

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209776Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA 209776

SUPPL # N/A

HFD #

Trade Name: Vabomere

Generic Name: meropenem and vaborbactam for injection

Applicant Name: Rempex Pharmaceuticals, Inc.

Approval Date: August 29, 2017

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years NCE exclusivity, 5 year GAIN exclusivity extension

d) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the

NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 50706

MERREM IV (meropenem for injection)

NDA# 202106

Meropenem and Sodium Chloride in Duplex Container for injection

NDA 209776 contains vaborbactam, an active moiety that has not been previously approved, in a fixed-combination with meropenem, a previously approved active moiety. Under the Agency's new interpretation described in the Agency's Guidance for Industry, *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products*, a drug substance is eligible for 5-year exclusivity if it meets the regulatory definition of new chemical entity, regardless of whether that drug substance is approved in a single-ingredient drug product, in a fixed-combination with another drug substance that contains no other previously approved active moiety, or in a fixed-combination with another drug substance that contains a previously approved active moiety.

However, meropenem is an "old antibiotic" (an antibiotic drug for which the first NDA was received before the enactment of FDAMA); therefore, DAIP is referring the 5-year exclusivity assessment for NDA 209776 to the CDER Exclusivity Board for further consideration.

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO

THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

### **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.



the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Jane Dean  
Title: Senior Regulatory Project Manager  
Date: 8/28/2017

Name of Division Director signing form: Sumathi Nambiar  
Title: Director, Division of Anti-Infective Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANE A DEAN  
08/28/2017

SUMATHI NAMBIAR  
08/29/2017

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 209776 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Vabomere Established/Proper Name: meropenem-vaborbactam Dosage Form: powder for injection, 1000mg/1000mg vial		Applicant: Rempex Pharmaceuticals, Inc., a wholly-owned subsidiary of The Medicines Company Agent for Applicant (if applicable):
RPM: Jane A. Dean, RN, MSN		Division: Division of Anti-Infective Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p style="margin: 0;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p style="margin-left: 20px;"> <input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:         </p> <p style="margin-left: 20px;"><i>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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>August 29, 2017</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Fast Track            | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> 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

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

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 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information were issued</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?</li> <li>• If so, specify the type</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approval, 8/29/17
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	6/14/17
• Review(s) <i>(indicate date(s))</i>	6/12/17
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 1/17/17 (2) DMEPA: 5/3/17; 6/12/17; 8/18/17; 8/24/17 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: 6/15/17 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: 8/16/17 Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	2/22/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	8/14/17
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Completed <b>(Do not include)</b>
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC If PeRC review not necessary, explain: _____</li> </ul>	8/2/17
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
❖ 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.) ( <i>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</i> )	
❖ 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)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	11/3/16
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	4/12/17
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	6/23/17
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	3/10/16; 7/3/14
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	8/29/17
Division Director Summary Review ( <i>indicate date for each review</i> )	8/29/17
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	8/29/17
PMR/PMC Development Templates ( <i>indicate total number</i> )	6

<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	6/8/17
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	6/8/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> ) <sup>5</sup>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	6/27/17
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	8/2/17
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	8/23/17
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	5/23/17
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	6/7/17; 8/10/17
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<sup>5</sup> 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).

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	7/14/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	Executive Summary: 8/28/17 Drug Substance: 6/5/17 Drug Product: 6/7/17 Process: 6/12/17 Microbiology: 5/12/17 Biopharmaceutics: 5/23/17 Facilities: 8/28/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	8/28/17
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections ( <i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable: 8/28/17 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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JANE A DEAN  
08/29/2017

**From:** Dean, Jane  
**Sent:** Tuesday, August 29, 2017 1:53 PM  
**To:** 'Andrew Friedman'  
**Cc:** Starr Shangle  
**Subject:** RE: Vabomere - Highlights Section

Thanks you so much, Andrew!

Jane

**From:** Andrew Friedman [<mailto:andrew.friedman@THEMEDCO.com>]  
**Sent:** Tuesday, August 29, 2017 1:47 PM  
**To:** Dean, Jane  
**Cc:** Starr Shangle  
**Subject:** Vabomere - Highlights Section

Dear Jane,  
Per our discussion, I am aware that you will be adding the year “2017” in the highlights section of the draft USPI for Vabomere, and provide permission to do so.

