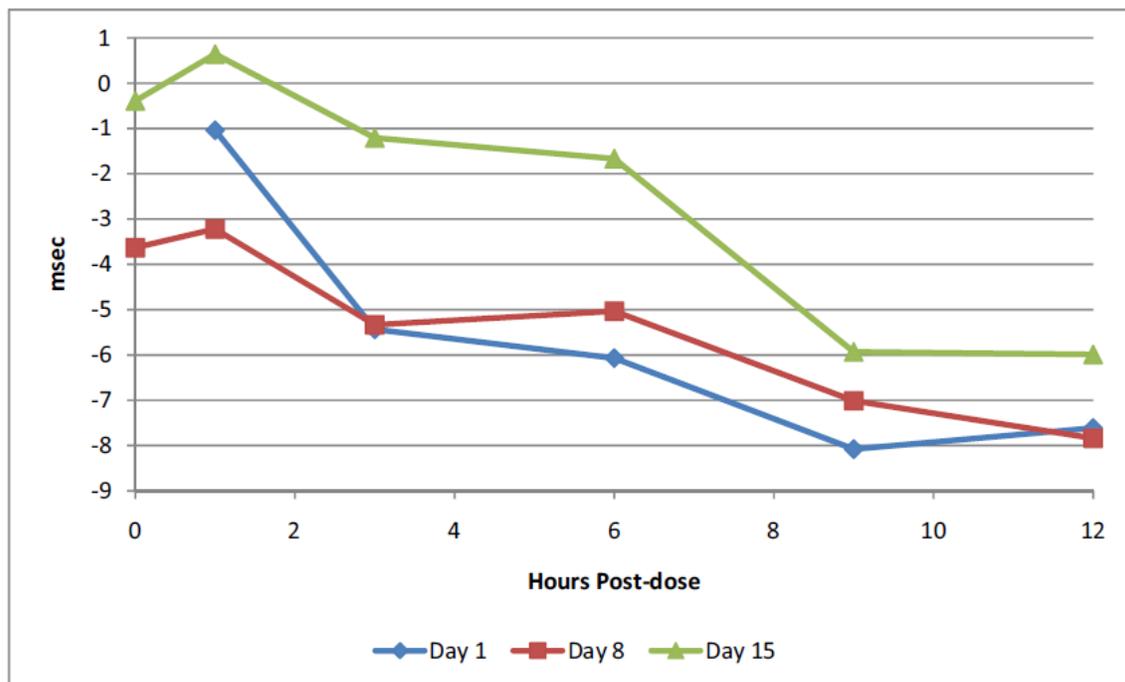
### 6.6.1 Study Subjects

The study included 30 patients (25 male, 5 female) between the ages of 19 and 65.

### 6.6.2 Primary Analysis

The primary endpoint was change from the Day 1 pre-dose baseline in QTcF (Figure 6).

**Figure 6: Mean Change from Day 1 Baseline in QTcF on Days 1, 8 and 15**



Source: Integrated Cardiac Safety Report, Figure 1, Page 18.

### 6.6.3 Categorical Analysis

The categorical analysis of QTcF is presented in Table 17. No patient had an increase in QTcF greater than 30 ms from baseline.

**Table 17: Number and Percentage of Patients with Categorical Changes in QTcF at Any Time after Treatment**

QTc Interval	Day 1 (N=30)	Day 8 (N=29)	Day 15 (N=29)
QTcF msec			
>450	1 (3.3%)	1 (3.4%)	2 (6.8%)
>480	0 (0%)	0 (0%)	0 (0%)
>500	0 (0%)	0 (0%)	0 (0%)

Source: Integrated Cardiac Safety Report, Table 3, Page 21.

## 6.6.4 Clinical Pharmacology

### 6.6.4.1 Pharmacokinetic Analysis

Pharmacokinetic parameters are reported in Table 18 and mean profiles are plotted in Figure 7.

