CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208610Orig1s000
208611Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
## ACTION PACKAGE CHECKLIST

### APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>NDA Supplement #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type:</th>
</tr>
</thead>
<tbody>
<tr>
<td>208610</td>
<td></td>
<td></td>
<td>(an action package is not required for SE8 or SE9 supplements)</td>
</tr>
<tr>
<td>208611</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Proprietary Name: delafloxacin
- Established/Proper Name: Baxdela
- Dosage Form: 450 Mg Tablet and 300 Mg IV
- Applicant: Melinta Therapeutics Agent for Applicant (if applicable):
- Division: Anti_Infective Products
- RPM: Fariba Izadi, PharmD

<table>
<thead>
<tr>
<th>NDA Application Type:</th>
<th>505(b)(1)</th>
<th>505(b)(2)</th>
</tr>
</thead>
</table>
- Efficacy Supplement: |           |           |
| 505(b)(1)             |           |           |

<table>
<thead>
<tr>
<th>BLA Application Type:</th>
<th>351(k)</th>
<th>351(a)</th>
</tr>
</thead>
</table>
- Efficacy Supplement: |        |        |
| 351(k)                |        |        |

**For ALL 505(b)(2) applications, two months prior to EVERY action:**

- Review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)

- **No changes**
- **New patent/exclusivity (notify CDER OND IO)**

**Date of check:**

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

### Actions

- **Proposed action**
- **User Fee Goal Date is 06-19-17**

### Previous actions (specify type and date for each action taken)

- **None**

### Application Characteristics

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

- **Received**

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1 The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

2 For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

3 Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Reference ID: 4113618
Review priority: [ ] Standard [x] Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)
[ ] Fast Track [ ] Rx-to-OTC full switch
[ ] Rolling Review [ ] Rx-to-OTC partial switch
[ ] Orphan drug designation [ ] Direct-to-OTC
[ ] Breakthrough Therapy designation

(Note: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CST SharePoint)

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

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

REMS:
[ ] MedGuide
[ ] Communication Plan
[ ] ETASU
[ ] MedGuide w/o REMS
[ ] REMS not required

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2
(approvals only)
  [ ] Yes [ ] No

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action [x] Yes [ ] No
  - Indicate what types (if any) of information were issued

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? [ ] No [x] Yes
  - If so, specify the type

- Patent Information (NDAs only)
  - Patent Information:
    Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.
    [ ] Verified
    [ ] Not applicable because drug is an old antibiotic

**CONTENTS OF ACTION PACKAGE**

**Officer/Employee List**
- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) [x] Included
- Documentation of consent/non-consent by officers/employees [x] Included

Reference ID: 4113618
### Action Letters
- Copies of all action letters *(including approval letter with final labeling)*
  - Action(s) and date(s)
  - Approval 06-19-17

### Labeling
- **Package Insert** *(write submission/communication date at upper right of first page of PI)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included
- **Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling** *(write submission/communication date at upper right of first page of each piece)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included
- **Labels** *(full color carton and immediate-container labels)* *(write submission/communication date on upper right of first page of each submission)*
  - Most recent draft labeling
    - Included
- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
    - 02-16-17
  - Review(s) *(indicate date(s))*
    - 02-07-17
- **Labeling reviews** *(indicate dates of reviews)*
  - RPM: 05-15-17
  - DMEPA: 02-03-17
  - DMPP/PLT (DRISK): 04-24-17
  - OPDP: None 04-24-17
  - SEALD: None
  - CSS: None
  - Product Quality: None
  - Other: None

### Administrative / Regulatory Documents
- **RPM Filing Review*/Memo of Filing Meeting** *(indicate date of each review)*
- All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee
  - 11-29-16
  - Stat 11-29-16
  - Clinical 11-28-16ci
  - Clinical Micro 11-17-16
  - Non-Clinical 11-16-17
  - Clin-Pharm 12-18-16
  - Quality Assessment 03-21-17
  - Not a (b)(2)
- **NDAs/NDA supplements only: Exclusivity Summary** *(signed by Division Director)*
  - Completed *(Do not include)*

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
### Application Integrity Policy (AIP) Status and Related Documents

- **http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm**

<table>
<thead>
<tr>
<th>Status</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicant is on the AIP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>This application is on the AIP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
  - If yes, Center Director's Exception for Review memo *(indicate date)*
  - If yes, OC clearance for approval *(indicate date of clearance communication)* |  | |
| Not an AP action |  | |

### Pediatrics (approvals only)

- Date reviewed by PeRC 05-17-17
  - If PeRC review not necessary, explain: ____

### Breakthrough Therapy Designation

- Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) N/A
- CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*
- CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)*
  - *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*

### Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*

- Included

### Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)

- N/A

### Minutes of Meetings

- If not the first review cycle, any end-of-review meeting *(indicate date of mtg)* N/A or no mtg
- Pre-NDA/BLA meeting *(indicate date of mtg)*
  - CMC-04-08-16 Clinical 02-25-16 Preliminary Comments
- EOP2 meeting *(indicate date of mtg)*
- Mid-cycle Communication *(indicate date of mtg)* 03-08-17
- Late-cycle Meeting *(indicate date of mtg)* 03-24-17
- Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*

Reference ID: 4113618
### Advisory Committee Meeting(s)
- Date(s) of Meeting(s)
  - No AC meeting

### Decisional and Summary Memos
- **Office Director Decisional Memo** *(indicate date for each review)*
  - 6-19-17
- **Division Director Summary Review** *(indicate date for each review)*
  - 6-19-17
- **Cross-Discipline Team Leader Review** *(indicate date for each review)*
  - 6-16-17
- **PMR/PMC Development Templates** *(indicate total number)*
  - 8

### Clinical
- **Clinical Reviews**
  - **Clinical Team Leader Review(s)** *(indicate date for each review)*
    - No separate review
  - **Clinical review(s)** *(indicate date for each review)*
    - 06-14-17
  - **Social scientist review(s)** *(if OTC drug)* *(indicate date for each review)*
    - None
  - **Financial Disclosure reviews(s)** or location/date if addressed in another review
    - OR
      - If no financial disclosure information was required, check here and include a review/memo explaining why not *(indicate date of review/memo)*
  - **Clinical reviews from immunology and other clinical areas/divisions/Centers** *(indicate date of each review)*
    - None
  - **Controlled Substance Staff review(s) and Scheduling Recommendation** *(indicate date of each review)*
    - N/A
  - **Risk Management**
    - **REMS Documents and REMS Supporting Document** *(indicate date(s) of submission(s))*
    - 05-22-17
    - **REMS Memo(s) and letter(s)** *(indicate date(s))*
    - **Risk management review(s) and recommendations** *(including those by OSE and CSS)* *(indicate date of each review and indicate location/date if incorporated into another review)*
  - **OSI Clinical Inspection Review Summary(ies)** *(include copies of OSI letters to investigators)*
    - 05-08-17

### Clinical Microbiology
- **Clinical Microbiology Team Leader Review(s)** *(indicate date for each review)*
  - No separate review 6-16-17
- **Clinical Microbiology Review(s)** *(indicate date for each review)*
  - 6-16-17

### Biostatistics
- **Statistical Division Director Review(s)** *(indicate date for each review)*
  - No separate review
- **Statistical Team Leader Review(s)** *(indicate date for each review)*
  - No separate review
- **Statistical Review(s)** *(indicate date for each review)*
  - 03-18-17

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5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).
<table>
<thead>
<tr>
<th>Clinical Pharmacology</th>
<th>□ None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pharmacology Division Director Review(s) <em>(indicate date for each review)</em></td>
<td>□ No separate review</td>
</tr>
<tr>
<td>Clinical Pharmacology Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>□ No separate review</td>
</tr>
<tr>
<td>Clinical Pharmacology review(s) <em>(indicate date for each review)</em></td>
<td>□ 03-27-17</td>
</tr>
<tr>
<td>OSI Clinical Pharmacology Inspection Review Summary <em>(include copies of OSI letters)</em></td>
<td>□ None requested</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonclinical</th>
<th>□ None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
<td></td>
</tr>
<tr>
<td>• ADP/T Review(s) <em>(indicate date for each review)</em></td>
<td>□ 04-25-17</td>
</tr>
<tr>
<td>• Supervisor Review(s) <em>(indicate date for each review)</em></td>
<td>□ No separate review</td>
</tr>
<tr>
<td>• Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
<td>□ 04-24-17, 05-26-17</td>
</tr>
<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <em>(indicate date for each review)</em></td>
<td>□ None</td>
</tr>
<tr>
<td>Statistical review(s) of carcinogenicity studies <em>(indicate date for each review)</em></td>
<td>□ No carc</td>
</tr>
<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>□ None Included in P/T review, page</td>
</tr>
<tr>
<td>OSI Nonclinical Inspection Review Summary <em>(include copies of OSI letters)</em></td>
<td>□ None requested</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product Quality</th>
<th>□ None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Quality Discipline Reviews</td>
<td></td>
</tr>
<tr>
<td>• Tertiary review <em>(indicate date for each review)</em></td>
<td>□ None</td>
</tr>
<tr>
<td>• Secondary review <em>(e.g., Branch Chief)</em> <em>(indicate date for each review)</em></td>
<td>□ 05-16-17</td>
</tr>
<tr>
<td>• Integrated Quality Assessment <em>(contains the Executive Summary and the primary reviews from each product quality review discipline)</em> <em>(indicate date for each review)</em></td>
<td>NDA 208610 Drug substance-03-14-17 Drug Product 3-6-17, 5-16-17, Process5-11-17 Facilities 04-03-17 NDA 208611 Drug substance-03-15-17 Drug Product 3-16-17, 5-15-17, Process3-10-17 Facilities 05-11-17</td>
</tr>
<tr>
<td>Reviews by other disciplines/divisions/Centers requested by product quality review team <em>(indicate date of each review)</em></td>
<td>Product Quality Micro 3-3-17 Biopharmaceutics 03-17-17</td>
</tr>
<tr>
<td>Environmental Assessment <em>(check one)</em> <em>(original and supplemental applications)</em></td>
<td></td>
</tr>
<tr>
<td>□ Categorical Exclusion <em>(indicate review date)</em> <em>(all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td>□ 03-06-17</td>
</tr>
<tr>
<td>□ Review &amp; FONSI <em>(indicate date of review)</em></td>
<td></td>
</tr>
<tr>
<td>□ Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
<td></td>
</tr>
</tbody>
</table>

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6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Reference ID: 4113618
<table>
<thead>
<tr>
<th>Facilities Review/Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change))</td>
</tr>
<tr>
<td>☑ Acceptable</td>
</tr>
<tr>
<td>☐ Withhold recommendation</td>
</tr>
<tr>
<td>☐ Not applicable</td>
</tr>
<tr>
<td>Day of Approval Activities</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>❖ For all 505(b)(2) applications:</td>
</tr>
<tr>
<td>● Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
</tr>
<tr>
<td>● Finalize 505(b)(2) assessment</td>
</tr>
<tr>
<td>❖ For Breakthrough Therapy (BT) Designated drugs:</td>
</tr>
<tr>
<td>● Notify the CDER BT Program Manager</td>
</tr>
<tr>
<td>(Send email to CDER OND IO)</td>
</tr>
<tr>
<td>❖ For products that need to be added to the flush list (generally opioids):</td>
</tr>
<tr>
<td>● Notify the Division of Online Communications, Office of Communications</td>
</tr>
<tr>
<td>● Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
</tr>
<tr>
<td>❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
</tr>
<tr>
<td>❖ Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
</tr>
<tr>
<td>❖ Ensure Pediatric Record is accurate</td>
</tr>
<tr>
<td>❖ Send approval email within one business day to CDER-APPROVALS</td>
</tr>
<tr>
<td>❖ Take Action Package (if in paper) down to Document Room for scanning within two business days</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FARIBA IZADI
06/19/2017
Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDAs) dated October 18, 2016 and received October 19, 2016, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

<table>
<thead>
<tr>
<th>NDA</th>
<th>Drug</th>
<th>Strength &amp; Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>208610</td>
<td>Baxdela (delafloxacin)</td>
<td>450 mg Tablets</td>
</tr>
<tr>
<td>208611</td>
<td>Baxdela (delafloxacin)</td>
<td>300 mg Injection</td>
</tr>
</tbody>
</table>

We also refer to the letter dated June 19, 2017 granting approval of these NDAs for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI).

Finally, we refer to our correspondence dated September 8, 2012 to your Investigational New Drug Applications 62772 and 76096 in which we granted Qualified Infectious Disease Product (QIDP) designation for Baxdela (delafloxacin) Tablets and Baxdela (delafloxacin) Injection for the treatment of ABSSSI and Community-Acquired Bacterial Pneumonia (CABP).

We note the indication for CABP was not submitted in these NDAs.

This letter is to inform you that your applications meet the criteria for the 5-year exclusivity extension under section 505E(a) of the Act. Five years of additional exclusivity will be added to any applicable exclusivity periods described in subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of section 505 of the Act; clauses (iii) and (iv) of subsection (c)(3)(E) and clauses (iii) and (iv) of subsection (j)(5)(F) of section 505 of the Act; or section 527 of the Act that are otherwise associated with the approval of these NDAs.

Reference ID: 4113262
If you have any questions, call Fariba Izadi, PharmD, Regulatory Project Manager, at (301) 796-0563.

Sincerely yours,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------------
SUMATHI NAMBIAR
06/19/2017

Reference ID: 4113262
Dear Peter,

We are reviewing your submission dated 19 May 2017 and have the following information requests as follow-up to question # 1.

Earlier in the review cycle, clinical submitted an IR pertaining to Subjects 840-307-3915 and 840-327-3667. In this IR, we requested additional information related to these subjects. Based on your recent comments, we are seeking the following clarifications to issues that were not sufficiently addressed in your original response:

- **Subject 303/840-307-3915**: 31 year old male with no prior medical or surgical history enrolled with a right leg cellulitis/erysipelas:
  - Was a hematology consult obtained following diagnosis of PE? If so, please forward the consult or provide a summary of the consultant’s impression. If a hematology consult was not obtained, please indicate this.
  - Was there documentation of a family history of venous thromboembolic events? If so, please provide supportive documentation.
  - Please provide additional information on this subject’s initial ankle fracture, i.e. which ankle was fractured, did he require a cast following fracture.
  - Was the subject hospitalized for his R leg cellulitis or was he treated on an outpatient basis? If he was hospitalized, did he receive DVT prophylaxis? Specify which leg contained the subsequent DVT.

- **Subjects 840-327-3667**: 41 year old male with a history of diabetes and obesity enrolled with a right leg cellulitis:
  - Please indicate whether this subject was hospitalized for his R leg cellulitis or whether he was treated on an outpatient basis? If he was hospitalized, was he provided DVT prophylaxis during his inpatient hospitalization?
  - Was any additional information pertaining to this event obtained (outside of your 6 April 2017 IR submission)?

Best regards

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

/s/

FARIBA IZADI
05/25/2017
Dear Peter,

We have the following Clinical Microbiology Post Marketing Request (PMR) for Baxdela, NDA 208610 and 208611 delafloxacin. Please review and let us know if the following proposed dates are acceptable to you.

Conduct US surveillance studies for five years from the date of marketing BAXDELA to determine if resistance to delafloxacin has developed in those organisms specific to the indication in the label for ABSSSI. The timetable you submitted on June, xx, 2017, states that you will conduct this study according to the following schedule:

- Final protocol submission: September 2017
- First interim report: July 2018
- Second interim report: July 2019
- Third interim report: July 2020
- Fourth interim report: July 2021
- Fifth interim report: July 2022
- Study completion date: September 2021
- Final report submission date: December 2022

Regards

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

/s/

FARIBA IZADI
05/25/2017
Dear Peter,

We are reviewing your submission dated May 05, 2017 and have the following comments from the non-clinical team.

The information provided in your May 05, 2107 submission is not sufficient to define the impact of the excipient, SBECED, on tissue distribution and fetal exposure to delafloxacin in the pregnant rat during the period of organogenesis. An embryo-fetal developmental toxicology (EFD) study ideally would address potential differences in fetal exposure and outcomes with the intravenous formulation of delafloxacin containing SBECED.