I appreciate your assistance with this very much.

Kind regards,  
Andrew

**Andrew F. Friedman PharmD**  
Sr. Vice President, Head of Regulatory Affairs  
The Medicines Company  
Tel + 1 973 290 6027  
Mobile + [REDACTED] (b) (6)  
[andrew.friedman@themedco.com](mailto:andrew.friedman@themedco.com)

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JANE A DEAN  
08/29/2017



NDA 209776

GAIN Exclusivity

Rempex Pharmaceuticals, Inc.  
a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director, Regulatory Affairs  
8 Sylvan Way  
Parsippany, NJ 07054

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 29, 2016, received December 29, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vabomere (meropenem and vaborbactam) for Injection for the treatment of patients 18 years and older with complicated urinary tract infections (cUTI) including pyelonephritis. We also refer to the letter dated August 29, 2017 granting approval of this NDA.

Finally, we refer to our correspondence dated December 19, 2013, to your Pre-Investigational New Drug Application 120040 in which we granted Qualified Infectious Disease Product (QIDP) designation for Vabomere (meropenem and vaborbactam) for Injection for the treatment of complicated Urinary Tract Infections (cUTI).

This letter is to inform you that your application meets 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 this NDA.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

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

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/s/  
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SUMATHI NAMBIAR  
08/29/2017

**From:** Dean, Jane

**Sent:** Wednesday, August 23, 2017 5:26 PM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (Vabomere) - follow-up from last week re [REDACTED] (b) (4) discussion

Hi, Starr -

Reference is made to your enquiry regarding possible approaches to include [REDACTED] (b) (4) in the Indications section of the Vabomere label. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] We believe that it is important to inform health care providers about the most appropriate use of the meropenem and vaborbactam combination and the benefits of the combination as compared to meropenem alone. In addition, exposure to additional agents that do not provide benefit may promote resistance among the exposed bacteria.

In a trial conducted to support an indication, although patients with infection due to a specific organism are a subgroup of the overall population, the outcomes in the subgroup are evaluated in the context of an adequate and well-controlled trial that is interpretable.

If you are still interested in the inclusion of [REDACTED] (b) (4) in the Indications section of the Vabomere label, an adequate and well-controlled trial will need to be conducted. Data from a case series of patients with cUTI due to [REDACTED] (b) (4) will not be sufficient to update the labeling. We are willing to work with you on the design of such a trial.

Jane

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/s/  
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JANE A DEAN  
08/23/2017

**From:** Dean, Jane  
**Sent:** Tuesday, August 22, 2017 12:48 PM  
**To:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (Vabomere) - information request  
**Importance:** High

Hi, Starr -

**In the Dilution Techniques section of Microbiology 12.4 of the labeling there is a statement,**  
[REDACTED] (b) (4)  
[REDACTED] **". Please provide a reference for the statement, and explain the rationale for any deviation from CLSI standard methods. We would appreciate a response, by the end of business, if possible.**

Thanks!

Jane

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JANE A DEAN  
08/22/2017

**From:** Dean, Jane [<mailto:Jane.Dean@fda.hhs.gov>]  
**Sent:** Thursday, August 17, 2017 11:47 AM  
**To:** Starr Shangle <[starr.shangle@THEMEDCO.com](mailto:starr.shangle@THEMEDCO.com)>  
**Subject:** NDA 209776 (Vabomere) - follow-up from today's telecon

Hi, Starr!

Question - did any patients with levofloxacin non-susceptible isolates receive levofloxacin as oral step down therapy? If so, please provide us with the subject IDs for those patients.

Per our conversation earlier today, please find the list of subjects in the m-MITT Population of Study 505 that we identified as having piperacillin/tazobactam-resistant baseline pathogens, using FDA breakpoints.