**Table 18: Mean (SD) Pharmacokinetic Parameters of Luliconazole**

Parameter	All Subjects			Tinea Pedis			Tinea Cruris		
	Study Day			Study Day			Study Day		
	1 N=20*	8 N=19	15 N=19	1 N=12	8 N=11	15 N=11	1 N=8	8 N=8	15 N=8
C <sub>min</sub> (ng/mL)	NA	1.594 (2.3173)	1.969 (2.4317)	NA	0.338 (0.2691)	0.664 (1.0446)	NA	3.322 (2.7951)	3.764 (2.6994)
C <sub>max</sub> (ng/mL)	2.2 (2.7896)	2.699 (2.9638)	3.637 (3.7718)	0.396 (0.7562)	0.565 (0.4393)	0.931 (1.2321)	4.906 (2.5053)	5.633 (2.3069)	7.358 (2.6618)
T <sub>max</sub> (hr)	18.6 (8.16)	9.8 (8.73)	6.1 (7.67)	16.9 (9.39)	12.4 (10.29)	5.8 (7.61)	21 (5.55)	6.3 (4.46)	6.5 (8.25)
t <sub>1/2</sub> <sup>***,‡</sup> (hr)	28.99 (209.615)	27.43 (143.108)	25.12 (145.369)	64.25 (255.49)	44 (182.958)	32.41 (197.749)	15.9 (6.82)	17.95 (31.667)	21.15 (99.404)
AUC <sub>0-24</sub> (ng*hr/mL)	38.17 (48.691)	51.05 (60.995)	62.11 (65.139)	6.88 (14.5)	10.41 (7.878)	18.74 (27.046)	85.1 (43.695)	106.93 (57.571)	121.74 (53.361)
AUC <sub>0-∞</sub> <sup>§</sup> (ng*hr/mL)	408.57 (776.631)	NA	NA	610.38 (1026.02)	NA	NA	105.84 (41.407)	NA	NA

Notes: ND = not determined, NA = not applicable,

\* number of subjects in C<sub>min</sub>, C<sub>max</sub>, and AUC<sub>0-24</sub>.

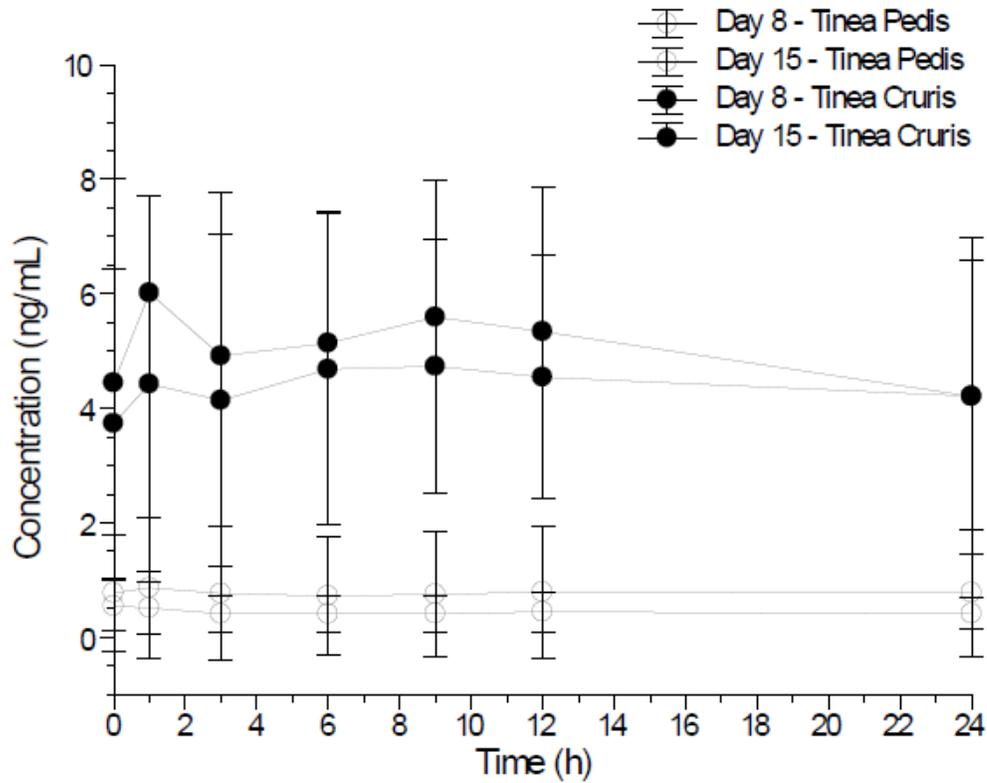
\*\* harmonic mean.