A tissue distribution study in pregnant rats treated orally and IV with the respective clinical formulations during the period of organogenesis is recommended. If this study does not demonstrate differences in tissue distribution to the fetus or the maternal reproductive tract, then an embryo-fetal developmental toxicology (EFD) study may not be needed. However, if the tissue distribution study demonstrates difference, particularly in fetal delafloxacin exposure, that may be attributed to SBECED, then an EFD study of the clinical IV formulation in rats should be performed as originally recommended.

**PMR/PMC xxxx-1**

**Description:** Conduct a tissue distribution study in pregnant rats treated during the period of organogenesis with the oral formulation and with the intravenous formulation of BAXDELA with the excipient sulfobutylether beta-cyclodextrin (SBECED) to assess on the distribution of the drug substance to the reproductive tract and developing fetus.

**PMR/PMC Schedule Milestones:**

- **Final Protocol Submission:** 10/2017
- **Study/Trial Completion:** XX/2018
- **Final Report Submission:** 06/2018

**PMR/PMC xxxx-2**

**Description:** If the results of the tissue distribution studies from PMR xxxx-1 demonstrate greater exposure of the fetus / maternal reproductive tract to delafloxacin with the intravenous formulation, conduct an embryo-fetal developmental toxicology study in pregnant rats treated during the period of organogenesis with the intravenous formulation of BAXDELA to identify possible effects of delafloxacin with the excipient sulfobutylether beta-cyclodextrin (SBECED) on fetal development during the period of organogenesis.

**PMR/PMC Schedule Milestones:**

- **Final Protocol Submission:** 07/2018
- **Study/Trial Completion:** XX/2019
- **Final Report Submission:** XX/2020

Reference ID: 4103062
Regards
Fariba
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FARIBA IZADI
05/25/2017
We agree to FDA’s proposals below

Peter DiRoma  
Head of Regulatory Affairs and Quality Assurance  
Melinta Therapeutics, Inc.  
Lincolnshire, IL

INFORMATION REQUEST

Good morning Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), Tablet.

The following request is conveyed on behalf of the Product Quality review team. We request a written response by Monday, April 24, 2017. Please provide your response via email followed by an official submission to the NDA.

1. Please reference your response (Sequence 0033) dated 3/29/2017 for NDA 208610, Table 1 NDA Module 3 Amendment Schedule:

   a) We note that the following two items had their status changed to “CBE-30”, with an updated association to your commitment made under NDA 208610 Sequence 0031:

<table>
<thead>
<tr>
<th>Commitment to Update Module 3</th>
<th>Date FDA Requested Commitment</th>
<th>Sections of NDA to be</th>
<th>Planned Submission Date to NDA</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor polymorphic forms via XRPD in 3 PPQ runs to provide additional assurance that Using XRPD, confirm the proposed in-process limit (NMT)</td>
<td>18 January 2017</td>
<td>3.2.P.3.3</td>
<td>See commitment made in NDA208610</td>
<td>CBE-30</td>
</tr>
<tr>
<td></td>
<td>03 February 2017</td>
<td>3.2.P.3.3 3.2.P.5.6</td>
<td>See commitment made in NDA208610 Sequence 0031</td>
<td>CBE-30</td>
</tr>
</tbody>
</table>
These two items, however, were not part of the commitment made in Sequence 0031, which was to establish a validated XRPD limit test as part of drug product release and to update drug product specifications accordingly. Information on these two items can instead be submitted to the Annual Report.

b) You had previously agreed to establish an in-process test for Particle Size Distribution (PSD) with appropriate limits for the [REDACTED], see below. This information should be submitted along with the validated XRPD method to the CBE-30 (under the PMC).

<table>
<thead>
<tr>
<th>Commitment to Update Module 3</th>
<th>Date FDA Requested Commitment</th>
<th>Sections of NDA to be updated</th>
<th>Planned submission date to NDA</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propose a suitable PSD test and limits for the [REDACTED]</td>
<td>03 March 2017</td>
<td>3.2.P.2.3 3.2.P.3.3 3.2.P.3.4</td>
<td>31 May 2017</td>
<td>Sponsor agrees to establish an in-process PSD test with the appropriate limits for the [REDACTED]</td>
</tr>
</tbody>
</table>

c) The following items which you had committed to submitting to the NDA on 31st May, 2017 should be submitted to the Annual Report.

b) Commitment to Update Module 3 | Date FDA Requested | Sections of NDA to be updated | Planned submission date | Status |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Justify a hold time [REDACTED]</td>
<td>18 January 2017</td>
<td>3.2.P.3.4 3.2.R</td>
<td>31 May 2017</td>
<td>The sponsor will monitor the 3 PPQ batches where the [REDACTED] samples will be tested for Total Aerobic Microbial Counts. The summary results to justify</td>
</tr>
</tbody>
</table>

| Batch record does not define any limits on holding periods of in-process materials | 18 January 2017 | 3.2.R | 31 May 2017 | The sponsor commits to conducting additional hold time studies of a PPQ batch in which the polymorphic form will be evaluated using XRPD |

2. We note that in your response Sequence 0033 dated 3/29/2017 you updated the tablet master batch records (3.2.R) and manufacturing process development report (3.2.P.2.3) with the new proposed in-process [REDACTED] of
NMT 0.1% . Please also update the other affected sections of the application with this limit, such as 3.2.P.3.3, 3.2.P.3.4, and 2.3.P.

Please acknowledge the receipt of this request.

Thank you,
Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Quality Assessment Lead (Acting) Div I/Branch I
Office of Program and Regulatory Operations
FDA/CDER/OPQ
luz.e.rivera@fda.hhs.gov
301 796 4013

Reference ID: 4113689
Dear Peter,
We are reviewing your NDA 208610 and 208611, delafloxacin submission dated October 19, 2016 and have the following comment.

We are lacking data regarding the reproductive toxicity of the excipient, sulfobutylether-beta-cyclodextrin, combined with your drug substance, delafloxacin. We would like to request a GLP embryo-fetal development and toxicity study in the rat with the final intravenous clinical formulation containing sulfobutylether-beta-cyclodextrin to address this deficiency. You may wish to consider conducting this study post-marketing, in the event that your drug product is approved.

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
04/13/2017
Dear Peter,

Please provide additional information on the two patients in the delafloxacin arm of Study 303 who had serious adverse events of pulmonary embolism. For patient 840-307-3915, provide the site of the deep vein thrombosis that developed. For patient 840-327-3667, provide any additional information on risk factors for pulmonary embolism and the results of the hematology evaluation of the patient.

Regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
04/06/2017
Dear Peter,

We have the following information request regarding the Carton & Container for NDA 208610 and NDA 208611 Baxdela.

We note that you listed all names and amounts of the excipients to the bottle label, blister pack carton for hospital use label, and bottle carton label. Please sort them alphabetically and provide the updated mock-up labels for review.

Regards
Fariba
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/s/

FARIBA IZADI
04/06/2017
Dear Peter,

As discussed on the phone, please find our proposed changes to the sections 3, 11, 13 and 16 of the prescribing information. Please do not hesitate to contact me if you have any questions.

Regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
03/27/2017
Dear Peter,

We are reviewing your submissions dated October 19, 2016 for NDAs 208610 and 208611 for delafloxacin and have the following information requests regarding the labeling.

Adverse reaction rates are ordinarily derived from all reported adverse events. Determining rates based on a subset of reported events that individual investigators believe to be causally related to drug exposure is discouraged. Excluding events from the rate calculation based on the judgment of individual investigators introduces bias and inconsistency in rate determinations. Please revise the table and listings in Section 6.1 to display adverse reactions irrespective of investigator-assessed causality, as in Table 9 of the Summary of Clinical Safety. Also, we note that hepatic adverse reactions are listed under several terms (e.g., hypertransaminasaemia, transaminases increased, ALT increased, AST increased). Adverse reactions that are reported under different terms, but that represent the same phenomenon, should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. We refer you to the guidance Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057).

Please don’t hesitate to contact me if you need additional information.

Regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
03/23/2017
Hello Peter,

We acknowledge receipt of your March 17, 2017, submission, containing your partial response to our Information Request letter dated March 14, 2017.

We continue reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and request. We request a written response by Thursday, March 23, 2017, in order to continue our evaluation of your NDA.

- Please submit additional long term stability data for 16DEL1.

Please acknowledge receipt of this request.

Thank you,
Luz

Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Quality Assessment Lead (Acting) Div I/Branch I
Office of Program and Regulatory Operations
FDA/CDER/OPQ
luz.e.rivera@fda.hhs.gov
301 796 4013

-----Original Message-----
From: Peter Di Roma [mailto:pdiroma@melinta.com]
Sent: Friday, March 17, 2017 3:14 PM
To: Rivera, Luz E (CDER); Izadi, Fariba
Subject: RE: FDA INFORMATION REQUEST NDA 208611 Feb 14 2017 - Additional IV Stability Data Sequence #030

Sorry, this time with the additional (30-month) IV stability data requested by FDA (which was just submitted across the NDA gateway). Peter

-----Original Message-----
From: Peter Di Roma
Sent: Friday, March 17, 2017 12:26 PM
To: 'Rivera, Luz E (CDER)'; 'Izadi, Fariba'
Subject: FDA INFORMATION REQUEST NDA 208611 Feb 14 2017 - Additional IV Stability Data Sequence #030

Hi Luz, Fariba:
We are submitting today our response across the NDA electronic gateway to FDA’s Information Request received on 14 February 2017.

This NDA amendment adds 30-month stability time point data for registration batches 14DEL1 and 14DEL2. Accordingly, Section 3.2.P.8.1 and Section 3.2.P.8.3 in NDA208611 have been updated. We have included a regression analysis and confirmation of current specifications through shelf-life, which is proposed to be 6 months for the injection formulation.

In addition, this NDA amendment also contains accelerated stability data for 16DEL1 which the FDA requested stability information for on 10 March 2017 as well as updated stability impurity results and sterility results for 13DEL1, 14DEL1 and 14DEL2 based on our commitments with the FDA at the PAI inspection completed on 17 February 2017. The information is also found in the aforementioned sections.

Please let me know if FDA has any questions.

Regards,
Peter

-----Original Message-----
From: DoNotReply@fda.hhs.gov [mailto:DoNotReply@fda.hhs.gov]
Sent: Tuesday, February 14, 2017 6:48 PM
To: Peter Di Roma
Cc: luz.e.rivera@fda.hhs.gov; Fariba.Izadi@fda.hhs.gov
Subject: INFORMATION REQUEST NDA 208611

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), Injection.

The following request is conveyed on behalf of the review team:
- Please submit additional long term stability data for the Delafloxacin Injection primary batches as soon as they are available.

Please acknowledge receipt of this request.

Thank you,
LCDR Luz E Rivera, Psy.D.
Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine).

The following request is conveyed on behalf of the Product Quality review team:

Please indicate if your team can commit to the following:

I. The following Product Quality information should be submitted via supplement(s):

1. Addition of the facility responsible for XRPD testing. The filing category should be selected based on FDA Guidance (See: Guidance for Industry Changes to an Approved NDA or ANDA).

2. Establish a validated XRPD limit test as part of product release. This information should be submitted as Changes Being Effected-30 Supplement.

3. Update drug product release specifications so commercial batches will have XRPD testing to confirm polymorphic form as a part of drug product final release testing. This information should be submitted as Changes Being Effected-30 Supplement.

Timeline for submission of reports:

Interim Report: 1st June, 2017
Final Report: 1st September, 2017
We request a written response by Thursday, March 23, 2017. Please provide your response via email followed by an official submission to the NDA.

We request that you acknowledge this communication upon receipt.

Best regards,

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Peter,

We have the following information requests regarding the carton and container labeling for NDA 208610 and 208611, delafloxacin.

1. Please include the equivalency statement in the vial and carton labels:
   Baxdela
   delafloxacin for Injection
   300 mg per vial
   (equivalent to 433 mg of delafloxacin meglumine)
   The equivalency statement should be placed on the side panel.

2. Revise the term that appears on immediate container and carton labels to the “single-dose” statement.

3. Please include list of excipients along with their quantitative description in the vial and carton labels.

4. Provide revised mock-up container labels following these recommendations:
   1. Include a salt equivalency statement on the proposed container labels to indicate the amount of active moiety related to the amount of active ingredient (salt). This equivalency statement should appear on the blister pack carton for hospital use label, bottle label, and bottle carton label; but not on the blister pack for hospital use label due to limited space. This equivalency statement should appear on the side panels of the labels such that it would not cause confusion with the boxed strength statement of “450 mg per tablet”. Change from (equivalent to 433 mg of delafloxacin meglumine)” to “Each tablet contains 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine).” For further details, refer to Naming of Drug Products Containing Salt Drug Substances Guidance for Industry.
   2. Per 21 CFR 201.25, include a bar code on the blister pack carton for hospital use label or ensure the bar code on the blister pack for hospital use label is entirely seen through an opening of the blister pack carton for hospital use label; and include a bar code on the bottle label.

Regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
03/14/2017
Dear Peter,

We are reviewing your submissions dated October 19, 2016 for delafloxacin and have the following information requests.

Please provide delafloxacin systemic exposure (i.e. AUC, Cmax) and safety profiles for patients receiving P-gp and/or BCRP inhibitors relative to patients receiving no P-gp and/or BCRP inhibitors in two Phase 3 studies (RX-3341-302 and RX-3341-303).

Please respond within three business days (no later than 3/16/2017).

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
03/14/2017
Hi Peter,

We have the following information request from our clinical team regarding NDA 208610 and 208611.

Please submit the Case Report form 303/840-322-3268.

Regards
Fariba
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/s/

FARIBA IZADI
03/10/2017
Dear Peter,

We are reviewing your NDA Submissions submitted 10-19-16 and request response to the following information requests by 03-09-17

1. A listing of all persons with all EKG results for Protocol 302.

Please do not hesitate to contact me if you have any questions

Regards
Fariba
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/s/

FARIBA IZADI
03/10/2017
Dear Peter,

We are reviewing your submissions dated October 19, 2016 for NDA 208610 & 208611, delafloxacin and request response to the following information requests by March 09, 2017.

1. We appreciate your revised labeling text for patients with End-Stage Renal Disease (ESRD) in your response to our information request on March 1st, 2017.

2. According to the results from in vitro studies, delafloxacin appears to be a substrate of P-gp and BCRP. Both P-gp and BCRP are expressed in the luminal membrane of enterocytes, endothelial cells in the brain, the brush border membrane of renal proximal tubules, and the canalicular membrane of hepatocytes where they limit the intestinal absorption, blood-brain barrier penetration, and facilitate excretion into the bile and urine. We acknowledged your rationale regarding GI absorption for not conducting an in vivo drug-drug interaction (DDI) study. Please provide further rationales regarding other organs (i.e. liver and kidney) for not conducting an in vivo DDI study.

Please do not hesitate to contact me if you have any questions.

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
03/10/2017
Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), Injection.

The following request is conveyed on behalf of the review team:
- We note that 16DEL1 was manufactured on June 8, 2016, and expect stability testing for this batch to be ongoing. Due to concerns related to invalidated stability data at multiple time points for the registration stability lots, any available stability data from DEL1 will be valuable in our evaluation. Therefore, provide available stability data for the scale-up batch# 16DEL.

We request a written response by Thursday, March 16, 2017. Please provide your response via email followed by an official submission to the NDA.

We request that you acknowledge this communication upon receipt.

Best regards,

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Mr. Di Roma:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Delafloxacin Tablets and Injection (Baxdela).

We also refer to the teleconference between representatives of your firm and the FDA on February 08, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your applications.

A record of the teleconference is enclosed for your information.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

{See appended electronic signature page}
Meeting Date and Time: February 08, 2017

Application Number: NDA 208610
NDA 208611

Product Name: Delafloxacin Tablets and Injection

Indication: Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

 Applicant Name: Melinta Therapeutics, Inc.