**Subject IDs in Study 505 for patients with piperacillin/tazobactam-resistant baseline pathogens (m-MITT Population)**

Meropenem-vaborbactam group:

REMPEX-505-100-002-506  
REMPEX-505-100-004-501  
REMPEX-505-100-004-502  
REMPEX-505-100-004-503  
REMPEX-505-100-006-502  
REMPEX-505-604-005-502  
REMPEX-505-642-002-503  
REMPEX-505-642-002-512  
REMPEX-505-642-003-503  
REMPEX-505-703-001-513  
REMPEX-505-703-005-505  
REMPEX-505-703-005-507  
REMPEX-505-804-002-512  
REMPEX-505-804-002-516  
REMPEX-505-804-002-534  
REMPEX-505-804-005-506  
REMPEX-505-804-005-521  
REMPEX-505-804-005-523  
REMPEX-505-804-005-533  
REMPEX-505-804-005-535  
REMPEX-505-804-005-537  
REMPEX-505-804-005-543  
REMPEX-505-804-007-506

Piperacillin/tazobactam group:

REMPEX-505-100-004-504  
REMPEX-505-112-004-502  
REMPEX-505-112-004-507  
REMPEX-505-203-002-509  
REMPEX-505-203-008-502

REMPEX-505-300-001-523  
REMPEX-505-703-001-511  
REMPEX-505-703-005-502  
REMPEX-505-804-001-511  
REMPEX-505-804-002-529  
REMPEX-505-804-002-531  
REMPEX-505-804-002-532  
REMPEX-505-804-005-507  
REMPEX-505-804-005-510  
REMPEX-505-804-005-530  
REMPEX-505-804-005-538  
REMPEX-505-804-005-541  
REMPEX-505-804-005-544  
REMPEX-505-804-006-501  
REMPEX-505-804-007-518

Also, the telecon scheduled for tomorrow has been cancelled.

Jane

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/s/  
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JANE A DEAN  
08/18/2017

**From:** Dean, Jane

**Sent:** Friday, August 18, 2017 4:01 PM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (Vabomere) - one additional comment re carton/container label

Hi, Starr – after reviewing your submission dated 8/17/17, the reviewer for the carton and container label has the following additional comment for you:

We note that the barcode has been placed at the bottom of the principal display panel of the container label. Barcodes placed in a horizontal position may not scan due to the curvature of the container. Consider reorienting the barcode on the container label to a vertical position to improve the scannability.

Jane

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/s/  
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JANE A DEAN  
08/18/2017

## Dean, Jane

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**From:** Dean, Jane  
**Sent:** Wednesday, August 16, 2017 4:44 PM  
**To:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (Vabomere) - division comments to the questions in your 8-1-17 submission (SDN #32) - correction  
**Attachments:** 8-16-17 labeling comments.pdf  
**Importance:** High

Starr, this is a correction of the earlier email I sent today because after sending it, I noticed I referenced the wrong date of your submission. The comments below address the questions in your cover letter dated 8/1/17. Please use this email as part of your archival record.

Since there was an issue with the earlier email containing all of the figures/tables in your submission, I have saved the comments here as a pdf file and am attaching it to this email.

Also, I am sending to you in a separate email the division's 8/16/17 proposed changes to your label. Please disregard the earlier email I sent today. There are no differences between the two documents but I believe keeping these two emails separate reduces any potential for ambiguity in the archival records.

Jane

8 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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JANE A DEAN  
08/16/2017

**From:** Dean, Jane  
**Sent:** Monday, August 14, 2017 2:53 PM  
**To:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (Vabomere) - carton and container labeling comments  
**Importance:** High

Hi, Starr – the division has the following comments for the carton and container:

Container Label and Carton Labeling

1. As currently presented, the National Drug Code (NDC) number is denoted by a placeholder (65293-XXX-XX). Add the intended numbers to the container label and carton labeling and submit for our review.
2. Define the abbreviation, g, and minimize the potential for misinterpretation, replace the first abbreviation “g” in the equivalency statement with the word “gram” so that the test reads, “\*Meropenem 1 gram (equivalent to 1.14 g meropenem trihydrate) and vaborbactam 1 g.
3. The information on the container label should read as follows:  
**For Intravenous Infusion Only**  
**Single Dose Only**  
**Discard Unused Portion After Use**
4. Also, the wording information **(Single Dose Only Discard Unused Portion After Use)** should **also** be included on the carton labeling below the current statement “**For Intravenous Infusion Only.**”
5. We encourage the use of **bold** font for these statements on both the container label and carton labeling.