‡ t<sub>1/2</sub> can be determined only in few subjects and should be interpreted with extreme caution due to the limited sampling window (24-h).

§ parameter was calculated only if t<sub>1/2</sub> was estimable. Since BLQ were replaced with 0.05 ng/mL, C<sub>max</sub> and AUC values in a subject with no measurable concentration will be 0.05 ng/mL and 1.2 ng\*h/mL, respectively.

Source: Clinical Study Report, Table 11, Page 57.

**Figure 7: Mean Plasma Concentration-Time Profiles of Luliconazole on Days 8 and 15**

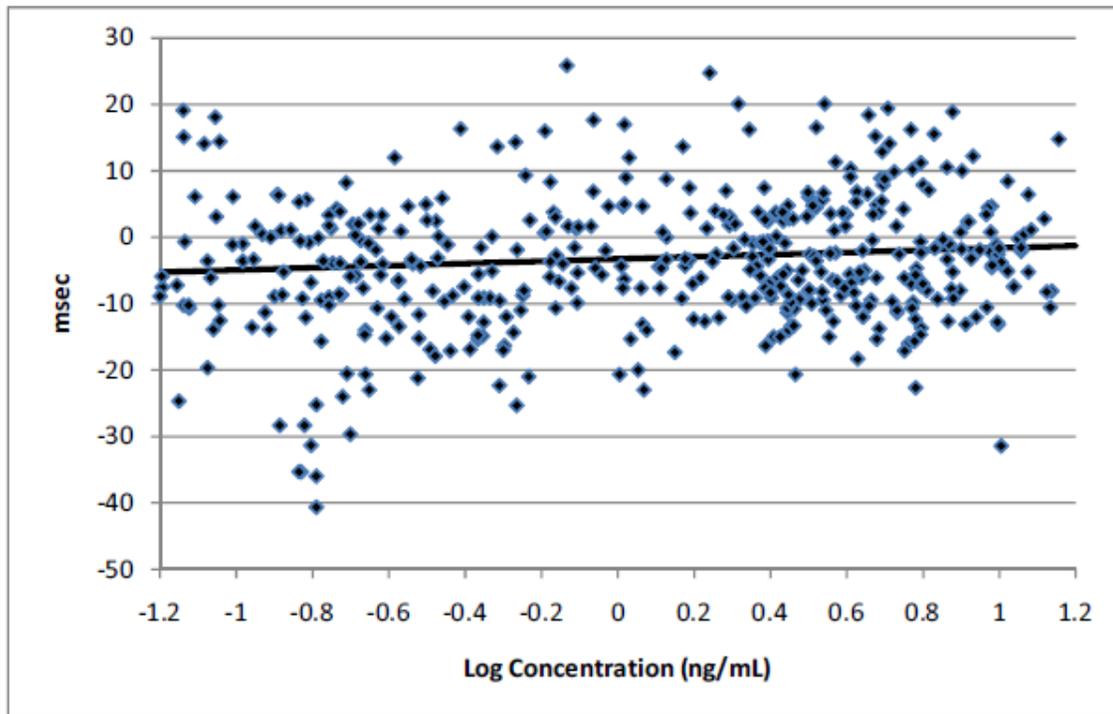


*Source: Clinical Study Report, Figure 4, Page 56.*

#### **6.6.4.2 Exposure-Response Analysis**

A significant relationship between luliconazole concentrations and change from baseline QTcF was not established (Figure 8).

**Figure 8: Change from Day 1 Pre-Dose Baseline in QTcF vs. Log Luliconazole Concentration**



*Reviewer's Comments: Study MP-1007 included many components of a thorough QT assessment (triplicate ECGs, central reading, adequate ECG collection times) and therefore is useful to better characterize the potential QT effect of luliconazole. It did not include a placebo or positive control, however, and can not be used by itself to exclude small changes in QT of about 10 ms. The results of this study are consistent with those of the TQT study (MP-1000-08) and suggest that luliconazole is not associated with QT prolongation. The exposures achieved in MP-1007 are roughly 4-fold those achieved in MP-1000-08 and do not show a relationship with change from baseline QTcF. The dose used in this study is 3 times the therapeutic dose.*