Meeting Chair: Thomas Smith, MD

Meeting Recorder: Luz E Rivera, Psy.D
Fariba Izadi, PharmD

FDA ATTENDEES

Office of Antimicrobial Products (OAP)
Edward Cox, MD MPH Director
John Farley, MD MPH Deputy Director

Division of Anti-Infective Products (DAIP)
Abimbola Adebowale, PhD Associate Director for Labeling
Carmen DeBellas, RPh, PharmD Chief, Project Management Staff
Tamara Feldblyum, PhD Acting Clinical Microbiology Team Leader
Dmitri Iarikov, MD PhD Acting Deputy Division Director
Fariba Izadi, RPh, PharmD Senior Regulatory Health Project Manager
Caroline Jingko, MD Clinical Reviewer
Terry Miller, PhD Pharmacology/Toxicology Team Leader
Sumathi Nambiar, MD, MPH Director -Via Phone
Thomas Smith, MD, MPH Clinical Team Leader
Joseph Toerner, MD, MPH Deputy Director for Safety
Kunyi Wu, PharmD Clinical Pharmacology Reviewer
Zhixia (Grace) Yan, PhD Acting Clinical Pharmacology Team Leader

Reference ID: 4066086
INTRODUCTION
We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

MEETING DISCUSSION
In response to Melinta’s questions regarding clinical issues, FDA indicated that the reviews are ongoing and no outstanding issues have been identified so far. The Division recommended that the AST device manufacturers should contact CDRH to design appropriate studies and develop data needed to support the device(s) clearance. The clearance process may be accelerated if information on proposed breakpoints and the proposed list of organisms included in the indications being sought is available to the device manufacturers during the NDA review. Additional information is available in the draft guidance, Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm521421.pdf.

Reference ID: 4066086
In response to Melinta’s CMC related questions, the Agency indicated that the reviews of both NDAs are still ongoing including assessment of the manufacturing facilities. Regarding polymorph testing, the Agency stated that using the verified method is acceptable until a validated method is available. Melinta stated that a fully validated XRD method will be available in May 2017 and inquired if a new testing facility for XRD can be submitted to the NDA. The Agency indicated that an internal discussion will be required to determine the impact of adding a new facility at this stage of the review and a decision will be communicated to Melinta.

Melinta agreed to update appropriate sections of the NDA with information submitted in response to the information requests by May 2017.

**MAJOR SAFETY CONCERNS/RISK MANAGEMENT**
There are no major safety concerns identified at this time and there is currently no need for a REMS.

**ADVISORY COMMITTEE MEETING**
Currently, we do not plan to hold an Advisory Committee Meeting.

**LATE CYCLE MEETING /OTHER PROJECTED MILESTONES**
The late cycle meeting is scheduled as follows:

- **Date:** April 07, 2017
- **Time:** 11:00 AM to 12:00 PM (EST)
- **Location:** 10903 New Hampshire Avenue
  White Oak Building 22, Conference Room: 1311
  Silver Spring, Maryland 20903
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/s/

SUMATHI NAMBIAR
03/08/2017
NDA 208610
INFORMATION REQUEST

Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please find attached the information request letter for NDA 208610.

We request a written response by Tuesday, March 14, 2017. Please provide your response via email followed by an official submission to the NDA.

We request that you acknowledge this communication upon receipt.

Best regards,

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 208610

Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

- Baxdela (Delafloxacin meglumine), 450 mg, Tablet

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by **Tuesday, March 14, 2017**, in order to continue our evaluation of your NDA.

**Drug Substance**

1. In your response to Question 1c in the Amendment dated 21-Feb-2017, you state that a test to confirm the chiral identity of the drug substance (delafloxacin meglumine) is not necessary. To confirm that the drug substance manufacturing process does not pose any risk of racemization to the meglumine salt and to justify that routine monitoring of the drug substance chirality is not necessary, provide the specific rotation results for the three full-scale PPQ batches (71249AA002, 71249AA003, and 71249AA004).

**Drug Process**

2. You are proposing We note, however, that you have not proposed any in-process controls on particle size distribution (PSD). We acknowledge that you have demonstrated consistent PSD control on in your pilot and engineering confirmation studies. However, this does not eliminate the need for in-process testing of the to ensure material with a consistent
PSD test and limits for the

Please propose a suitable

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
APPEARS THIS WAY ON ORIGINAL
Dear Peter,

We are reviewing your submissions dated 10-19-16 for delafloxacin and request response to the following information request by March 02, 2017.

Please note that I will be out of office until March 6th. My colleague Alison Rodgers who is also copied on this email has kindly accepted to forward your response to the team. Please reply to all when you respond.

We noted that sulfobutylether-β-cyclodextrin (SBECD) accumulated extensively in subjects with end-stage renal disease (ESRD) with or without hemodialysis in the renal impairment study. The two studies you referred to (a single-dose study by Hafner V et al. and a multiple-dose study with only 8 subjects with ESRD by Luke DR et al.) do not provide enough safety information.

Please provide additional safety data.

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
02/27/2017
NDA 208610

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Melinta Therapeutics, Inc.
300 Tri-State International
Suite 272
Lincolnshire, IL 60069

ATTENTION: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance

Dear Mr. DiRoma:

Please refer to your New Drug Application (NDA) dated and received October 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Delafloxacin Tablets, 450 mg.

We also refer to your correspondence, dated and received November 22, 2016, requesting review of your proposed proprietary name, Baxdela.

We have completed our review of the proposed proprietary name, Baxdela and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your November 22, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
  (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-0330. For any other information regarding this application, contact Fariba Izadi, Regulatory Project Manager in the Office of New Drugs, at 301-796-0563.

Sincerely,

[See appended electronic signature page]

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research
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-/s/-

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/16/2017
NDA 208611

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Melinta Therapeutics, Inc.
300 Tri-State International
Suite 272
Lincolnshire, IL 60069

ATTENTION: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance

Dear Mr. DiRoma:

Please refer to your New Drug Application (NDA) dated and received October 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Delafloxacin for Injection, 300 mg/vial.

We also refer to your correspondence, dated and received November 22, 2016, requesting review of your proposed proprietary name, Baxdela.

We have completed our review of the proposed proprietary name, Baxdela and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your November 22, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-0330. For any other information regarding this application, contact Fariba Izadi, Regulatory Project Manager in the Office of New Drugs, at 301-796-0563.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/16/2017
Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), Injection.

The following request is conveyed on behalf of the review team:
- Please submit additional long term stability data for the Delafloxacin Injection primary batches as soon as they are available.

Please acknowledge receipt of this request.

Thank you,
LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Peter,

We are reviewing your submissions dated Oct 19, 2016 for NDA 208610 and 208611 and have the following information requests.

- Please provide a listing of intravenous drug users for each of your phase 2 and 3 studies.
- Please provide a listing of patients with ABSSSIs classified as cellulitis or wound infection who underwent incision and drainage at any time during the studies. Please include site identifier numbers.
- Clarify how “type of infection” was classified, as we have observed that several patients not classified as having a “major cutaneous abscess” had an incision and drainage performed on Day 1 of study enrollment.

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

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/s/

FARIBA IZADI
02/09/2017
Sent: 02/08/2017 08:27:20 PM  
To: pdiroma@melinta.com  
CC: luz.e.rivera@fda.hhs.gov  
BCC:  
Subject: INFORMATION REQUEST NDA 208610  

NDA 208610  
INFORMATION REQUEST  

Melinta Therapeutics, Inc.  
Attention: Peter DiRoma  
Vice President Regulatory Affairs and Quality Assurance  
300 Tri-State International  
Lincolnshire, ILL 60069  

Dear Mr. DiRoma:  

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), 450 mg, Tablet.  

Find attached the information request and comments conveyed on behalf of the Review Team. Please acknowledge the receipt of this request.  

Thank you,  
LCDR Luz E Rivera, Psy.D.  
Quality Assessment Lead (Acting), Div. I, Branch I  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research
NDA 208610

INFORMATION REQUEST

Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

- Baxdela (Delafloxacin meglumine), 450 mg, Tablet

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by Tuesday, February 21, 2017, in order to continue our evaluation of your NDA.

Drug Substance Issues

1. Please address the following regarding the drug substance specification in Section 3.2.S.4:
   a. You indicated that a risk assessment was performed (using pilot-scale drug substance batches 71263AA001, 71263AA002, 71299AA001, and 71263AA003) to determine that testing for elemental impurities is not necessary. However, per ICH Q3D, data from 3 representative production-scale lots or 6 representative pilot-scale lots should be provided to support that testing for elemental impurities is not necessary. Provide the additional data to support your proposal to omit elemental impurities testing from the drug substance specification.
2. Please address the following regarding your stability studies in Section 3.2.S.7:
   a. The primary stability results (for batches 71263AA001, 71263AA002, and 71299AA001) did not include the results for appearance, X-ray diffraction, and microbial counts. Provide the missing stability data.
   b. Provide the mass balance results for the solution stress studies.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 208611
INFORMATION REQUEST

Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), Injection.

The following request is conveyed on behalf of the review team:

- Please be advised that per USP <71> tables 2 and 3, 150 mg from each of 20 vials is required for each filter/organism (6 total) used in sterility method suitability testing. Consequently, 120 total vials will be required for sterility method suitability testing. Given that 150 mg from each vial must be tested, each filter must be exposed to 3 g of drug product during method suitability testing. Please revise the sterility method suitability testing protocol accordingly.

Please respond by Monday, February 13, 2017.

Please acknowledge receipt of this request.
Thank you,
LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Mr. DiRoma,

Please find the attached Information Request for NDA 208610. If you have any questions, contact Luz Rivera. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov
NDA 208610

INFORMATION REQUEST

Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), 450 mg, Tablet.

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a written response by February 17, 2017 in order to continue our evaluation of your NDA.

Process
If you have any questions, please contact Luz Rivera, Quality Assessment Lead (Acting), at (301) 796 4013, or luz.e.rivera@fda.hhs.gov.

Sincerely,

Steven Kinsley

- S

Steven Kinsley, PhD
Signing on behalf of:
LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Division I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Peter,

We are reviewing your applications received October 19, 2016 and request response to the following by January 31, 2017.

We noticed that the delafloxacin plasma concentrations of the first three time points for Subject 1404 and Subject 1507 in Study RX-3341-110 after receiving 300 mg IV single dose were unexpectedly high. Additionally, the plasma concentrations aforementioned were included in the non-compartment analysis (NCA) and reported for Study RX-3341-110, but excluded from the population PK dataset. Please provide the rationales for the unexpected high plasma concentrations for these two patients. Provide the rationales for different inclusive/exclusive criteria for data used in NCA and population PK analysis. In addition, provide raw plasma concentration data of these two patients along with the quality control sample concentrations and calibration curve concentrations for RX-3341 in the same analytical run with these two patient samples.

Regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
01/31/2017
Dear Peter,

We are reviewing your submissions dated October 19, 2016 and have the following information requests from our Biopharmaceutics team.

Please submit these two datasets for all subjects from study rx-3341-110. In addition, please submit a population PK dataset for subjects with ESRD from study rx-3341-110 that includes data from both two treatment periods (i.e. with hemodialysis and without hemodialysis). This dataset should include the same demographic and laboratory information as given in the population PK data for IV delafloxacin (pkin1.xpt).

Regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
01/31/2017
INFORMATION REQUEST

Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), 300 mg, Injection.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a written response by Monday, February 6, 2017, in order to continue our evaluation of your NDA.

Drug Product

Please provide leachable data for Delafloxacin lyophilized drug product on stability and for the reconstituted and diluted product to demonstrate safety of the container closure system. If this information has been submitted in the NDA, indicate the appropriate sections.

If you have any questions, please contact, Quality Assessment Lead (Acting), at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -S
Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -S,
0.9.2342.19200300.100.1.1=2001555007
Date: 2017.01.23 17:31:11 -05'00'
NDA 208610
INFORMATION REQUEST

Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), 450 mg, Tablet.

Find attached the information request and comments conveyed on behalf of the Review Team. Please acknowledge the receipt of this request.

Thank you,

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 208610

INFORMATION REQUEST

Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), 450 mg, Tablet.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a written response by Wednesday, February 1, 2017, in order to continue our evaluation of your NDA.

PROCESS
4. Please address the following items from your proposed commercial manufacturing batch record (MBR):
Facilities

1. Per Form FDA 365h and Module 3, Alcami Carolinas Corporation (FEI 1049418) is proposed as an “Alternate Testing Location for drug product”. Please specify the tests performed at this facility and clarify what stage of drug product testing (i.e. in-process, release, stability) is performed.

If you have any questions, please contact me, Quality Assessment Lead (Acting), at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
APPEARS THIS WAY ON ORIGINAL
INFORMATION REQUEST

Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), 300 mg, Injection.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a written response by Wednesday, February 1, 2017, in order to continue our evaluation of your NDA.

Microbiology:

1. Regarding the manufacturing process:

   a. Please provide in-process bioburden limit(s).

   b. Please specify the production process parameters.

2. Regarding process validation and/or evaluation:

   [Redacted]
3. Regarding control of the drug product:

   a. Sterility testing was validated. Please note that per USP <71>, the drug product batch size requires that the contents of 20 vials be tested. Please provide sterility test validation data that is performed using the appropriate number of vials per USP <71>.

Comments:

1. For future container-closure testing, it is advised that positive controls should be run at the time of testing.
If you have any questions, please contact me, Quality Assessment Lead (Acting), at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Melinta Therapeutics, Inc.
Attention: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance
300 Tri-State International
Lincolnshire, ILL 60069

Dear Mr. DiRoma:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baxdela (Delafloxacin meglumine), 300 mg, Injection.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a written response by **Thursday, January 19, 2017**, in order to continue our evaluation of your NDA.

1. Provide two samples representative of each conforming and non-conforming vials of Baxdela (Delafloxacin meglumine), Injection.

Submit the vials to the following address:

    LCDR Luz E Rivera
    Food and Drug Administration
    Center for Drug Evaluation and Research
    White Oak Building 75, Room: 4649
    10903 New Hampshire Avenue
    Silver Spring, Maryland

    *Use zip code 20903 if shipping via United States Postal Service (USPS).*
    *Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

**Process:**

2. The three registration batches showed varied percentage of vials for 13DEL1, 14DEL1 and 14DEL2, respectively). Upon
re-inspection the percentage of vials demonstrating were deemed lower based on exclusion of vials belonging to categories 2 and 3. Per your updated visual inspection program, vials are classified as either conforming or non-conforming. Your current release specifications describe general acceptable “appearance” criteria, but do not include a description of what would be considered as “non-conforming”. Please provide the specific criteria by which vials are classified as conforming versus non-conforming during in-process checks to ensure batch to batch consistency in the visual inspection of manufactured vials.

3. You have provided in-process test results for the registration and scale-up batches (3.2.P.3.4). Based on those results, we have the following comments:

   a. Based on the in-process test results of the scale-up batch (16DEL1), the assay value at % of the total volume was below the acceptance range. The assay value at % total volume was above the acceptance range. The assay value at % of the total volume is intended to provide information for accurate adjustment of the total volume to %, while maintaining the final assay value within the acceptance criteria. Please explain the reason for exceeding the set acceptance criteria of the final assay value despite the use of a formula for accurate adjustment of the final volume and comment on the procedure you will follow for future commercial batches if the assay value exceeds the set acceptance criteria at this stage.

   b. Please provide in-process test results for manufacturing steps for the registration and scale-up batches for evaluation.
8. Please provide a tabular summary of equipment used for both registration batches as well as scale-up batch, including size, and estimated use of capacity.

9. We were unable to locate a summary of yield data for the registration batches (13DEL1, 14DEL1, and 14DEL2) and the scale-up batch (16DEL1). Please submit a tabular summary of yield data for those batches.

If you have any questions, please contact me, Quality Assessment Lead (Acting), at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Peter,

We are reviewing your submissions received 10-19-16 for NDA 208610 and 208611, delafloxacin, and have the following information requests.

1) Provide an annotated CRF for Protocol RX-3341-303.

2) Revise the AE domain for Studies RX-3341-201 and RX-3341-201 such that all terms are presented in upper case similar to the presentation of AE data sets for Protocols RX-3341-302 and RX-3341-303.

3) For both RX-3341-302 and RX-3341-303, all laboratory data from abroad sites (i.e. country site numbers: 191, 348, 376, 428, 724, 784) should be presented in the appropriate US conversions and units of analysis. For example, such lab values as creatinine (Cr) and non-fasting glucose should be converted into mg/dL and not presented as mcmol/L and mmol/L, respectively. If you have done so already, please tell us where the appropriately converted US laboratory data can be found.

Regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
12/13/2016

Reference ID: 4026902
Melinta Therapeutics, Inc.
Attention: Peter Di Roma
Vice President, Regulatory Affairs and Quality Assurance
300 George Street, Suite 301
New Haven, CT 06511-6663

Dear Mr. Di Roma:

Please refer to your New Drug Applications (NDAs) dated October 18, 2016, received October 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Delafloxacin Tablets and Injection.

We also refer to your submissions dated October 29, November 09 and 22, 2016.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), these applications are considered filed 60 days after the date we received your applications. The review classifications for these applications are Priority. Therefore, the user fee goal date is June 19, 2017. These applications are also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm)

We are reviewing your applications according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 26, 2017.

Reference ID: 4022559
In addition, the planned date for our internal mid-cycle review meeting is January 25, 2017.

We are not currently planning to hold an advisory committee meeting to discuss these applications.

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

**PREScribing INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the **PLR Requirements for Prescribing Information** and **PLLR Requirements for Prescribing Information** websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

**PROMOTIONAL MATERIAL**

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

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266
Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and you believe the labeling is close to the final version. For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your request for a full waiver of pediatric studies for these applications. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

*See appended electronic signature page*

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
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/s/

SUMATHI NAMBIAR
12/05/2016
Dear Mr. Di Roma,

We are reviewing your submissions dated October 19, 2016 for NDA 208610 and NDA 208611 (delafloxacin tablet and IV) and have the following information requests.

1. According to the proposed dosing regimen, one option is to treat patients with 450 mg oral tablet Q12 hours for 5 to 14 days. However, this proposed oral only dosing regimen was not evaluated in any ABSSSI patients. In addition, systemic exposure of delafloxacin resulted from the to-be-marketed tablet was only measured in healthy subjects, but not in ABSSSI patients. Please clarify whether ABSSSI has any impact on the pharmacokinetics, especially absorption, of delafloxacin for the oral tablet.

2. Please provide your response to our information requests sent on 11/25/2016 as shown below before 12/9/2016.

   1. As you are using the model to predict exposures for doses less than 300 mg, we request that you include studies with doses lower than 300 mg in your population PK analysis for IV delafloxacin. Specifically, please include study RX-3341-101 in the population PK model for IV delafloxacin and update the population PK parameter estimates for IV delafloxacin based on inclusion of this study.

   2. Please provide datasets, modeling control streams, and a define file for the sulfobutylether cyclodextrin population PK model. Datasets should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Please provide the modeling control stream for the complete model mentioned on page 19 of PK-3341-010 final report. If available, provide additional PK data from sulfobutylether cyclodextrin from studies other than RX-3341-110 and update the population PK model.

   3. If available, provide an updated population PK model for delafloxacin that uses all available IV and oral PK data (including all the available dose levels) or provide a justification why the IV and oral PK for delafloxacin cannot be characterized using the same population PK model.

   4. Provide tables and/or plots comparing the simulated exposures (AUC and Cmax) of IV delafloxacin, sulfobutylether cyclodextrin and oral delafloxacin based on the appropriate pop PK model for the following patient groups using the dosing proposed in labeling: patients with normal renal function, patients with mild renal impairment, patients with moderate renal impairment, patients with severe renal impairment, patients with ESRD undergoing hemodialysis, and patients with ESRD patients who are not undergoing hemodialysis.

Regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax:  (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
12/01/2016
NDA 208610

PROPRIETARY NAME
ACKNOWLEDGEMENT

Melinta Therapeutics, Inc.
300 Tri-State International
Suite 272
Lincolnshire, Illinois 60069

ATTENTION: Peter DiRoma
Vice President Regulatory Affairs and Quality Assurance

Dear Mr. DiRoma:

Please refer to your New Drug Application (NDA) dated October 18, 2016, received October 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Delafloxacin Tablet, 450mg.

We acknowledge receipt of your correspondence dated and received November 22, 2016, requesting a review of your proposed proprietary name, Baxdela.

If the application is filed, the user fee goal date will be February 20, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet G. Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. For any other information regarding this application, contact Fariba Izadi, PharmD, Regulatory Project Manager, in the Office of New Drugs at (301) 796-0593.

Sincerely,

{See appended electronic signature page}

Janet G. Higgins
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Reference ID: 4019832
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/s/

JANET G HIGGINS
11/29/2016
Dear Mr. Di Roma,

We are reviewing your submissions dated October 19, 2016 for NDA 208610 and NDA 208611 (delafloxacin tablet and IV) and have the following information requests.

1. As you are using the model to predict exposures for doses less than 300 mg, we request that you include studies with doses lower than 300 mg in your population PK analysis for IV delafloxacin. Specifically, please include study RX-3341-101 in the population PK model for IV delafloxacin and update the population PK parameter estimates for IV delafloxacin based on inclusion of this study.

2. Please provide datasets, modeling control streams, and a define file for the sulfobutylether cyclodextrin population PK model. Datasets should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Please provide the modeling control stream for the complete model mentioned on page 19 of PK-3341-010 final report. If available, provide additional PK data from sulfobutylether cyclodextrin from studies other than RX-3341-110 and update the population PK model.

3. If available, provide an updated population PK model for delafloxacin that uses all available IV and oral PK data (including all the available dose levels) or provide a justification why the IV and oral PK for delafloxacin cannot be characterized using the same population PK model.

4. Provide tables and/or plots comparing the simulated exposures (AUC and Cmax) of IV delafloxacin, sulfobutylether cyclodextrin and oral delafloxacin based on the appropriate pop PK model for the following patient groups using the dosing proposed in labeling: patients with normal renal function, patients with mild renal impairment, patients with moderate renal impairment, patients with severe renal impairment, patients with ESRD undergoing hemodialysis, and patients with ESRD patients who are not undergoing hemodialysis.

Please do not hesitate to contact me if you have any questions.

Regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov
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/s/

FARIBA IZADI
11/25/2016
NDA 208610
NDA 208611

NDA ACKNOWLEDGMENT

Melinta Therapeutics, Inc.
Attention: Peter Di Roma
Vice President, Regulatory Affairs and Quality Assurance
300 George Street, Suite 301
New Haven, CT 06511-6663

Dear Mr. Di Roma:

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

Name of Drug Product: Baxdela (delafloxacin) 450 mg Tablets
Baxdela (delafloxacin) Injection

Date of Application: October 18, 2016
Date of Receipt: October 19, 2016

Our Reference Number: NDA 208610 Baxdela (delafloxacin) 450 mg Tablets
NDA 208611 Baxdela (delafloxacin) Injection

Unless we notify you within 60 days of the receipt date that these applications are not sufficiently complete to permit a substantive review, we will file the applications on December 18, 2016, in accordance with 21 CFR 314.101(a).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).
The NDA numbers provided above should be cited at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

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

If you have any questions, call Fariba Izadi, PharmD, Regulatory Project Manager, at (301) 796-0593.

Sincerely,

[See appended electronic signature page]

Carmen DeBellas, PharmD, RPh  
Chief, Project Management Staff  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research
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/s/

CARMEN L DEBELLAS
10/24/2016
IND 62772

MEETING MINUTES

Melinta Therapeutics, Inc.
Attention: Brian P Braun, Senior Director of Quality Assurance
300 George Street
Suite 301
New Haven, CT 06511

Dear Mr. Braun:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Baxdela™ (delafloxacin) Tablets, 450 mg.

We also refer to the meeting between representatives of your firm and the FDA on March 8, 2016. The purpose of the meeting was to discuss updated CMC information (Module 3) for the oral formulation of delafloxacin.

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

If you have questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: CMC Pre-NDA

Meeting Date and Time: March 8, 2016, 1:00 PM – 2:00 PM, EST
Meeting Location: 10903 New Hampshire Avenue
                   White Oak Building 22, Conference Room: 1419
                   Silver Spring, Maryland 20903

Application Number: IND 62772
Product Name: Baxdela™ (delafloxacin) Tablets, 450 mg
Indication: Treatment of acute bacterial skin and skin structure infections (ABSSSI)
Sponsor/Applicant Name: Melinta Therapeutics

Meeting Chair: Balajee Shanmugam
Meeting Recorder: Navdeep Bhandari

FDA ATTENDEES
Balajee Shanmugam, Ph.D. Acting Branch Chief
Dorota Matecka, Ph.D. CMC Lead
Monica Cooper, Ph.D. Drug Substance Reviewer (by phone)
Milton Sloan, Ph.D. Drug Product Reviewer
Terry Miller, Ph.D. PharmTox Reviewer
Elsbeth Chikhale, Ph.D. Biopharmaceutics Lead
Om Anand, Ph.D. Biopharmaceutics Reviewer
Navdeep Bhandari, Pharm.D Regulatory Health Project Manager
Caroline Jjingo, M.D. Medical Officer
Wendelyn Schmidt, Ph.D. PharmTox Team Leader

SPONSOR ATTENDEES
Brian Braun Senior Director, Quality Assurance
Eugene Sun Interim CEO and Head R&D
Peter Di Roma Vice-President, Regulatory Affairs/Quality Assurance
Kevin Conway Vice-President, Program Management
Maxwell Reeve Director Drug Substance Development
Danping Li Director, Formulations Development
Consultant
Consultant

Reference ID: 3914343
Reference ID: 4113689
1.0 BACKGROUND

A Type B meeting briefing package was submitted February 4, 2016, for a March 8, 2016, CMC meeting with Melinta Therapeutics.

2.0 DISCUSSION

The Agency sent preliminary responses on March 3, 2016, to the Sponsor. The Sponsor asked to discuss questions 2 and 8. A slide deck was provided by the Sponsor on March 7, 2016 (attached below).

2.0 Questions

Question 1

Has the sponsor satisfactorily characterized the formation of polymorphs and proposed adequate controls to address recommendations by the FDA at the EOP-2 CMC meeting?

Agency Response:

Yes, we agree you have adequately characterized the drug substance polymorphic forms. The adequacy of the controls will be evaluated during the NDA review.

Discussion:

This topic was not discussed.

Question 2

Has the sponsor adequately qualified process impurity \( \text{[removed]} \) and is the proposed release limit reasonable?

Agency Response:

No. The referenced 4-week oral toxicology study with delafloxacin in dogs (Study \#0436DR37.001) is not acceptable for the safety qualification of process impurity \( \text{[removed]} \). No No-Observed-Adverse-Effect-Level (NOAEL) for orally administered delafloxacin could be determined in dogs due to the potentially confounding effects of emesis on drug exposure observed in all treatment groups. Therefore, for safety qualification of impurity \( \text{[removed]} \) at the desired specified level that exceeds the qualification threshold of 0.15% (as described in ICH...
Q3A\(^1\), additional justification from available nonclinical studies with delafloxacin will be required.

Alternatively, you may consider conducting a standard GLP 4-week oral toxicology study in an appropriate species, other than dog, with toxicokinetic analysis and appropriate recovery period. The primary test article for this study should be your final drug product containing delafloxacin at levels that meet or exceed the requested higher impurity limits. The toxicology study should be conducted in an appropriate species administered your final drug product daily, with an appropriate recovery period, to determine a No-Observed-Adverse-Effect-Level (NOAEL), a maximum tolerable dose (MTD), and reversibility of any drug-related toxicity, if possible. Plan to provide a rationale for your dose selection and/or projected multiples of human exposure in the proposed animal study. Plan to submit the final, signed, study report containing this nonclinical information for review in your NDA. You may consider submitting the animal study protocol for review and comment prior to initiating the study. We would need at least 30 days to evaluate any animal protocols you submit to the Division for review.

**Discussion:** The Sponsor’s discussion for Question 2 centered on their rebuttal to the Division’s written comments regarding the process impurity \(\text{(b)(4)}\) (submitted to the Division via email the evening before the meeting). It was agreed that the Division would be provided additional time to adequately address their proposed approach of using the dose adjustment factor and results from the 2013 GLP dog toxicology to qualify the impurity at the requested levels. The Sponsor’s responses to our written comments and the preliminary Division verbal responses following the Sponsor’s presentation of their proposal to answer Question #2 at the face to face meeting are provided below. Additional Division comments for Question #2 will be communicated to the Sponsor in the upcoming next few weeks.

**Sponsor Discussion:**

- \(\text{(b)(4)}\) is a process-related impurity \(\text{(b)(4)}\) with weak pharmacologic activity against bacteria.

- The Sponsor referred to two nonclinical studies in dogs to support qualification of \(\text{(b)(4)}\) at a desired specified limit of \(\text{(b)(4)}\)\%, above the qualification threshold of 0.15% described in ICH Guidance Q3A\(^1\).

- The referenced studies include two GLP 4-week oral toxicology study in dogs with delafloxacin (Study No. 0436DR37-001 and RD-00-566). Study No. RD-00-566 [2001] was conducted by Abbott Labs using a nonclinical lot not tested for \(\text{(b)(4)}\). Study No. 0436DR37-001 [2013] was conducted by Melinta to qualify impurities detected in the

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final delafloxacin DS/DP, particularly [b] (4). There were no other animal toxicology studies conducted with nonclinical lots of delafloxacin tested for [b] (4).

- The Sponsor agreed that emesis observed in the latest dog tablet study (2013) may have been a confounding factor and may have limited dose exposure. To compensate for the lower delafloxacin dose exposure in the latest dog tablet study (2013), the Sponsor proposed to use a dose adjustment factor derived from the 2001 dog capsule study (RD-00-566), that incorporated AUC/dose ratios to compensate for relatively low dose exposure observed in the latest tablet dog study.

- Dose adjustment factor (3.6) was derived by dividing the highest AUC/dose ratio (0.36) attained in the 2001 GLP dog capsule study by that determined at the NOAEL (320 mg/kg/day) in the dog tablet study (AUC/dose ratio of 0.10) [0.36/0.10].

- The Sponsor believes that robustness of the GLP tablet toxicity study in dogs (2013) should allow use of this study for qualification of impurities with adjustment for unexpectedly lower dose exposure due to emesis when exposure is compensated with the dose adjustment factor obtained from the first GLP dog study (2001).

- In response to the possible use of the dog toxicology studies with intravenously administered delafloxacin to support systemic safety of [b] (4) detected in the oral tablet, the Sponsor responded that the exposures were not high enough to adequately qualify levels of [b] (4) detected in the tablet.

- The oral dog tablet toxicology study (2013) is not considered pivotal as stated in response to the Division’s question as to why it was not included in the list of studies planned for submission to the NDA.

**Division’s Comments (preliminary):**

- After a cursory review, the Sponsor’s approach to compensate for low drug exposures in the dog tablet study (2013) using a dose modification factor derived from the dog capsule study (2001) appears to be a reasonable, creative, approach

- Emesis observed at all doses in the latest dog tablet study (2013) was likely a confounding factor on delafloxacin exposure and as such, no NOAEL could be determined from this study.

- While the study design of the 2013 tablet study appears adequate, and there were no findings of toxicity in this study, the emesis observed at all dose levels and absence of a NOAEL likely precludes its use to qualify [b] (4).
• The Sponsor’s proposed approach to incorporate a dose adjustment factor to compensate for low exposures in the 2013 tablet study derived from the previously conducted dog capsule study with better AUC/dose ratios, while creative, may be flawed. This approach is dependent on another pivotal GLP oral dog toxicology study with delafloxacin in which emesis was a primary finding observed at all dose levels, associated with variable drug exposures between individual animals within each group, and from which no NOAEL could be determined.

• The above comments represent a preliminary response to the Sponsor’s proposed approach discussed in the face to face meeting. The Pharm/Tox review team will further examine the written rebuttal to the Division’s written comments and will provide a more thorough written response in the next few weeks.

• In response to the Sponsor’s general question regarding the qualification of impurities in the intravenous vs oral administration of delafloxacin, the Division mentioned that intravenous administration of the drug may not adequately evaluate the local toxicity of orally administered drug and its impurities, particularly of a drug like delafloxacin which clearly had emetic properties,

(Note: It was erroneously stated in the meeting by the pharm/tox reviewer that he observed emesis in the intravenous rat toxicology studies conducted with delafloxacin. What was meant instead was that he observed emesis in the intravenous dog toxicology studies with delafloxacin. The Sponsor indicated that delafloxacin was a “biliary toxicant” and therefore would cause some local irritation which was likely responsible for the emesis.)