If you have any questions, please don't hesitate to call me/email me.

Jane

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/s/  
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JANE A DEAN  
08/14/2017

**From:** Dean, Jane  
**Sent:** Tuesday, August 08, 2017 11:19 AM  
**To:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (mereopenem0vaborbactam) - revised language and timelines for PMRs/PMCs

Hi, Starr, this email is being sent as a revision of the email sent on July 28, 2017 outlining the division's proposed language and timelines for the PMRs and PMCs. The yellow highlights have been removed since it is important that all dates listed below be included in your official submission. Also, I modified the reference to the proprietary name, changing it from all caps to just the initial letter capitalized.

Below are the PMRs/PMCs with suggested wording and timelines. If any changes need to be made, please send them back in an email noting where the changes are and the Division will review them. Once the Division and Rempex have agreed to the language and dates, you can submit your official letter to your NDA.

If you have any questions, please do not hesitate to call me/email me.

Thanks,

Jane

---

PMR 3248-1: Conduct a Phase 1, open-label, sequential study to assess the pharmacokinetics (PK), safety, and tolerability of Vabomere and the PK of meropenem and vaborbactam in children from birth to < 18 years of age with selected serious bacterial infections.

Final Protocol Submission: Submitted November 2, 2015  
Study/Trial Completion: 09/2019  
Final Report Submission: 03/2020

PMR 3248-2: Conduct a Phase 2, (b) (4), randomized, single-blind, (b) (4) study to determine the PK, safety, and tolerability of Vabomere (b) (4) piperacillin/tazobactam in the treatment of children with Complicated Urinary Tract Infection (cUTI) including acute pyelonephritis (b) (4)

Draft Protocol Submission: 05/2018  
Final Protocol Submission: 09/2018  
Study/Trial Completion: 09/2021  
Final Report Submission: 03/2022

PMR 3248-3: Phase 2 open-label, active comparator study to evaluate the PK, safety, and tolerability of multiple doses of Vabomere vs comparator in neonates ( $\leq$  90 days of age) with late onset sepsis.

Draft Protocol Submission: 11/2019  
Final Protocol Submission: 03/2020  
Study/Trial Completion: 12/2024  
Final Report Submission: 06/2025

PMR 3248-4: Conduct a US surveillance study for five years from the date of marketing to determine if resistance to Vabomere has developed in those organisms specific to the indications in the label.

Final Protocol Submission: 09/2017  
Interim Study Report: 09/2018  
Interim Study Report: 09/2019  
Interim Study Report: 09/2020  
Interim Study Report: 09/2021  
Study/Trial Completion: 09/2022  
Final Report Submission: 12/2022

PMR 3248-5: Conduct a “Thorough QT/QTc Study” to evaluate whether Vabomere has a threshold pharmacologic effect on cardiac repolarization.

Draft Protocol Submission: 11/2017  
Final protocol submission: 01/2018  
Study completion: 08/2018  
Final report submission: 01/2019

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/s/  
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JANE A DEAN  
08/08/2017



NDA 209776

## INFORMATION REQUEST

Rempex Pharmaceuticals, a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director Regulatory Affairs  
3033 Science Park Road Suite 200  
San Diego, CA 92121

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 13, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Meropenem and vaborbactam for injection

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 **Friday, August 11, 2017**, in order to continue our evaluation of your NDA.

1. New Drug Applications should describe the manufacturing process used for registration batch production as well as the process proposed for commercial manufacture. Additionally, NDAs should accurately describe equipment and processes implemented at the proposed manufacturing facilities. As such, provide any necessary updates to the (b) (4) vaborbactam manufacturing process described in Module 2 and 3.