## 7 APPENDIX

### 7.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	The proposed dosing is expected to be approximately 1 g of cream (10 mg of Luliconazole) daily for 14 days in tinea pedis and daily for 7 days in tinea cruris and tinea corporis.	
Maximum tolerated dose	<p>The maximum dose evaluated in clinical studies was 5 g of cream (50 mg of Luliconazole) applied under occlusion in a single dose or daily for 7 days to the backs (normal skin) of male Japanese volunteers. The maximum plasma levels of luliconazole were observed in the US Maximal Use PK study approximately 3.0 g of luliconazole cream applied topically once daily for 15 days to the affected area and adjacent area (the top surface of both feet up to the ankles for moderate to severe tinea pedis or groin, thigh and the abdomen for moderate to severe tinea cruris). The 3g of luliconazole represents approximately 3 times the proposed clinical dose</p> <p>The NOAEL in general toxicity studies was 250 mg/kg after 4-week percutaneous dosing in rats (250-fold higher than human equivalent dose, HED). The NOAEL in dogs was assumed to be 25 mg/kg after 4-week percutaneous dosing and 26-week percutaneous dosing (75-fold higher than HED).</p>	
Principal adverse events	<p>No dose limiting adverse events were observed in any of the Japanese or US PK studies. In the single dose and 7 day PK studies conducted in Japan, 2 subjects experienced adverse events. In the Japanese single dose study (N=9), one subject reported throat pain, increase in white blood cell count, increase in neutrophils, and decrease in lymphocytes. The adverse events were mild and resolved without treatment, and causal relationship with the application of test drug was judged as “no relevance”. In the multiple dose study (N=6), one subject had elevated triglycerides. The causation was judged as “Not related”.</p> <p>In the US Maximal Use study luliconazole was applied for 15 days (tinea cruris; N = 15 enrolled) and (tinea pedis; N = 15) enrolled). There were no reported adverse events included that were probably or definitely related. Two (2) subjects reported 3 AEs that were “possibly related”, including 2 reports of mild application site pruritus and 1 report of mild white blood cell (WBC) count decreased.</p>	
Maximum dose tested	Single Dose	5 g of cream (50 mg of Luliconazole)
	Multiple Dose	3 - 5 g of cream (30 to 50 mg of Luliconazole) daily for 15 days.

		Maximum drug levels were observed in the maximal use setting in subjects with tinea cruris applying 3 g daily.
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (geometric SD) Cmax = 0.64 (1.95) mcg/L; AUC = 13.15 (1.60) mcg*h/L;
	Multiple Dose	Japanese Study (healthy volunteers) Mean (geometric SD) 1 <sup>st</sup> Dose: Cmax = 0.64 (1.95) mcg/L; AUC = 8.50 (2.10) mcg*h/L;  7 <sup>th</sup> Dose: Cmax = 1.32 (1.96) mcg/L; AUC = 17.56 (2.10) mcg*h/L  US Study (tinea cruris) Mean (geometric SD) 1 <sup>st</sup> Dose: Cmax = 4.90 (2.50) mcg/L; AUC = 32.81 (16.00) mcg*h/L;  7 <sup>th</sup> Dose: Cmax = 5.63 (2.30) mcg/L; AUC = 54.40 (30.09) mcg*h/L
Range of linear PK	Not Evaluated.	
Accumulation at steady state	In the Japanese multiple dose study, steady state was observed at day 3. No additional after accumulation was observed thereafter. In the US PK study, steady state was observed at day 8 (7 <sup>th</sup> dose). Mean plasma concentration-time profiles were comparable on Days 8 and 15 with a trend of slightly higher concentrations on Day 15.	
Metabolites	Three metabolites have been identified; (b)(4) and M10 (IND 76,049 Section 2.6.2 Table 23). The three conformational analogues were tested against the genus <i>Trichophyton</i> . The MICs against <i>Trichophyton</i> were 15-250 times higher for the (b)(4) and 120-1000 times higher for the (b)(4) than for native luliconazole. The MICs for the major metabolite, M10, were >16 µg/mL. Antifungal activities of analogues were very weak compared to luliconazole. The presence of the (b)(4) was assessed in clinical studies and was below the level of detection in plasma and urine in the Japanese studies. (b)(4) was detected in the US Maximal Use study for tinea pedis with a mean Cmax of	