**Question 3**

*Does the FDA agree with the manner in which updated relative response factors for impurities have been applied to analytical batch and stability data planned for the NDA?*

**FDA Response:** Yes, your approach is acceptable.

**Discussion:**

This topic was not discussed.

**Question 4**

*Does the Agency agree that the stability protocols for the 10 and 100-count bottles adequately bracket the commercial 20-count bottle for the purposes of stability analysis in the NDA?*

**Agency Response:**
Your proposal to bracket the commercial 20-count bottles appears reasonable.

**Question 5**

*Can the sponsor provide drug product (tablet) stability data (30 month) after the 30-day NDA filing period when the formal FDA NDA review begins?*

**Agency Response:**

Under the “Program” you can submit minor updates to the NDA within 30-days of submitting the NDA. Therefore, FDA does not agree with the proposal to submit stability data after the thirty day filing period but you may be able to do so within 30-days of submission.

**Discussion:**

*This topic was not discussed.*

**Question 6**

*Melinta would like to confirm the conditions under which the expiration dating for the oral drug product (tablet) formulation can be extended by NDA annual reporting.*

**Agency Response:**

Expiration date will be determined based on the evaluation of the data submitted in the NDA. Note that current guidelines provide the applicant to extend expiry period following the approved stability protocol via annual reporting. We recommend that you refer to the following guidance document:


**Discussion:**

*This topic was not discussed.*

**Question 7**

*Does the Agency agree that sponsor investigations to assess the polymorphic form in the drug product are sufficient and routine testing for polymorphic form in commercial tablets is not needed?*

**Agency Response:**

This is a review issue and will be evaluated upon review of the data submitted.

**Discussion:**
This topic was not discussed.

**Question 8**

Does the Agency agree that Melinta has conducted sufficient dissolution development studies to support proposing a dissolution specification of NLT \( \frac{b}{d} \% (Q) \) at \( \frac{b}{d} \) minutes?

**Agency Response:**

No, we do not agree that the discriminating ability of the proposed in vitro-drug dissolution method has been adequately established.

Based on the limited data and information in the Briefing Package, we consider that the proposed dissolution method is not appropriate. We recommend that additional experiments be conducted to optimize the dissolution method for your proposed product prior to NDA filing.

In addition, the following comments should be addressed in the dissolution package to be submitted in the NDA:

1. Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting the dissolution and establish that your method is discriminating with regard to these critical material attributes (CMA) and critical process parameters (CPP) affecting the dissolution.

2. We acknowledge that the limited data provided in the dissolution method development report indicate that Delafoxacin is a low solubility and low permeability drug substance and \( \frac{b}{d} \) is justified based on the solubility data. However, dissolution on Delafoxacin Tablets, 450 mg (Lot#13DE009) using the method \( \frac{b}{d} \) [Table 58; page #97-98/111] is very rapid and complete; the dissolution data indicate that \( \frac{b}{d} \) may not be warranted. Revise the dissolution method or justify \( \frac{b}{d} \) based on the dissolution data.

3. It is noted that the proposed dissolution method is not discriminating \( \frac{b}{d} \). The proposed dissolution method may NOT be considered discriminating \( \frac{b}{d} \). The comparison of formulations made with markedly different manufacturing processes is not an acceptable approach for investigating the discriminating power of a dissolution method. Submit data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the
dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions with ± 10-20% change to the specification-ranges of these variables) for the most relevant critical manufacturing variables (e.g. drug substance particle size, solid state, etc.).

4. Since the product contains a drug substance with low solubility, please optimize and evaluate the dissolution. Also, optimize the dissolution.

5. In addition, submit dissolution data in additional dissolution media.

6. To obtain a discriminating dissolution method, you may also explore the possibility of using any other appropriate compendial apparatus.

Note that the adequacy of the proposed acceptance criteria for your product will be made during the NDA review process based on the totality of the provided dissolution data.

**Discussion:**

The Sponsor presented their proposal to optimize the existing dissolution method and to submit a dissolution method development report in the NDA. FDA indicated that in general, the Sponsor’s approach appears appropriate. The Sponsor asked for clarification regarding the Agency’s preliminary comments on the formulation. The FDA clarified that no reformulation of the proposed drug product is requested. FDA clarified that meaningful variations (i.e. ± 10-20%) to the proposed formulation can be used to investigate the discriminating ability of the dissolution method. The Sponsor indicated that they will provide a list of critical material attributes and critical process parameters that affect dissolution.

**Question 9**

*Does the FDA agree with the proposed content and format of Module 3 to support the NDA for Delafloxacin Tablet, 450 mg?*

**Agency Response:**

FDA has no objections to the proposed content and format of Module 3.

**Discussion:**

*This topic was not discussed.*
**Question 10**

*Melinta proposes to name delafloxacin as the free acid on product labelling. Is this acceptable to the FDA?*

**Agency Response:**

This appears to be in agreement with the USP salt policy.

**Discussion:**

This topic was not discussed.
Question 2
Has the sponsor adequately qualified process impurity and is the proposed release limit reasonable?

Agency Response:
No. The referenced 4-week oral toxicology study with delafloxacin in dogs (Study #0436DR37.001) is not acceptable for the safety qualification of process impurity. No No-Observed-Adverse-Effect-Level (NOAEL) for orally administered delafloxacin could be determined in dogs due to the potentially confounding effects of emesis on drug exposure observed in all treatment groups. Therefore, for safety qualification of impurity at the desired specified level that exceeds the qualification threshold of 0.15% (as described in ICH Q3A1), additional justification from available nonclinical studies with delafloxacin will be required.

Alternatively, you may consider conducting a standard GLP 4-week oral toxicology study in an appropriate species, other than dog, with toxicokinetic analysis and appropriate recovery period. The primary test article for this study should be your final drug product containing at levels that meet or exceed the requested higher impurity limits. The toxicology study should be conducted in an appropriate species administered your final drug product daily, with an appropriate recovery period, to determine a No-Observed-Adverse-Effect-Level (NOAEL), a maximum tolerable dose (MTD), and reversibility of any drug-related toxicity, if possible. Plan to provide a rationale for your dose selection and/or projected multiples of human exposure in the proposed animal study. Plan to submit the final, signed, study report containing this nonclinical information for review in your NDA. You may consider submitting the animal study protocol for review and comment prior to initiating the study. We would need at least 30 days to evaluate any animal protocols you submit to the Division for review.

Melinta Response:
As background, is a process-related impurity. The 4-week oral tablet study in dogs (0436DR37-001) was conducted to qualify impurities found in the final delafloxacin drug substance/product. Dogs were chosen for this qualification study over rats study since dogs are more sensitive to the adverse systemic toxicity of delafloxacin and a practical species for the administration of the tablet formulation. This study was a comprehensive GLP toxicology evaluation with the high dose (480 mg/kg/day) exceeding that
administered in previous dog toxicity studies where adverse systemic effects were observed at 320 mg/kg/day (RD-00-566, RD-02-564).

We agree with the FDA reviewer that emesis may be a confounding factor in the tablet dog study (0436DR37-001), and thus may be a factor in limiting dose exposure, particularly relative to previous dog studies using the delafloxacin drug substance administered orally in gelatin capsules (RD-00-566, RD-02-564). Dose exposure as indicated by the delafloxacin AUC/dose ratio, which ranges from 0.07 to 0.12 in the dog tablet study, is lower than the ratios of 0.17 to 0.36 determined in the previous pivotal GLP toxicology dog studies which allowed a robust assessment of toxicity (RD-00-566, RD-02-564). Figure 2 illustrates the AUC/dose ratios for the GLP dog tablet study relative to those of the pivotal GLP oral toxicology studies in dogs. As a cross-species comparison, the AUC/dose ratios for the pivotal rat toxicology studies are similar to those of the pivotal dog studies, with ratios ranging from 0.25 to 0.32 for the GLP oral 4-week rat toxicology study (RD-02-763).

Figure 2. Delafloxacin Dose Exposure (AUC/Dose Ratio) in Dogs Following Repeat Oral Dosing of Formulated Tablets or Drug Substance in Capsules

To adjust for the apparent lower delafloxacin dose exposure in the dog tablet study, which could affect dose exposure to , we propose to add a dose adjustment factor based on historical AUC/dose ratios. The dose adjustment factor was conservatively derived by dividing the highest AUC/dose ratio (0.36), attained in the pivotal GLP repeat-dose toxicity studies in dogs, by that determined at the NOAEL (320 mg/kg/day) in the tablet dog study (AUC/dose ratio of 0.10). A dose adjustment of 3.6 (0.36/0.10) can then be applied to compensate for the relatively low dose exposure seen in the tablet dog study. The recalculated qualification level based on the dose exposure adjustment factor of 3.6 is shown in Table 1.

In summary, although we agree with the FDA response that delafloxacin dose exposure may be a confounding factor in the dog tablet study, the robustness of the GLP tablet toxicity study in dogs should allow use of this study for the qualification of impurities with adjustment for the unexpectedly lower dose exposure as determined by the AUC/dose ratios for delafloxacin.
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<th>Tox Study Impurity NOAEL Dose (mg/kg/day)</th>
<th>Safety Qualification Level (%) based on free acid</th>
<th>Safety Qualification Level (%) based on salt</th>
<th>Safety Qualification Level (%) based on salt (adjusted for low dose exposure)</th>
<th>Drug Substance Acceptance Criteria based on salt (%)</th>
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Question 8

Does the Agency agree that Melinta has conducted sufficient dissolution development studies to support proposing a dissolution specification of NLT % (Q) at minutes?

Agency Response:

No, we do not agree that the discriminating ability of the proposed in vitro-drug dissolution method has been adequately established.

Based on the limited data and information in the Briefing Package, we consider that the proposed dissolution method is not appropriate. We recommend that additional experiments be conducted to optimize the dissolution method for your proposed product prior to NDA filing.

Melinta’s Proposal in response to FDA’s Comments for Question 8:

Summary: The formulation for Delafloxacin Tablets, 450 mg was developed to rapidly disintegrate and be readily absorbed in the human body. Melinta agrees with the FDA’s response and will conduct additional dissolution method development work prior to submission of the NDA 208610 (tablet) to find conditions that provide more discrimination. The sponsor would like to use the pre-NDA meeting to discuss our approach to study dissolution method design to ensure alignment with FDA expectations. We propose to support this method development using lab-scale batches that vary critical material attributes (CMAs) and critical process parameters (CPPs). The new method will be used to assess on-going stability samples as well as retain samples from other clinical batches made using our proposed commercial process. Our intent is to provide this information in Module 3 of the tablet NDA comparing the existing dissolution method versus the new dissolution method.

FDA Recommendation #1: Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting the dissolution and establish that your method is discriminating with regard to these critical material attributes (CMA) and critical process parameters (CPP) affecting the dissolution.

Melinta Proposal:

Based on the development work, Melinta has identified CMAs and CPPs that may impact delafloxacin tablet dissolution. We will develop a new dissolution method and ascertain its discriminating power by testing tablets prepared by varying material, formulation and process attributes listed below:
**FDA Recommendation #2:**

We acknowledge that the limited data provided in the dissolution method development report indicate that Delafloxacin is a low solubility and low permeability drug substance is justified based on the solubility data. However, dissolution on Delafloxacin Tablets, 450 mg (Lot#13DE009) using the method [Table 58; page #97-98/111] is very rapid and complete; the dissolution data indicate that or justify the dissolution method data.

**Melinta proposal:**

The sponsor will redesign the dissolution method.

**FDA Recommendation #3:**

It is noted that the proposed dissolution method is not discriminating. The proposed dissolution method may NOT be considered discriminating. The comparison of formulations made with markedly different manufacturing processes is not an acceptable approach for investigating the discriminating power of a dissolution method. Submit data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions with ±10-20% change to the specification-ranges of these variables) for the most relevant critical manufacturing variables (e.g. drug substance particle size, solid state, etc.).

**Melinta proposal:**

Please see response above to FDA Recommendation #1.

The sponsor’s opinion is that no optimized dissolution method developed can discriminate all potential material or process changes. As a result, varying certain parameters (at +/- 20% of nominal) may not produce significant dissolution changes. What is the FDA position on this point?

The sponsor seeks further clarification as to what constitutes dissolution discrimination for a certain parameter change (i.e. tablet hardness). Is it acceptable if the method just discerns rank-order changes at single sampling points such as 15 or 30 minutes?
**FDA Recommendation #4:**

*Since the product contains a drug substance with low solubility, please optimize and evaluate the dissolution. Also, optimize the dissolution.*

**Melinta proposal:**

We want clarify that FDA is not expecting Melinta to re-optimize the tablet formulation but simply asking us to evaluate the discriminating ability of dissolution method [\(b\)]

The to-be-marketed oral formulation was used in the pivotal bioequivalence study (RX-3341-115). This is the same formulation that is being used in our recently completed Phase 3 clinical trial (study RX-3341-303) in ABSSSI. Our tablet formulation has already been optimized and as such no further formulation development work is needed.

Please see the response to FDA recommendation #1 (above) for a discussion of CMAs used in the formulation.

**FDA Recommendation #5:**

*In addition, submit dissolution data [\(b\)].*

**Melinta proposal:**

After we have determined our optimized dissolution method we will run it per FDA’s suggestion. [\(b\)] This information will be included in the NDA.

**FDA Recommendation #6:**

*To obtain a discriminating dissolution method, you may also explore the possibility of using any other appropriate compendial apparatus. Note that the adequacy of the proposed acceptance criteria for your product will be made during the NDA review process based on the totality of the provided dissolution data.*

**Melinta proposal:**

Based on development work to date, the sponsor believes the current dissolution apparatus (USP Paddle Apparatus 2) can potentially be made more discriminating. The use of an alternate compendial apparatus such as USP Basket Apparatus 1 will be evaluated, if necessary.
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/s/

NAVDEEP BHANDARI
04/08/2016
Dear Mr. Di Roma,

Attached, please find our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 29, 2016 between Melinta and the Division of Anti-Infective Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

As stated in our January 05, 2016 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at

Reference ID: 3893099
Reference ID: 4113689
Please do not hesitate to contact me if you have any questions.

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

Preclinical/Toxicology

**Question 1:** A rigorous and comprehensive nonclinical program with delafloxacin has been conducted to support its use in the treatment of ABSSSI. Is the proposed nonclinical package acceptable for FDA to conduct a substantial review?

**FDA Response:** Yes, from a pharmacology/toxicology perspective, the non-clinical studies conducted with delafloxacin appear acceptable to conduct a substantial review.

Also, please note that as of June 30, 2015, all human drugs and biologic products approved after this date must comply with labeling requirements described in the Pregnancy and Lactation Labeling (PLLR) Final Rule (Dec. 2014). You may refer to both the published PLLR Final Rule (2014) and the FDA Draft Guidance for Industry “Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format” for information that may be helpful to you.

A link to the PLLR Final Rule and the FDA Draft Guidance for Industry are included below.

https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for-

**Microbiology**

**Question 2:** For the S. anginosus group of organisms (S. anginosus, S. constellatus, and S. intermedius), the Sponsor will have a total number of S. anginosus group organisms of approximately 171 isolates from recent surveillance MIC data (2014 and 2015 US and EU surveillance studies). Although this will be less than 100 each of the individual species within the S. anginosus group of organisms, the Sponsor feels that this will be an adequate number of S. anginosus group organisms since these organisms are phylogenetically related with comparable susceptibility patterns to delafloxacin. **Does the FDA concur that this number of surveillance isolate MIC data is acceptable to support inclusion of the S. anginosus group of organisms in the delafloxacin USPI?**
**FDA Response:** Yes, the number of isolates proposed for surveillance data against *S. anginosus* group is acceptable. However a decision regarding inclusion of these organisms in the USPI will only be made after review of the NDA.

**Question 3:** Is the proposed content and format of the microbiology sections of the NDA acceptable?

**FDA Response:** The content and format proposed to submit the microbiology data and information is appropriate.

In addition to the summary data listed in 2.1.6, Appendices 6 and 11, we also recommend that the summary of the clinical microbiology data should also include the following:

- MIC values and subject microbiological outcome for each baseline pathogen within the proposed indication. Please list all subsets of organisms demonstrating unique mechanisms of resistance and virulence separately.