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



Luz  
Rivera

Digitally signed by Luz Rivera  
Date: 8/04/2017 11:35:09AM  
GUID: 502abbaa000025b89fdb52a977a3d336



NDA 209776

TO: Ms. Starr Shangle, Senior Director Regulatory Affairs  
Authorized Agent for Rempex Pharmaceuticals, a wholly owned subsidiary of The  
Medicines Company

FROM: LCDR Luz E Rivera

SUBJECT: Information Request

APPLICATION: NDA 209776

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 13, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Meropenem and vaborbactam for injection

The analytical methods were submitted to an FDA laboratory for verification. For the most part the FDA lab was able to verify the methods; however, some interfering peaks were observed in the blank and in a few instances Systems Suitability was not met. We request a written response by **Monday August 7, 2017**, to the observations provided below:

1. Identification, Assay & Related Substances in Vaborbactam (current 4/4/17)
2. Determination of Related Substances in Meropenem-Vaborbactam for Injection (Version 2.0)

Summary of Observations:

1. “Identification, Assay & Related Substances in Vaborbactam (current 4/4/17)”
  - Several system suitability criteria were not met. See table below. Items noted in red are failures.

---

## System Suitability

(b) (4)



2. Determination of Related Substances in Meropenem-Vaborbactam for Injection (Version 2.0)
  - System Suitability was not met for the number of theoretical plates required for the Meropenem reference standard (specification: NLT (b) (4)/Observed: (b) (4)). No check analysis was performed for this method.
3. The relative retention time tables for **both methods** were generally unreliable for assigning impurity peaks.
  - For example, (b) (4) in the *drug substance* method was observed in the original analysis at RRT (b) (4) whereas the firm's RRT table assigns (b) (4) at (b) (4). Using the firm's table alone, this peak would have been assigned as an unspecified impurity and failed the drug substance unspecified impurities specification. It was only due to additional spiking experiments performed by the FDA lab that it was identified as (b) (4). FDA lab suggests that the RRTs be more closely evaluated.
  - The Applicant claims the two impurities, (b) (4) and (b) (4), were formed during the sample preparation step of analysis and, therefore, a new method was developed to address this issue. FDA lab testing shows that these two impurities are still present; however, they are below the acceptance criteria set by the Applicant.

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



Luz  
Rivera

Digitally signed by Luz Rivera  
Date: 8/01/2017 05:24:30PM  
GUID: 502abbaa000025b89fdb52a977a3d336



**From:** Dean, Jane  
**Sent:** Friday, July 28, 2017 5:22 PM  
**To:** starr.shangle@themedco.com  
**Cc:** Andrew Friedman (andrew.friedman@THEMEDCO.com)  
**Subject:** NDA 209776 (meropenem-vaborbactam) - PMRs/PMCs

Hi, Starr, below are the PMRs/PMCs with suggested wording and timelines. If any changes need to be made, please send them back in an email noting where the changes are and the Division will review them. Once the Division and Rempex have agreed to the language and dates, you can submit your official letter to your NDA. The dates/timelines highlighted in yellow are the only ones you should include when you submit these officially.

If you have any questions, please do not hesitate to call me/email me.

Thanks,

Jane

---

PMR 3248-1: Conduct a Phase 1, open-label, sequential study to assess the pharmacokinetics (PK), safety, and tolerability of VABOMERE and the PK of meropenem and vaborbactam in children from birth to < 18 years of age with selected serious bacterial infections.

Study/Trial Completion: 09/2019

Final Report Submission: 03/2020

PMR 3248-2: Conduct a Phase 2, (b) (4), randomized, single-blind, (b) (4) study to determine the PK, safety, and tolerability of VABOMERE (b) (4) piperacillin/tazobactam in the treatment of children with Complicated Urinary Tract Infection (cUTI) including acute pyelonephritis

(b) (4)  
Draft Protocol Submission: 05/2018

Final Protocol Submission: 09/2018

Study/Trial Completion: 09/2021

Final Report Submission: 03/2022

PMR 3248-3: Phase 2 open-label, active comparator study to evaluate the PK, safety, and tolerability of multiple doses of VABOMERE vs comparator in neonates ( $\leq 90$  days of age) with late onset sepsis.

Draft Protocol Submission: 11/2019

Final Protocol Submission: 03/2020

Study/Trial Completion: 12/2024

Final Report Submission: 06/2025

PMR 3248-4: Conduct a US surveillance study for five years from the date of marketing to determine if resistance to VABOMERE has developed in those organisms specific to the indications in the label.