	0.052, 0.068 and 0.066 ng/mL at Day 1, 8 and 15 respectively. For mean C <sub>max</sub> for subjects with tinea cruris is 0.054, 0.083 and 0.083 at Day 1, 8 and 15 respectively. Due to the limited number of values above the levels of detection, AUC was not calculated.	
Absorption	Absolute/Relative Bioavailability	5.42 +/- 1.19% at 1 <sup>st</sup> application 3.44 +/- 0.88% after 7 days of 50 mg daily
	T <sub>max</sub>	<ul style="list-style-type: none"> <li>• Single Dose: 18 (4 – 24) hours</li> <li>• Multiple dose: 6 (4 – 8) hours (Japan)</li> <li>• Multiple dose: 5.5 (4.5 – 8.2) hours (US)</li> <li>• Metabolites not assayed since they are below LOQ in plasma in Japanese study. In US study the T<sub>max</sub> for the (b)(4) was observed at 2.7 (2.4 – 4.0) hours</li> </ul>
Distribution	V <sub>d</sub> /F or V <sub>d</sub>	Not Evaluated
	% bound	Not Evaluated
Elimination	Route	<ul style="list-style-type: none"> <li>• In abraded skin rat models, 17% was excreted in feces and 6.7% in urine. No elimination of luliconazole was observed in human urine.</li> <li>• Biliary and enterohepatic in dogs</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Not Evaluated</li> <li>• Not Evaluated</li> </ul>
	CL/F or CL	Not Evaluated
Intrinsic Factors	Age	Not Evaluated
	Sex	Not Evaluated
	Race	Not Evaluated
	Hepatic & Renal Impairment	Not Evaluated
Extrinsic Factors	Drug interactions	The effects of Luliconazole on CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) were studied using human liver microsomes. The inhibition against CYP2C19 and CYP3A4 were the highest. Since the human plasma

		protein binding ratio of Luliconazole was 99.8 – 99.9%, it was estimated that the unbound plasma Luliconazole concentration in human plasma was 3.81 – 7.62 pg/mL (0.01 – 0.02 nM). At these levels there was no possibility of changes in the plasma concentrations of concomitantly administered drugs which would have any clinical significance due to interactions between Luliconazole and microsomal drug metabolizing systems when Luliconazole was used as a percutaneous external medicine. Refer to Section 2.6.4.7 of IND 79,049 or Section 2.6.4.7 of IND (b) (4) for additional details.
	Food Effects	Not Evaluated
Expected High Clinical Exposure Scenario	For treatment of tinea skin infections (the indication sought), it is highly unlikely that a dose of greater than 5 g of cream (50 mg) could be applied to the feet (tinea pedis), the groin (tinea cruris) or to localized infections on the body (tinea corporis). Therefore, the clinical pharmacology described herein is reflective of a maximal clinical exposure.	

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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QIANYU DANG  
04/30/2013

FANG LI  
04/30/2013

KEVIN M KRUDYS  
04/30/2013

NORMAN L STOCKBRIDGE  
04/30/2013

# **REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION**

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 204153

**Application Type:** New NME NDA

**Name of Drug:** Luzu (luliconazole) Cream, 1%

**Applicant:** Medicis Pharmaceutical Corporation

**Submission Date:** December 11, 2012

**Receipt Date:** December 11, 2012

## **1.0 Regulatory History and Applicant's Main Proposals**

New NME NDA for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis.

## **2.0 Review of the Prescribing Information (PI)**

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## **3.0 Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by March 1, 2013. The resubmitted PI will be used for further labeling review.

## 5.0 Appendix

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### Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

---

### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- NO** 4. White space must be present before each major heading in HL.

**Comment:** *Add white space.*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

## Selected Requirements of Prescribing Information (SRPI)

*Comment: Add for W+P.*

**YES**

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

*Comment:*

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

*Comment:*

#### Highlights Limitation Statement

**NO**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

*Comment: See above language.*

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

*Comment:*

#### Initial U.S. Approval

**NO**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

*Comment: Not yet approved.*

## Selected Requirements of Prescribing Information (SRPI)

### Boxed Warning

- N/A** 12. All text must be **bolded**.  
Comment:
- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).  
Comment:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.  
Comment:
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)  
Comment:
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).  
Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.  
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.  
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.  
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
Comment:

### Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”  
Comment: *NME, product class under discussion.*

### Dosage Forms and Strengths

## Selected Requirements of Prescribing Information (SRPI)

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- NO** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: Remove [REDACTED] <sup>(b)(4)</sup> from the manufacturer name.

### Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: Replace with above bullet for PI and PPI.

### Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: Replace.

---

## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

**YES**

## Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

**Comment:**

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

**Comment:**

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

**Comment:**

- YES** 34. When a section or subsection is omitted, the numbering does not change.

**Comment:**

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Comment:**

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

**Comment:**

- YES** 37. All section and subsection headings and numbers must be **bolded**.

**Comment:**

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>

## Selected Requirements of Prescribing Information (SRPI)

<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- NO** 39. 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 PI upon approval.

**Comment:** See above comment and send language.

- N/A** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

**Comment:**

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

## Selected Requirements of Prescribing Information (SRPI)

### Comment:

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

### Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

### Comment:

#### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

### Comment:

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CRISTINA Petruccelli Attinello  
02/06/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information	
NDA # 204153	
Proprietary Name: Luzu Established/Proper Name: (luliconazole) Dosage Form: Cream Strengths: 1%	
Applicant: Medicis Pharmaceutical Corporation Agent for Applicant (if applicable): n/a	
Date of Application: December 11, 2012 Date of Receipt: December 11, 2012 Date clock started after UN: n/a	
PDUFA Goal Date: December 11, 2013	Action Goal Date (if different): November 27, 2013
Filing Date: February 8, 2013	Date of Filing Meeting: January 28, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1	
Proposed indication(s)/Proposed change(s): for the treatment of interdigital tinea pedis, tinea cruris, tinea corporis	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i></b>	
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): 076049				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		x		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>x</p>																		

<i>Designations and Approvals list at:</i> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
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<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	x			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		x		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			x	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?<sup>1</sup>            If not, explain (e.g., waiver granted).</p>	x			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	x			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	x			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?	<b>x</b>			
<ul style="list-style-type: none"> <li>If yes, were all of them submitted on time?</li> </ul>	<b>x</b>			
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	<b>x</b>			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	<b>x</b>			
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<b>x</b>			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<b>x</b>			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<b>x</b>			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<b>x</b>			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	x			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	x			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			x	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			x	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	x			PeRC RPM to be notified promptly.
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?		x		
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>		x		Deferral requested, but no pediatric plan included. Comment in 74-Day Letter to be sent.
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>		x		
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		x		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	x			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		x		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	x			
Is the PI submitted in PLR format? <sup>4</sup>	x			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			x	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x			Consult Request pending.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	x			Consult Request pending.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			Consult Request pending.
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	x			Clin Micro 1/24/13, QT IRT pending
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 10/27/10, 12/16/09	x			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 7/18/12	x			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 2/17/11, 7/7/10	x			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 28, 2013

**NDA #:** 204153

**PROPRIETARY NAME:** Luzu

**ESTABLISHED/PROPER NAME:** (Iuliconazole)

**DOSAGE FORM/STRENGTH:** Cream, 1%

**APPLICANT:** Medicis Pharmaceutical Corporation

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** for the treatment of interdigital tinea pedis, tinea cruris, tinea corporis

**BACKGROUND:** New NME NDA, part of The Program.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Cristina Attinello	Y
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	David Kettl		Y
Clinical	Reviewer:	Gary Chiang	Y
	TL:	David Kettl	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Chinmay Shukla	Y
	TL:	Donny Tran	Y
Biostatistics	Reviewer:	Yuqing Tang	Y
	TL:	Mohamed Alesh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kumar Mainigi	Y
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ray Frankewich	Y
	TL:	Shulin Ding	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Carlos Mena-Grillasca	
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Kelly Kitchens		Y
Other attendees	Janet Anderson		Y
	Cathy Tran-Zwanetz		Y
	Susan Walker		Y
	Julie Beitz		Y
	Maria Walsh		Y
	Giuseppe Randazzo		Y

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined

<p><b><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></b></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<ul style="list-style-type: none"> <li>● Reason: the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</li> </ul>
<ul style="list-style-type: none"> <li>● Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>● If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>● Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<b>Comments:</b>	
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<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Julie Beitz, MD	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): April 26, 2013 (DDDDP target date)	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CRISTINA Petruccelli Attinello  
02/06/2013