- MIC values and subject clinical outcome for each baseline pathogen within the proposed indication. Please list all subsets of organisms demonstrating unique mechanisms of resistance and virulence separately.

- Zone diameters and subject microbiological outcome for each baseline pathogen within the proposed indication. Please list all subsets of organisms demonstrating unique mechanisms of resistance and virulence separately.

- Zone diameters and subject clinical outcome for each baseline pathogen within the proposed indication. Please list all subsets of organisms demonstrating unique mechanisms of resistance and virulence separately.

- For each subset of pathogens requiring defined MIC breakpoints, all individual isolates in the range of MICs from two dilutions below the susceptible and two dilutions above the resistant provisional breakpoints.

- For each subset of pathogens requiring defined zone diameter breakpoints, all individual isolates in the range of zone diameters from 4 to 6 millimeters above the susceptible and 4 to 6 millimeters below the resistant provisional breakpoints.

- For each group of organisms, a histogram showing the number of isolates at each MIC from clinical trials overlaying isolates from non-clinical studies. Organisms with characterized phenotypic resistance and virulence markers should be presented as a subset.

- For each group of organisms, a histogram showing the number of isolates at each zone diameter from clinical trials overlaying isolates from non-clinical studies. Organisms with characterized phenotypic resistance and virulence markers should be presented as a subset.
**Question 4:** Is the proposed microbiology electronic review aid to be provided in the NDA acceptable?

**FDA Response:** Yes, it is acceptable.

**Clinical Pharmacology**

**Question 5:** Has the Agency confirmed that the ECG waveform data from the TQTc Study RX-3341-111 submitted to the FDA ECG warehouse on March 14, 2012 (Upload Request ID: 20120314080254) is suitable for FDA review? Secondly, does FDA prefer that the recently converted HL7 electronic waveform data from QT trial M01-365 be submitted through the ECG warehouse or instead included in the NDA?

Does FDA also want to have CV/QT study electronic waveform data from QT trial M01-365 (200-, 800-, 1200-mg doses oral formulation) converted into HL7 format included in the NDA?

**FDA Response:** We have previously reviewed the ECG waveform data from the TQTc Study RX-3341-111 and concluded that the data were acceptable. Please submit waveform data from QT trial M01-365 to the FDA ECG warehouse.

**Question 6:** Does the Agency agree that the pharmacokinetic data sets and files the Sponsor will be providing are adequate to support the Agency’s review of the Clinical Pharmacology and Biopharmaceutics Modules of the NDA?

**FDA Response:** The proposed submission of the PK datasets and files appears appropriate to support the Agency’s review of the Clinical Pharmacology and Biopharmaceutics Modules of the NDA. In addition, we request that you submit NONMEM datasets with IDs that will facilitate linking to the original unique subject IDs. In addition to control streams and outputs of models, if simulations have been conducted as part of your analyses, dataset and codes (R, SAS, etc.) for simulations and analyses (such as graphing) should be submitted to aid our review.

Please note that additional Biopharmaceutics comments will be discussed at the upcoming CMC meetings for IND 62772 and IND 76096, scheduled on March 8, 2016 and April 5, 2016, respectively.

**Question 7:** Is the proposal for a pharmacology reviewer guide acceptable?

**FDA Response:** The proposal for a Clinical Pharmacology Reviewer guide is acceptable.

**Clinical Safety, Clinical Efficacy, and Biostatistics**

**Question 8:** Does the Agency agree with the content, structure, and format of the example SDTM data sets for study ML-3341-302?
**FDA Response:** Based on our preliminary review, the example SDTM data sets for study ML-3341-302 appear to be acceptable. However, we might have additional requests once the NDA is submitted.

Please also submit a define.pdf if you use define.xml v1.0 for printing purposes. If you submit a define.xml 2.0, you do not need to include a define.pdf. For the evaluation of sample data, please follow the procedure described on the website [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm)

Please also refer to the *Study Data Standards Resources* website for any information regarding submission of standardized data.

**Question 9:** Is the proposed content/format of the safety data intended to be provided at 4-Month NDA Safety Update acceptable?

**FDA Response:** Your proposal is acceptable.

**Question 10:** Does the Agency agree that the proposed safety and efficacy tables for 2.7.3 and 2.7.4 are acceptable?

**FDA Response:** The proposed safety and efficacy tables are acceptable. However, we will further assess this at the time of the NDA submission.

**Question 11:** Is it acceptable if the Sponsor provides lesion photographs taken in the Phase 3 trials in electronic format upon request during NDA review?

**FDA Response:** Please submit a dataset that includes all treated patients from both Phase 3 trials including only variables depicting the patient ID and treatment assignment. We will take a 10% random sample of these patients and request that case report forms (CRFs) for these patients be included in the NDA. We would like you to submit the lesion photographs for the 10% random sample. We might request additional photographs during the review, if the need arises.

Please contact esub@fda.hhs.gov about how to submit lesion photograph image data in a manageable format that is acceptable for FDA review and archives.

**Question 12:** Does the Agency have any unresolved issues regarding data analysis and/or discussion for Melinta to consider and address?

**FDA Response:** We recommend that you include a brief algorithm in the Reviewer Guide of your NDA submission which describes how results from all primary, secondary and major safety analyses were derived (e.g. the dataset and names of variables used). This would help to limit potential discrepancies between Reviewer and Sponsor analysis results. In addition, SAS programs can be provided. Please ensure that ADaM datasets with define.xml 2.0 (or define.xml 1.0 and define.pdf) will be submitted for each study. Study analysis datasets should be traceable
to the tabulation datasets. If the ADaM datasets were created based on CRF raw data, please also submit the CRF raw data as well.

Note that we may need to further address issues regarding data analysis after the NDA is submitted.

**Question 13:** Does FDA agree with Melinta’s proposed site-specific data sets to be included in the NDA?

**FDA Response:** Please refer to the attached document.

**Regulatory**

**Question 14:** To assist in planning, especially under NDA Priority Review timeline, Melinta would like to know FDA’s current position regarding the need for an FDA Advisory Committee to assess the ABSSSI NDA for delafloxacin?

**FDA Response:** It is premature to determine if there is a need for an FDA Advisory Committee.

**Question 15:** For the purposes of complying with FDA Financial Disclosures guidelines, Melinta proposes Phase 2/3 studies in Table 4 titled “Key Studies in Support of ABSSSI Indication as the “covered studies.” Does FDA agree?

**FDA Response:** Yes, your proposal is acceptable. Note that additional financial disclosures may be required if previously conducted non-ABSSSI studies are needed to support the safety of the currently proposed NDA, or in the future when an efficacy supplement is submitted for a new indication.
The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator’s site address or contact information since the time of the clinical investigator’s participation in the study, we request that this updated information also be provided.

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

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf ) for the structure and format of this data set.
Attachment 1