Final Protocol Submission: 09/2017

Interim Study Report: 09/2018

Interim Study Report: 09/2019

Interim Study Report: 09/2020  
Interim Study Report: 09/2021  
Study/Trial Completion: 09/2022  
Final Report Submission: 12/2022

PMR 3248-5: Conduct a “Thorough QT/QTc Study” to evaluate whether VABOMERE has a threshold pharmacologic effect on cardiac repolarization.

Draft Protocol Submission: 11/2017  
Final protocol submission: 01/2018  
Study completion: 08/2018  
Final report submission: 01/2019.

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/s/  
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JANE A DEAN  
07/31/2017

**From:** Dean, Jane  
**Sent:** Friday, July 28, 2017 3:49 PM  
**To:** 'Starr Shangle'  
**Cc:** Andrew Friedman  
**Subject:** NDA 209776 (meropenem-vaborbactam) - RE: Question on FDA's label comments

Hi, Starr – the Division has the following response to your questions below:

Given that it is difficult to reliably rule out an association between an adverse event and study drug in clinical trials, for the purpose of reporting the rates of adverse events in Section 6.1 of the labeling, the Division considers all treatment emerging adverse events as possibly causally related to study drug. This approach has been implemented for other antimicrobial products.

Jane

---

**From:** Starr Shangle [<mailto:starr.shangle@THEMEDCO.com>]  
**Sent:** Friday, July 28, 2017 10:34 AM  
**To:** Dean, Jane  
**Cc:** Andrew Friedman  
**Subject:** Question on FDA's label comments

Hi Jane,

We are actively preparing a response to the label FDA provided last week. We would greatly appreciate clarification on some of FDA's revisions to Section 6 in order to expedite our ability to respond:

- Can FDA clarify if they included adverse events that were both related and unrelated (eg., Treatment Emergent AEs) in their proposed changes to Section 6.1?
- If so, what criteria did FDA use to select events that were added? This question relates specifically to Table 3, Adverse Reactions Occurring in 1% or Greater, and the following section, Adverse Reactions Occurring in less than 1%.

Many thanks for helping us to understand FDA's direction.  
Starr

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/s/  
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JANE A DEAN  
07/31/2017

**From:** Dean, Jane

**Sent:** Friday, July 28, 2017 3:47 PM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (meropenem-vaborbactam) - response to your proposal re renal dosing submitted 7/19/17, SDN #31

Hi, Starr – the clinical pharmacology review has the following response to your proposal about renal dosing in the above referenced submission:

Based on our review of the provided data and the results of our additional analyses, we agree with your proposed VABOMERE dosing of 2 gram (meropenem 1 g- vaborbactam 1 g) every 8 hours for patients with eGFR of  $\geq 30$  –49 mL/min/1.73m<sup>2</sup>. We also agree to administer doses of VABOMERE after a hemodialysis session for patients maintained on hemodialysis.

Jane

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/s/  
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JANE A DEAN  
07/31/2017

**Subject:** NDA 209776 (meropenem-vaborbactam) - draft FDA label along with tables in the text of the email on safety margins.  
**Attachments:** NDA 209776 Package Insert draft labeling 7-21-17.docx

**From:** Dean, Jane  
**Sent:** Friday, July 21, 2017 1:56 PM  
**To:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (meropenem-vaborbactam) - draft FDA label along with tables in the text of the email on safety margins.

Hi, Starr – I'm attaching the FDA revised label to this email for your team's review. Please address each "comment bubble" when returning the label to us. Touch base with me before you send the label back, please.

Jane

(b) (4)

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/s/  
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JANE A DEAN  
07/21/2017

**From:** Dean, Jane  
**Sent:** Tuesday, July 11, 2017 3:12 PM  
**To:** Andrew Friedman (andrew.friedman@THEMEDCO.com)  
**Cc:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (meropenem-vaborbactam) - responses to your questions prior to this Thursday's telecon  
**Importance:** High

Hi, Andrew – below are the responses to your questions from the clinical pharmacology reviewer and the pharmacometric reviewer.

1. We understand FDA's guidance to use eGFR in the label. [REDACTED] (b) (4)

**FDA response:** You may provide us the results of your analyses. We recommend you use eGFR for dose adjustment in patients with renal impairment based on the reasons we stated in our response following the late cycle meeting. Additionally, the eGFR calculated by the MDRD Study equation is routinely reported by clinical laboratories. Hence, the eGFR is widely available to clinicians and the MDRD Study equation is now accepted as a more accurate estimate of glomerular filtration rate [REDACTED] (b) (4) [REDACTED]<sup>1,2</sup>.

References:

<sup>1</sup>: Miller WG. Reporting estimated GFR: A laboratory perspective. Am J Kidney Dis 52:645-648, 2008

<sup>2</sup>: Stevens LA, Nolin TD, Richardson MM et al. Comparison of Drug Dosing Recommendations Based on Measured GFR and Kidney Function Estimating Equations. Am J Kidney Dis 54:33-42, 2009

2. Can the FDA please clarify if  $fT > MIC$  for meropenem was considered in your simulations?

We have a concern that since the antibacterial effects of meropenem are linked to the proportion of the dosing interval that free drug concentrations exceed the MIC ( $fT > MIC$ ), a simulation that utilized only AUC for both drugs might result in dosage regimens that produce suboptimal meropenem PK-PD exposures. This might be particularly true for the eGFR group of 30-49 ml/min/1.73 m<sup>2</sup> where lower doses are recommended to be administered every [REDACTED] (b) (4) hours. We would very much appreciate additional detail regarding the methodology utilized.

**FDA response:** In addition to assessing AUC across different renal function groups, we conducted a Monte Carlo simulation of meropenem plasma concentrations to determine the probabilities of target attainment of meropenem PK/PD target ( $T_{CF > MIC} / \tau$ ) at our recommended dose adjustments in each renal function group. Results of probabilities of PK/PD target attainment with 45%  $T_{CF > MIC} / \tau$  of the meropenem PK/PD

target were provided in our late cycle response document and are presented here again in Table 1. With our recommended dose adjustment, percent probabilities of PK/PD target attainment based on 45%  $T_{CF>MIC}/\tau$  of the meropenem PK/PD target is 99% for simulated patients with eGFR of 30-49 ml/min/1.73 m<sup>2</sup> at an meropenem-vaborbactam MIC value of 8 µg/mL.

**Table 1. Probability of PK/PD target attainment by meropenem-vaborbactam MIC at the review team recommended dosing regimens based on a 45%  $T_{CF>MIC}/\tau$  PK/PD target among simulated patients by renal function group (by eGRF, mL/min/1.73m<sup>2</sup>)**

MIC (µg/mL)	eGFR ≥ 50	eGFR 40-50	eGFR 30-40	eGFR 20-30	eGFR 10-20	eGFR <10
0.12	1	1	1	1	1	1
0.25	1	1	1	1	1	1
0.5	1	1	1	1	1	1
1	1	1	1	1	1	1
2	1	1	1	1	1	1
4	1	1	1	1	1	1
8	1	0.99	0.99	0.99	0.97	0.97
16	0.94	0.75	0.81	0.81	0.75	0.79
32	0.39	0.18	0.24	0.27	0.27	0.28
64	0.03	0.01	0.02	0.03	0.03	0.02

3. Regarding the FDA’s simulations:

- a. Can FDA please clarify the number of patients used and the number of simulations performed?

**FDA Response:** A total of 295 subjects along with their covariate information (e.g. body weight and age) were included in each of the following renal function groups (eGFR of 5 to <15, 15 to <30, 30 to <40, 40 to <50, 50 to <80, 80 to 120 mL/min/1.73 m<sup>2</sup>). The number of subjects in the dataset (n=295) was selected as it is the total number of subjects from Study 505 and 506 who were included in the population PK dataset (merpkin.xpt). The simulation was conducted 100 times using NONMEM code “mer-final-ctl.txt” provided in the submission. The eGFR values were generated by sampling from a uniform distribution over the eGFR range for each renal function group. The correlation between eGFR and other covariates (e.g. age, gender, and race) was ignored. The same dataset was used to simulate PK profiles of meropenem and vaborbactam.