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

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

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
[m5]
 | datasets
 | bimo
 | site-level
```

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

1 Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files
References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

For general help with eCTD submissions: ESUB@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FARIBA IZADI
02/25/2016
IND 62772

SPECIAL PROTOCOL AGREEMENT

Melinta Therapeutics, Inc.
Attention: Peter Di Roma
Vice President, Regulatory Affairs and Quality Assurance
300 George Street, Suite 301
New Haven, CT 06511

Dear Mr. Di Roma:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for delafloxacin oral tablet.

We acknowledge your request dated June 01, 2015, received on June 01, 2015, for a special protocol assessment of a clinical protocol. The protocol is titled “A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Efficacy and Safety of IV and Oral Delafloxacin compared with Vancomycin + Aztreonam in Patients with Acute Bacterial Skin and Skin Structure Infections”.

We note that this protocol includes revisions based on comments provided in our May 22, 2015 letter.

We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as “Special Protocol Assessment - Amendment”. This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act.

As stated on page 9 in the “Guidance for Industry: Special Protocol Assessment,” a special protocol assessment documents our agreement that the design and planned analysis of a study can adequately address objectives in support of a regulatory submission. However, final determinations for marketing application approval are made after a complete review of a marketing application and are based on the entire data in the application.
If you have any questions, call Fariba Izadi, PharmD, Regulatory Health Project Manager, at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
07/01/2015
IND 62772

SPECIAL PROTOCOL ASSESSMENT – NO AGREEMENT

Melinta Therapeutics, Inc.
Attention: Peter Di Roma
Vice President, Regulatory Affairs and Quality Assurance
300 George Street, Suite 301
New Haven, CT 06511

Dear Mr. Di Roma:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for delafloxacin oral tablet.

We acknowledge your request dated and received April 23, 2015 for a special protocol assessment of a clinical protocol. The protocol is titled “A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Efficacy and Safety of IV and Oral Delafloxacin compared with Vancomycin + Aztreonam in Patients with Acute Bacterial Skin and Skin Structure Infections”.

We have completed our review and, based on the information submitted, have determined that the design and planned analysis of your study do not adequately address the objectives necessary to support a regulatory submission.

We have the following comments:

**Clinical Pharmacology:**

Reference ID: 3762571
Reference ID: 4113689
(b) (4)
We recommend that patients with severe renal impairment (eGFR of 15-29 mL/min/1.73 m$^2$) be excluded from the proposed Phase 3 trial (RX-3341-303) or the dose of IV delafloxacin be decreased in patients with severe renal impairment.
If you choose to revise this protocol and submit another request for special protocol assessment prior to study initiation, it should address all the issues itemized above and be prominently labeled as a "Special Protocol Assessment – Resubmission." In addition, your cover letter should clearly reference the date and type of your original SPA submission as well as the
following SPA reference number: 1. To facilitate review of your SPA resubmission, send a copy of the cover letter to Fariba Izadi, Pharm.D.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting and will be limited to the discussion of this protocol. For additional information, refer to FDA’s “Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants” at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm153222.pdf

If you have any questions, call Fariba Izadi, PharmD, Regulatory Health Project Manager, at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
05/22/2015
IND 76096

SPECIAL PROTOCOL - AGREEMENT

Rib-X Pharmaceuticals, Inc.
Attention: Rebecca Nortz, RAC
Senior Manager, Regulatory Affairs
300 George Street, Suite 301
New Haven, CT 06511

Dear Ms. Nortz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for Delafloxacin I.V. (RX-3341).

We acknowledge your request dated August 12, 2013, received on August 12, 2013, for a special protocol assessment of a clinical protocol. The protocol is titled “A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate The Efficacy And Safety Of IV and Oral Delafloxacin compared With Vancomycin ± Aztreonam In Patients With Acute Bacterial Skin And Skin Structure Infections.”

We note that the protocol included in your SPA resubmission includes revisions discussed in our March 29, 2013, Special Protocol-No Agreement letter and in the April 9, 2013, meeting between you and this Division.

We have completed our review and, based on the information submitted, we agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as “Special Protocol Assessment - Amendment”. This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act.

As stated on page 9 in the “Guidance for Industry: Special Protocol Assessment,” a special protocol assessment documents our agreement that the design and planned analysis of a study can adequately address objectives in support of a regulatory submission. However, final determinations for marketing application approval are made after a complete review of a marketing application and are based on the entire data in the application.

We have the following responses to your questions:

Reference ID: 3358875
Reference ID: 4113689

Reference ID: 3358875
**Question 1**
Does the FDA agree that the 450 mg delafloxacin tablet formulation is therapeutically equivalent to the 300 mg IV dose and that it can be used for the IV to oral switch described in Protocol 303?

**FDA Response:** We agree that the 450 mg delafloxacin oral tablet is appropriate for the purposes of an oral switch in your proposed Phase 3 trial. However, the tablet would not be considered bioequivalent to the IV formulation. The regulatory definition of “therapeutic equivalence” is as follows: Drug products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Drug products are considered to be therapeutically equivalent only if they meet these criteria:

- They are pharmaceutical equivalents (contain the same active ingredient(s); dosage form, and route of administration; and strength)
- They are assigned by FDA the same therapeutic equivalence codes starting with the letter “A.”
- Designates a brand name drug or a generic drug to be the Reference Listed Drug (RLD)
- Assigns “therapeutic equivalence” codes based on data that a drug sponsor submits in an ANDA to scientifically demonstrate that its product is bioequivalent (i.e., performs in the same manner as the Reference Listed Drug)

**Question 2**
The key PK driver for delafloxacin efficacy is AUC, with the best PK/PD relationship having been shown to be AUC/MIC. If Rib-X demonstrates bioequivalence for AUC only for the 300 mg IV infusion dose and the projected 450 mg oral tablet dose according to FDA’s Guidelines for establishing bioequivalence, we believe that such data will support label language for section 12 of the delafloxacin USPI similar to that found in the USPI for levofloxacin. Does the FDA agree?

**FDA Response:** It is premature at this point to discuss specific labeling language. However, the levofloxacin labeling example is not directly applicable to delafloxacin. The plasma concentration profile for delafloxacin after IV administration is not “similar” to the oral concentration-time profile, despite a “comparable” extent of exposure (AUC). A statement may be included in the label alluding to the comparable exposure achieved by the 300 mg IV formulation and the 450 mg tablet formulation. The statement about the oral and IV route of administration being considered interchangeable is unlikely to be included in the delafloxacin label. In the levofloxacin label, it is apparent that the same dosage strength given by a different route (e.g. 500 mg oral tablet compared to 500 mg IV) results in comparable exposure and a somewhat similar Cmax. However, a 50% higher oral dose of delafloxacin would be required to achieve comparable exposure.

**Question 3**
It was noted in our Phase 2B ABSSSI study (RX-3341-202) that patients with a body mass index of 30 or greater showed a statistically significantly better outcome (investigator assessment of cure) on delafloxacin compared to vancomycin. Because this outcome and the importance of
identifying a more effective treatment of ABSSSI in patients with a high body mass index (BMI), we have included in the secondary endpoint analysis a test for superiority of delafloxacin compared to vancomycin in patients with BMI ≥ 30. Does the Agency agree with the addition of this secondary endpoint in Study RX-3341-303?

**FDA Response:**

Your proposal to test for superiority for the secondary endpoint of investigator’s assessment of cure at the follow-up visit is acceptable. The clinical interpretation of superiority at the follow-up visit will be a review issue which will take into account whether a difference in response was also demonstrated at an earlier timepoint and the adequacy of vancomycin dosing.

Furthermore, because findings from subgroup analyses may be limited by the lack of proper randomization which can result in patient imbalances of important risk factors, we recommend stratifying the initial randomization by BMI status at baseline (i.e. BMI < 30, BMI ≥ 30) as well as by infection type.

**Question 4**

We have pre-specified a sub-analysis of obese patients in the first Phase 3 pivotal study (RX-3341-302) and are replacing it as a key secondary outcome in the second Phase 3 pivotal study (RX-3341-303). If the analysis of the obese subpopulation from both pivotal studies is consistent in demonstrating a clinically meaningful difference in the efficacy of these patients on delafloxacin, we believe it is important to provide this information in the USPI so that physicians can make informed decisions regarding treatment of this difficult to treat population. Does the FDA agree in principle with inclusion of such data in Section 14 of the USPI?

**FDA Response:** Description of the results in the obese subpopulation in Section 14 of the USPI is ultimately a review issue which will depend upon the robustness of the evidence presented, consistency across studies, the adequacy of vancomycin exposure in the comparator arm, and whether any efficacy differences at the follow up visit were also detected at an earlier timepoint.

**Question 5**

We propose that patients with severe renal insufficiency (estimated GFR of 15-29) should receive delafloxacin by 1 hour intravenous infusion at 200 mg. Does the FDA agree with this dosing recommendation?

**FDA Response:** The preliminary data appear to support a dose adjustment in patients with severe renal impairment. Based on the supportive evidence that you have provided, the proposed dose adjustment of 200 mg IV delafloxacin is acceptable. We recommend that you consider inclusion of patients with severe renal impairment in the Phase 3 trial to help evaluate the performance of the dose adjustment. However, we note that you do not recommend a corresponding dose adjustment to the oral tablet, so these patients may have to continue on IV therapy for the duration of the trial.
**Question 6**
Does the FDA have any additional comment on the Protocol or Statistical Analysis Plan for Study 303?

**Statistical Comments:**

1. As conveyed in our earlier statistical comments for your submission regarding Study 302 May 04, 2012, noninferiority comparisons at later follow-up time points are not recommended as the results cannot be interpreted due to uncertainties in the available evidence of treatment effect and the lack of non-inferiority margins. Pre-specified superiority testing of the secondary endpoints is considered meaningful. For Study 303, it is acceptable to use the following order for hierarchical testing of superiority:

   i. Sustained clinical response based on the investigator’s assessment of signs and symptoms of infection at the Follow-up visit.
   ii. Sustained clinical response based on the investigator’s assessment of signs and symptoms of infection in patients with a BMI $\geq 30$ at the Follow-up visit.
   iii. Sustained clinical response based on the investigator’s assessment of signs and symptoms of infection at the Late Follow-up visit.
   iv. Percent of patients who had a reduction of erythema of 30% or greater at 48 – 72 hours when digital measurements are used.
   v. Reduction in pain as measured by ePRO
   vi. Microbiologic response in all patients

2. Section 11.2 of the SAP which states the primary analysis is stratified by baseline infection category does not appear to be consistent with Section 3.8.3 of the protocol which states the primary analyses is performed without stratification. We recommend that the primary analysis is not stratified by any factor(s) and evaluated based on the ITT population, including all randomized patients. However, a stratified analysis by baseline infection types can be included as a sensitivity or supportive analysis.

3. We recommend that you use the same statistical approaches in both the primary analyses and secondary analyses, where applicable. For example, the methods for handling missing data in the primary analysis should also be used in the secondary analyses. Therefore, analyses using only observed data or LOCF imputation should only be considered only as sensitivity or exploratory analyses.

4. Robustness of noninferiority findings in the primary analysis based on a 20% reduction in lesion size should also be evaluated using various sensitivity analyses. Treatment differences should be evaluated for higher reductions (e.g., $\geq20\%$), and at various timings of assessment (e.g. 48-60, 60-72, 72+ hours) along with complete resolution of signs and symptoms at EOT, TOC and at late follow-up visits.

5. You have proposed two measurements on day 3 which are 12 hours apart. Please pre-specify which of the measurements will be used for the primary analyses.
6. We recommend that lesion measurement and digital photography is also performed on Day 5 since all patients will be treated for at least 5 days. This would also provide for a better assessment of possible effects on lesion size associated with an IV to oral switch in delafloxacin patients starting on Day 4.

7. You state in the exclusion criteria that patients receiving a single dose of a short-acting antimicrobial drug for ABSSSI would be limited to no more than 25% of the randomized patients at each site. Such a limitation should refer to all randomized patients rather than randomized patients at each site. Therefore, exclusion criteria would apply to all enrolled patients rather than being site dependent. We would emphasize that the number of patients receiving prior antibiotic therapy is minimized as much as possible since the potential effects on an early endpoint at 48-72 hours following treatment are unclear and can confound the treatment effect. If feasible, you could also consider stratifying the initial randomization by prior antibacterial to improve primary analysis comparisons.

**Clinical Pharmacology Comments:**

1. We recommend that you characterize the effect of food on your final oral tablet formulation.

2. We recommend that you conduct a hepatic impairment trial.

3. The interaction potential for delafloxacin on P-gp (substrate, inhibitor, inducer) should be characterized.

You are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].


Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to IND 76096, clinical protocol submitted on August 12, 2013, your clinical protocol number, if available, and that it contains the FDA Form 3674 that was to accompany that submission.

If you have already submitted the certification for this submission, please disregard the above.

If you have any questions, call Fariba Izadi, Pharm.D, Regulatory Project Manager, at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD  
Acting Division Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHERINE A LAESSIG
08/19/2013
IND 76096

SPECIAL PROTOCOL - AGREEMENT

Rib-X Pharmaceuticals
Attention: Rebecca Nortz, RAC
Senior Manager, Regulatory Affairs
300 George Street, Suite 301
New Haven, CT 06511

Dear Ms. Nortz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i)
of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for RX-3341 (delafloxacin).

We acknowledge your request dated December 21, 2012, received on December 26, 2012, for
the resubmission of a special protocol assessment of a clinical protocol. The protocol is titled “A
Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate the
Efficacy and Safety of Delafloxacin compared with Vancomycin ± Aztreonam in Patients with
Acute Bacterial Skin and Skin Structure Infections.”

We note that this protocol includes revisions noted in our July 20, 2012, letter.

We have completed our review and, based on the information submitted, agree that the design
and planned analysis of your study adequately address the objectives necessary to support a
regulatory submission. If you choose to revise this protocol, submit your modifications
as “Special Protocol Assessment - Amendment”. This agreement is subject to modification
only as outlined in section 505(b)(4)(C) of the Act.

As stated on page 9 in the “Guidance for Industry: Special Protocol Assessment,” a special
protocol assessment documents our agreement that the design and planned analysis of a study
can adequately address objectives in support of a regulatory submission. However, final
determinations for marketing application approval are made after a complete review of a
marketing application and are based on the entirety of the data in the application.

We also have the following responses to your questions and comments.

1. The primary efficacy endpoint will be ≥ 20% decrease in lesion erythema size compared
to baseline in the ITT population at 48 to 72 hours after initiation of treatment as
determined by digital measurements of the leading edge.
**FDA Response:**
We agree.

2. Sustained clinical responses at the Follow-Up (Day 14 ± 1) and Late Follow-up (Day 21-28) visits are secondary efficacy endpoints with the following ordering for hierarchical testing of superiority:

2) Sustained clinical response at Follow-up visit
3) Sustained clinical response at late Follow-up visit
4) Percent of patients who had a reduction of erythema of 30% or greater at 48 – 72 hours
5) Clinical response in MRSA patients at FU visit
6) Reduction in Pain as measured by ePRO
7) Microbiological response in MRSA patients
8) Microbiological response in all patients

**FDA Response:**
Assuming only superiority testing is performed for the above endpoints, the ordering for hierarchical testing is acceptable. Note, however, that the SAP (Section 8.4) for Study 302 states that noninferiority rather than superiority testing will be performed for 4) through 8) above. Please clarify if you plan to conduct noninferiority or superiority testing. As stated previously, only pre-specified superiority testing of the secondary endpoints is considered meaningful.

For clinical response at follow-up visit(s), we expect that signs and symptoms related to the ABSSSI have resolved.

3. All patients randomized to the vancomycin arm will receive aztreonam, which will be discontinued if a Gram negative organism is not isolated on pre-therapy cultures.

**FDA Response:**
We agree.

4. The FDA has reviewed our thorough QT study package and had no comments or recommendations, therefore, our plan for Study 302 is to collect ECG tracings at baseline and later if clinically indicated.

**FDA Response:**
We agree.

5. In addition to an infection encompassing a surface area of at least 75 cm², patients must also have at least two of the following signs/symptoms of systemic infection:
   - Lymph node enlargement due to the present infection
   - Fever $\geq 38°C$ in the time frame of Screening Visit to 24 hours post receiving first dose of study drug
   - Lymphangitis

Reference ID: 3257342
Reference ID: 4113689
• Elevated white blood cells of $\geq 10,000$ cells/$\mu$L in the time frame of Screening Visit to 24 hours post receiving first dose of study drug
• Elevated C reactive protein ($> 50.0$ mg/L)
• Purulent or seropurulent drainage or discharge

**FDA Response:**
We agree; these criteria are acceptable.

6. SAP changes as a result of FDA’s comments include:
   • Agree with FDA on separation of SAPs with one for FDA and one for EU
   • Signs & symptoms are assessed at each study visit and hematology/serum chemistry/urinalysis have been added at Day 3, 7, and End of Therapy
   • NI margin of 10% has been made consistent throughout the SAP
   • Agree with FDA’s recommendations to perform additional sensitivity analyses (See Section 3.7.3 of the protocol)
   • An additional section on the handling of missing data has been added in Section 3.78 of the protocol and Section 8.2 of the SAP

**FDA Response:**
We agree.

7. Central Laboratory Information: [Redacted]

   Central Laboratory is a leading microbiology services company that will be used for the in vitro susceptibility testing of all clinical isolates. The laboratory is CLIA certified through 2014 (ID number [Redacted]). Using microbroth dilution techniques, isolates will be tested according to M07-A9 (Volume 32, No. 2, Jan. 2012) using standards M100-S22 Jan 2012.

**FDA Response:**
Acknowledged.

8. Request for two reports from posters in SPA #1:
   • Rubino et al., 2010 ICAAC poster “Pharmacokinetic-Pharmacodynamic Target Attainment Analyses Supporting Delafloxacin Phase 3 Dose Regimen Decisions” apparently was not finalized into a report
   • Burak et al, 2009 ICAAC poster “Pharmacokinetics and Pharmacodynamics of Delafloxacin in S. aureus Murine Thigh Infection Models” is in report form and has been sent to the FDA June 25, 2008 (Serial No. 0020) and also included in this submission

**FDA Response:**
Acknowledged.

9. Clinical Futility Interim Analysis: An interim analysis will be conducted in order to evaluate whether to stop the study for futility, with respect to the non-inferiority of
delafloxacin compared to vancomycin relative to the FDA primary endpoint. Does the FDA agree?

**FDA Response:**
There are concerns of potential biases which may result from conducting an interim analysis, especially in a noninferiority setting. If an interim analysis is to be conducted, it is important that an independent data monitoring committee (DMC) be appointed and a detailed charter be provided for review. The DMC charter should include specific details regarding the operational procedures with firewalls to protect against potential operational biases, decision rules, composition of the DMC members and their conflict of interest statements. We also recommend that the interim analysis for futility be performed in a blinded manner using pre-specified criteria.

10. Overlapping Sites: In conducting two pivotal trials in ABSSSI, would the FDA agree with using some of the same sites in both trials with no more than 30% of patients being enrolled from sites duplicated in both studies? This will ensure quality of data by allowing us to utilize high quality study sites. Additionally by capping the overlap, we can be sure to a good diversity of patients.

**FDA Response:**
We recommend that the trials are conducted independently with no overlapping sites to provide independent substantiation of the evidence of efficacy and safety. Sharing sites between the two trials could make the trial results correlated, increasing the chance for potential systematic biases and data integrity issues.

11. Fever: Because of FDA’s recommendation that fever is no longer required for study entry, we propose to obtain body temperature measurements every 12 hours, by the study staff rather than every 6 hours by patients. Does the FDA agree?

**FDA Response:**
We agree. Many patients with ABSSSI may not exhibit a febrile response and resolution of fever is no longer a primary endpoint measure. Monitoring temperature every 12 hours by study staff rather than every 6 hours by patients is acceptable.

In addition, we have the following comments.

**Clinical Microbiology Comments**
1. Provide quality control (QC) parameters for delafloxacin. Routine QC parameters should be provided using the testing of standard reference strains recognized by the Agency such as those obtained from American Type Culture Collection (ATCC). The methods used should be in accordance with the standardized methods such as those recommended by the Clinical Laboratory Standards Institute (CLSI) M23 guidelines. Without susceptibility test quality control parameters any susceptibility data for delafloxacin will not be considered.
2. Consider performing additional non-clinical studies for delafloxacin comparing the disk diffusion method and broth dilution method using standard CLSI methods especially against gram-positive bacteria (e.g. *S. pneumoniae*, *S. aureus*, *E. faecalis*). When these experiments are done use the same bacterial isolates for both the broth and disk diffusion work. The isolates tested should consist of isolates with different resistance patterns to other antimicrobials. If possible pick isolates with different mechanisms of resistance. The isolates tested can be limited to what will be the target pathogens for delafloxacin. At least 15 isolates of each target pathogen should be used in the study.

3. You have performed a number of studies evaluating the development of resistance to delafloxacin against gram-positive bacteria (e.g. *S. aureus*). Consider also evaluating the development of delafloxacin resistance to other gram-positive bacteria (e.g., *S. pneumoniae*, *E. faecalis*) or other organisms that are potential pathogens that will be included in the package insert.

**Statistical Comments:**

1. If a stratified primary analysis is performed, then the stratification factor categories should correspond to those stratification factor categories used in the initial randomization. For example, if the initial randomization is stratified by four categories of infection type (cellulitis/erysipelas, wound infection, major cutaneous abscess, burn infection), then the primary analysis should be similarly stratified by these four categories. It appears from the SAP (Section 11) that the primary analysis will be based on two infection categories for efficacy analyses while the initial randomization will be stratified by four categories of infection.

2. It should also be noted that unstratified (i.e. unadjusted) analyses should be reported alongside all stratified analyses. Results from both analyses would be expected to be consistent.

3. The approach for handling missing data by classifying them as failures in the primary analysis is acceptable. We recommend that the approach used in the primary analysis is also applied in secondary and other supportive analyses, wherever possible, so that findings among the analyses may be more comparable.

**Clinical Pharmacology Comments:**

1. Please provide a rationale why the exclusion criterion for renal impairment was revised to allow the enrollment of patients with a creatinine clearance of 15-30 mL/min. In the absence of a renal impairment study, we recommend excluding those patients since renal excretion has been shown to be a major elimination pathway for delafloxacin in the mass balance study.

2. Both clinical data and PK/PD simulations support the efficacy of delafloxacin against *S. aureus* isolates with an MIC of 0.5 mcg/mL. Therefore, the 300 mg q12h dose proposed in your Phase 3 clinical trial is acceptable. However, it appears that the proposed dosing regimen is unlikely to achieve the PK/PD targets for stasis or 1-log kill at an MIC of
1.0 mcg/mL; thus patients with organisms having MIC values greater than or equal to 1.0 mcg/mL may be at increased risk of treatment failure.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager, at (301) 796-0563.

Sincerely,

(See appended electronic signature page)

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHERINE A LAESSIG
02/07/2013
LATE-CYCLE COMMUNICATION DOCUMENTS
Dear Mr. Di Roma:

Please refer to your New Drug Applications (NDAs) dated October 19, 2016 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NDA 208610 Baxdela (delafloxacin) Tablets and NDA 208611 Baxdela (delafloxacin) Injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on April 07, 2017.

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

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Thomas Smith, MD, MPH
Clinical Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Late Cycle Meeting Minutes
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: April 07, 2017
11 AM to 12 PM (EST)

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Numbers: 208610 & 208611

Product Name: Baxdela (delafloxacin)

Applicant Name: Melinta Therapeutics Inc.

Meeting Recorder: Fariba Izadi, PharmD

FDA ATTENDEES

Office of Antimicrobial Products (OAP)
John Farley, MD MPH Deputy Director

Division of Anti-Infective Products (DAIP)
Abimbola Adebowale, PhD Associate Director for Labeling
Janelle Charles, PhD Statistical Reviewer
Carmen DeBellas, RPh, PharmD* Chief, Project Management Staff
Fariba Izadi, RPh, PharmD Senior Regulatory Health Project Manager
Caroline Jjingo, MD Clinical Reviewer
Terry Miller, PhD Pharmacology/Toxicology Team Leader
Sumathi Nambiar, MD, MPH MD, MPH Director
Amy Nostrandt, DVM, PhD Pharmacology/Toxicology Reviewer
Jalal Sheikh, PhD Clinical Microbiology Reviewer
Thomas Smith, MD, MPH Clinical Team Leader
Joseph Toerner, MD, MPH Deputy Director for Safety

Office of Clinical Pharmacology (OCP)
John Lazor, PharmD Division Director
Jeff Florian, PhD Pharmacometrics Team Leader
Kunyi Wu, PharmD Clinical Pharmacology Reviewer

Reference ID: 4090009
Late-Cycle Meeting Minutes

Office of Medical Policy
Nyedra Booker, PharmD* Patient Product Information Specialist

Office of Surveillance and Epidemiology (OSE)
Janet Higgins* Regulatory Project Manager
Sevan Kolejian, PharmD* Safety Evaluator, Division of Medication Error & Prevention Analysis (DMEPA)
Mingfeng Zhang, MD, PhD Epidemiologist
Till Olickal, PhD, PharmD Risk Management Analysis
Aleksander Winiarski, PharmD* Team Leader Safety Regulatory Project Management Staff

Office of New Drug Products (ONDP)
Yushi Feng, Ph.D Product Quality Reviewer
Balajee Shanmugam, Ph.D Acting Branch Chief
Luz Rivera, PsyD* Acting Product Quality Assessment Lead

Office of Scientific Investigation
Janice Pohlman, MD, MPH * Team Leader, Good Clinical Practice Assessment Branch (GCPAB)

MELINTA ATTENDEES
Sue Cammarata, M.D. Chief Medical Officer
Peter DiRoma Regulatory and Quality Assurance
Kelly Ford, Ph.D. Director Manufacturing, Science and Technology
Eugene Sun, M.D. Chief Executive Officer

Clinical Pharmacology Consultant
CMC Consultant

Via Phone *

BACKGROUND

NDA 208610 Baxdela (delafoxacin) Tablets and NDA 208611 Baxdela (delafoxacin) Injection were submitted on October 19, 2016.

Proposed indication: Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

PDUFA goal date: June 19, 2017

FDA issued a background package in preparation for this meeting on March 24, 2017.
Melinta submitted preliminary questions to support the discussion via email on March 29, 2017, and officially on April 05, 2017. Melinta responded to FDA’s March 24, 2017, comments in the Late Cycle Review briefing package on April 04, 2017, and proposed an agenda for the late cycle review meeting on April 04, 2017.

Melinta amended the proposed agenda for the LCM on April 05, 2017.

FDA responded to Melinta’s Preliminary Questions on April 05, 2017. These are appended to the minutes.

**DISCUSSION**

1. **Introductory Comments** – Welcome, introductions, ground rules, objectives of the meeting.

2. **Substantive Review Issues**
   **Discussion:** The Division stated that no substantive review issues have been identified to date.

3. **Minor Review Issues**
   **Discussion:** Melinta stated some approved IV formulations, such as NEXTERONE (amiodarone) and CARNEXIV (carbamazepine), containing sulfobutylether-β-cyclodextrin (SBECD) are labeled without requirements for dose adjustment in patients with renal impairment and questioned if the Agency had different labeling requirements for this excipient when used in IV formulations. Melinta referred the Division to their submission dated April 04, 2017 for details.

   The Division acknowledged Melinta’s concern. The Division pointed out that NEXTERONE was approved in 2008 with no dose adjustment in patients with renal impairment but is indicated for the treatment of life-threatening arrhythmias. Likewise, CARNEXIV was approved in 2016 with the labeling language that CARNEXIV should generally not be used in patients with moderate or severe renal impairment. The CARNEXIV case reflected the Agency’s current understanding of nephrotoxicity and non-renal toxicity regarding SBECD. EMA published a guideline regarding SBECD-containing formulations in 2014. In the case of delafloxacin, there is accumulation of SBECD in patients with ESRD and since there is a lack of safety data in humans, the Division does not have sufficient information to provide a dose recommendation for the IV formulation of delafloxacin in patients with ESRD.

4. **Information Requests**
   **Discussion:** The product quality team will respond to Melinta on the ongoing evaluation of the analytical method issue discussed at a teleconference on April 06, 2017.
Melinta inquired if there were any outstanding issues related to facility inspections. The Division responded the Office of Process and Facilities is currently completing an Inspectional Assessment.

5. Postmarketing Requirements/Postmarketing Commitments

Discussion: Melinta asked if the product quality Postmarketing Commitments and the Changes Being Effected-30 (CBE-30s) supplements already under discussion should be submitted separately. The Division responded that the Postmarketing Commitments and the associated Changes Being Effected 30 (CBE-30) supplements for NDA 208610 should be submitted independently of the CBE-30 supplement for NDA 208611. The Division clarified that the two outstanding issues in NDA 208611 can be submitted under one CBE-30 supplement.

6. Major Labeling Issues

Discussion: Melinta asked when they would receive draft labeling and how the final labeling discussions would be handled. They asked if they would receive any more information requests and if teleconferences would need to be scheduled.

The Division stated that the proposed changes to sections 3, 11, 13 and 16 of the prescribing information section of the label were sent to Melinta on March 27, 2017. The Division stated that they are currently working to complete the label review and are awaiting feedback from consulting Divisions. The Division will provide Melinta with a copy of the final draft in early May. The Division asked Melinta to review the label, note any counterproposals, and respond back to Division. The Division stated that a teleconference will be scheduled to negotiate labeling if needed.

7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.
FDA Responses to Melinta’s Preliminary Questions
Late Cycle Meeting: 04-07-17

**Question 1:** Will FDA accept sponsor’s remaining responses to outstanding CMC information requests for NDA 208611 as CBE-30 submissions i.e. results from the on-going requalification of the Sterility Test method?

**Rationale:** This is in regards to FDA’s January 18th request for sterility test requalification data per USP <71>. We have previously committed to providing the data collected from upcoming PV (process validation) runs (NDA 208611, Serial No. 014). These runs are currently scheduled to be conducted in April and May (b)(4). Once this data is collected according to the validation protocol submitted to the FDA (NDA 208611, Serial No. 021), the sponsor will commit to update the NDA accordingly as a CBE-30.

**FDA Response:** Yes, the proposal to submit information on the requalification of the sterility test method as a CBE-30 is acceptable.

**Question 2:** Can the sponsor provide PV data to support more suitable In-Process Control (IPC) limits at (b)(4) % of (b)(4) as a CBE-30 in lieu of the proposed specification in NDA 208611?

**Rationale:** The sponsor has originally proposed an IPC specification (b)(4) in the NDA based on data from 3 registration runs (13DEL1, 14DEL1, and 14DEL2). Due to past data management issues identified associated with these batches, additional data will need to be collected to ensure an appropriate specification. We would like to set a provisional specification of (b)(4) % of target (b)(4) based on our analysis of assay and manufacturing process variability. The final release specification would remain unchanged. We plan to assess the IPC limits based on 3 PV runs we are planning to execute at (b)(4) in April-May timeframe and tighten the IPC specification if supported by the data. We commit to setting an IPC limit as a CBE-30. Is this acceptable?

**FDA Response:** Yes, the proposal to submit the IPC information as a CBE-30 is acceptable.

**Question 3:** Can FDA provide their summary of PTA (Probability of Target Attainment) in severe renal impairment prior to the meeting on April 7th? This will help us address FDA’s comments on April 7th.

**Rationale:** This will help us address FDA’s comments on April 7 regarding appropriate dosing in patients with renal impairment.

**FDA Response:** The PTA analysis results for S. aureus, E.coli, and P. aeruginosa for 450 mg every 12 hours PO are summarized in Tables 1, 2, and 3. The values identified in this analysis are similar to the values identified in your provided PTA report (PK-3341-015, Table 20).

Reference ID: 4090009
Table 1 displays the percent probabilities of PK-PD target attainment by MIC for PO delafloxacin in patients with severe renal impairment based on 450 mg every 12 hours PO. Results are shown for net bacterial stasis and 1-log_{10} CFU reduction based on fAUC24:MIC for *S. aureus* among simulated patients.

**Table 1: PTA for *S. aureus* among simulated severe renal impairment patients**

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<thead>
<tr>
<th>MIC</th>
<th>Stasis</th>
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Table 2 displays the percent probabilities of PK-PD target attainment by MIC for PO delafloxacin in patients with severe renal impairment based on 450 mg every 12 hours PO. Results are shown for net bacterial stasis and 1-log_{10} CFU reduction based on fAUC24:MIC for *E. coli* among simulated patients.

**Table 2: PTA for *E. coli* among simulated severe renal impairment patients**

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<th>MIC</th>
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Table 3 displays the percent probabilities of PK-PD target attainment by MIC for PO delafloxacin in patients with severe renal impairment based on 450 mg every 12 hours PO. Results are shown for net bacterial stasis and 1-log$_{10}$ CFU reduction based on FAUC24:MIC for \textit{P. aeruginosa} among simulated patients.

Table 3: PTA for \textit{P. aeruginosa} among simulated severe renal impairment patients

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<thead>
<tr>
<th>MIC</th>
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**Question 4:** We would like to confirm that the FDA is recommending 200mg IV q12h with transition to 450 oral q12h in severe renal impairment? FDA’s comment only mentions the oral formulation.

**Rationale:** We are proposing 200mg IV q12h with transition to 450mg oral q12h in severe renal impairment. The sponsor has prepared a rationale for dosing in patients with severe renal impairment and an analysis regarding the risk of SBECED in patients with renal impairment in a recent information amendment (April 4, 2017, NDA 208610, Serial # 036).

**FDA Response:** The three dosing regimens (IV only, IV to oral, and oral only) shown below are all considered acceptable for patients with severe renal impairment.

- 200 mg every 12 hours administered over 60 minutes by IV infusion for 5 to 14 days
- 200 mg every 12 hours administered over 60 minutes by IV infusion, then switch to 450 mg oral every 12 hours at the discretion of the physician for a total duration of 5 to 14 days
- 450 mg oral every 12 hours for 5 to 14 days

**Question 5:** Please clarify why “within one hour after completion of a hemodialysis session” does not represent off-dialysis. Would the FDA clarify if they have information to consider otherwise?
**Rationale:** Melinta conducted the evaluation of delafloxacin pharmacokinetics in patients with ESRD according to the FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function (March 2010) by including an evaluation under dialysis and non-dialysis (between dialysis) conditions. Melinta believes that within one hour after completion of hemodialysis session represents off-dialysis since the major elimination path for delafloxacin is renal. There is not an expectation that there would be appreciable change in hepatic elimination in ESRD to result in drastically different total elimination in ESRD before the next dialysis session.

**FDA Response:** We appreciate that you have evaluated patients with ESRD on hemodialysis under dialysis and non-dialysis conditions according to the draft FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function (March 2010). The draft guidance does not specify timing of drug administration with respect to dialysis. Of note, the draft guidance also recommends studying patients with ESRD not yet on dialysis, but we recognize that this may be a difficult population to enroll.

Delafloxacin is not purely eliminated by the kidney. Glucuronidation and potentially bile secretion contribute to elimination as well as a very small contribution by oxidative metabolism. Transporters (i.e. P-gp and BCRP) may be involved in both elimination and oral absorption. It is not known if uremic solutes impact the disposition of delafloxacin by having an effect on P-gp, BCRP, and glucuronidation. Hemodialysis removes uremic solutes and with the administration of delafloxacin within one hour of hemodialysis, the effect of uremic solutes on the pharmacokinetics of delafloxacin maybe under estimated.

**Question 6:** We would like to discuss FDA labeling recommendations received to date in regards to dosing in ESRD and the 2% AE Table.

**Rationale:** Please see the sponsor’s Information Amendment to NDA 208610 (Serial # 0035, March 31, 2017), which has an updated 2% Adverse Event Table as requested by FDA. The sponsor agrees to report pooled hepatic events in product labeling. The changes are consistent with hepatic reactions which are reported in Table 9 of the Summary of Clinical Safety in NDA 208610. The events which are specific to LFTs can be correctly categorized with the term “Abnormal Liver Function Tests” under the System Organ Class of Investigations. This is also consistent with other FDA approved antibiotic labeling (e.g. CIPRO, ZYVOX). In addition, the term “Abnormal Liver Function Tests” is consistent with the FDA Adverse Reaction guidance, “Adverse reactions should be classified using meaningful and specific terms that best communicate the nature and significance of the reaction.”

**FDA Response:** We do not recommend the IV formulation of delafloxacin in this sub-population mainly due to the extensive accumulation of SBECD in patients with ESRD and its unknown toxicity. We do not recommend the oral formulation of delafloxacin in this sub-population due to the unknown impact of ESRD on glucuronidation, P-gp, and BCRP. Please also see response in Q3. We are in receipt of your revisions to the 2% AE table and it is under review.

**Question 7:** Will the FDA be able discuss remaining review issues and potential timeline for the remainder of the NDA review?
**Rationale:** If there are remaining review issues, the sponsor would like to discuss what they are and expected timing for our response.

**FDA Response:** As noted in our background document for the late cycle meeting, our reviews are ongoing.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS D SMITH
04/27/2017
Dear Mr. Di Roma:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NDA 208610 Baxdela (delafloxacin) Tablets and NDA 208611 Baxdela (delafloxacin) Injection.

We also refer to the Late-Cycle Meeting (LCM) scheduled for April 07, 2017. Attached is our background package, including our agenda, for this meeting.

Please email a list of your attendees to Fariba.Izadi@FDA.HHS.Gov, at least one week prior to the meeting.

For each foreign visitor, complete and email the enclosed Foreign Visitor Data Request Form at least one week prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Reference ID: 4075036
If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES
Late-Cycle Meeting Background Package
Foreign Visitor Request Form
LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: April 07, 2017
11 AM to 12 PM (EST)

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: NDA 208610
NDA 208611

Product Name: Baxdela (Delafloxacin) Tablets and Injection

Indication: Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Applicant Name: Melinta Therapeutics, Inc.

FDA ATTENDEES

Office of Antimicrobial Products (OAP)
Edward Cox, MD MPH Director
John Farley, MD MPH Deputy Director

Division of Anti-Infective Products (DAIP)
Abimbola Adebowale, PhD Associate Director for Labeling
Carmen DeBellas, RPh, PharmD Chief, Project Management Staff
Dmitri Iarikov, MD PhD Acting Deputy Division Director
Fariba Izadi, RPh, PharmD Senior Regulatory Health Project Manager
Caroline Jjingo, MD Clinical Reviewer
Terry Miller, PhD Pharmacology/Toxicology Team Leader
Sumathi Nambiar, MD, MPH Director
Thomas Smith, MD, MPH Clinical Team Leader
Joseph Toerner, MD, MPH Deputy Director for Safety
Kunyi Wu, PharmD Clinical Pharmacology Reviewer
Zhixia (Grace) Yan, PhD Acting Clinical Pharmacology Team Leader

Office of New Drug Products (ONDP)
Yushi Feng, Ph.D Product Quality Reviewer
Steven Frisbee, Ph.D Product Quality Reviewer
Jason God, Ph.D Product Quality Microbiology Reviewer
Danuta Gromek-Woods Ph.D Product Quality Reviewer
Arwa El Hagrasy, Ph.D Product Quality Reviewer
Balajee Shanmugam, Ph.D Acting Branch Chief

Office of Process and Facilities (OPF)
Christina Capacci-Daniels, Ph.D Team Lead, Division of Inspectional Assessment
INTRODUCTION

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

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

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

Discipline Review Letters

No Discipline Review letters have been issued to date.

Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

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

LCM AGENDA

1. Introductory Comments – 5 minutes (Fariba Izadi/Thomas Smith)
   Welcome, introductions, ground rules, objectives of the meeting
2. Discussion of Minor Review Issues – 15 minutes
   Based on our analysis, the simulated mean steady-state $\text{AUC}_{24h}$ of delafloxacin in patients with severe renal impairment

Reference ID: 4075036
that the 450 mg Q12h oral dose maybe appropriate in patients with severe renal impairment. At the 450 mg Q12h oral dose, the simulated mean steady-state AUC_{24h} of delafloxacin in patients with severe renal impairment is 48% higher compared to patients with normal renal function. However, the delafloxacin exposure in patients with severe renal impairment receiving 450 mg Q12h orally would be lower than that in patients who received 450 mg Q12h IV in Study RX-3341-201, where no major safety concerns were identified with the 450 mg Q12h IV dose.

In addition, the use of delafloxacin (IV and oral) in patients with ESRD may not be appropriate for the following reasons:

a) The unknown risk of extensive accumulation of SBECID in patients with ESRD receiving IV delafloxacin;
b) The unknown impact of ESRD on delafloxacin disposition following oral dosing as no observed data are available in patients with ESRD receiving oral delafloxacin;
c) In the renal impairment study, as delafloxacin was administered within one hour after completion of a hemodialysis session, it may not adequately describe delafloxacin exposure in subjects on an off-dialysis day.

3. Additional Applicant Data – 15 minutes (Applicant)
4. Information Requests – 5 minutes
5. Major labeling issues – 10 minutes
   Draft label review will be provided as per schedule.
6. Review Plans – 5 minutes
   Continue review of NDAs to meet the PDUFA Goal Date under the Program of June 19, 2017
7. Wrap-up and Action Items – 5 minutes
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<tr>
<td>HOSTING OFFICIAL</td>
<td>Name: Fariba Izadi, PharmD</td>
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<td>Title: Regulatory Health Project Manager</td>
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<td>Office/Bldg.: Building 22, Room 6232</td>
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For Official Use Only

Reference ID: 4075036
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
03/24/2017