- b. Can the FDA also clarify how many simulated patients are included in each of the eGFR bins in Figure 1?

**FDA Response:** In most of the bins, there were 29500 subjects. For the eGFR range of 5 to <30 mL/min/1.73 m<sup>2</sup>, the subject number is less than 29500, as a total of 59000 subjects were divided into three groups, <10, 10 to <20, and 20 to <30 mL/min/1.73 m<sup>2</sup>. This is because different grouping is presented in Figure 1 than was used for the overall simulation (see above).

- c. Can the FDA also clarify how patient BSA was incorporated into your simulations?

**FDA Response:** BSA and other covariates for subjects in the simulation dataset were obtained from Study 505 and 506 with observations included in your submitted population PK dataset (merpkn.xpt).

4. We understand FDA's guidance regarding administering a maintenance dose of Vabomere prior to a dialysis session to avoid the potential accumulation of vaborbactam. We would appreciate further discussion of the benefit/risk of this approach in a follow up teleconference.

**FDA response:** We welcome the further discussion of the benefit/risk of administering Vabomere before or after a hemodialysis session.

The telecon is scheduled to start with you at 11:30am this Thursday, 7/13/17. Please provide the conference call-in information. Thanks!

Jane

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/s/  
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JANE A DEAN  
07/11/2017

**From:** Dean, Jane  
**Sent:** Wednesday, June 28, 2017 12:00 PM  
**To:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (meropenem-vaborbactam) - FDA Clinical Pharmacology Analyses on Dose Adjustments

Hi, Starr – here is the information we said we would send to you during the late cycle telecon on 6/23/17:

In the Late Cycle meeting on June 23, 2017, the Applicant requested the FDA’s analyses regarding the recommended dosage adjustments of VABOMERE in patients with renal impairment. Our response to the Applicant’s request is as follows.

In reviewing the Applicant’s proposed dose adjustments for patients with renal impairment, we found that the dose adjustments do not provide comparable exposures of meropenem and vaborbactam in some patients with renal impairment relative to patients with normal renal function. We conducted additional analyses and recommend the following dose adjustments of VABOMERE in patients with renal impairment (Table 1).

**Table 1. VABOMERE Dose Adjustments for cUTI Patients (including Pyelonephritis) with Reduced Renal Function - The Applicant’s Proposal vs. FDA’s Recommendation**

Applicant Proposed Dosing Regimen	FDA Recommended Dosing Regimen	
(b) (4) Recommended Dosage Regimen for VABOMERE (meropenem and vaborbactam) <sup>b</sup>	eGFR(mL/min/1.73m <sup>2</sup> ) <sup>c</sup>	Recommended Dosage Regimen for VABOMERE (meropenem and vaborbactam) <sup>b</sup>
(b) (4)	≥50	VABOMERE 4 g (2 g-2 g) q8h
(b) (4)	≥30-49	VABOMERE 4 g (2 g-2 g) q12h
(b) (4)	≥15-29	VABOMERE 2 g (1 g-1 g) q12h
(b) (4)	<15	VABOMERE 1 g (0.5 g-0.5 g) q12h <sup>d</sup>

Simulations from Population PK Analyses

Using the Applicant's population PK model, we conducted simulations to predict meropenem and vaborbactam AUCs for patients with various levels of renal function (i.e., eGFR) at both the Applicant's proposed dosing regimens and the FDA's recommended dosing regimens (Table 1). The simulations were conducted assuming that patients with ESRD receive VABOMERE after hemodialysis is completed. The simulation dataset was created based on the demographics of Phase 3 studies (Study 505 and 506, n=295) and a comparable number of eGFR values was simulated using a uniform distribution in each renal function group. A total of 100 simulations were run to generate the PK profiles. The mean PK profiles of 100 simulations were used to calculate the daily AUC using the trapezoidal method.

In addition, the following reference AUC values for meropenem and vaborbactam were used to evaluate whether the simulated exposures are considered to be safe or not:

The 90<sup>th</sup> percentiles of AUC<sub>0-24,ss</sub> observed from the infected patients from Study 506 (based on n=23):

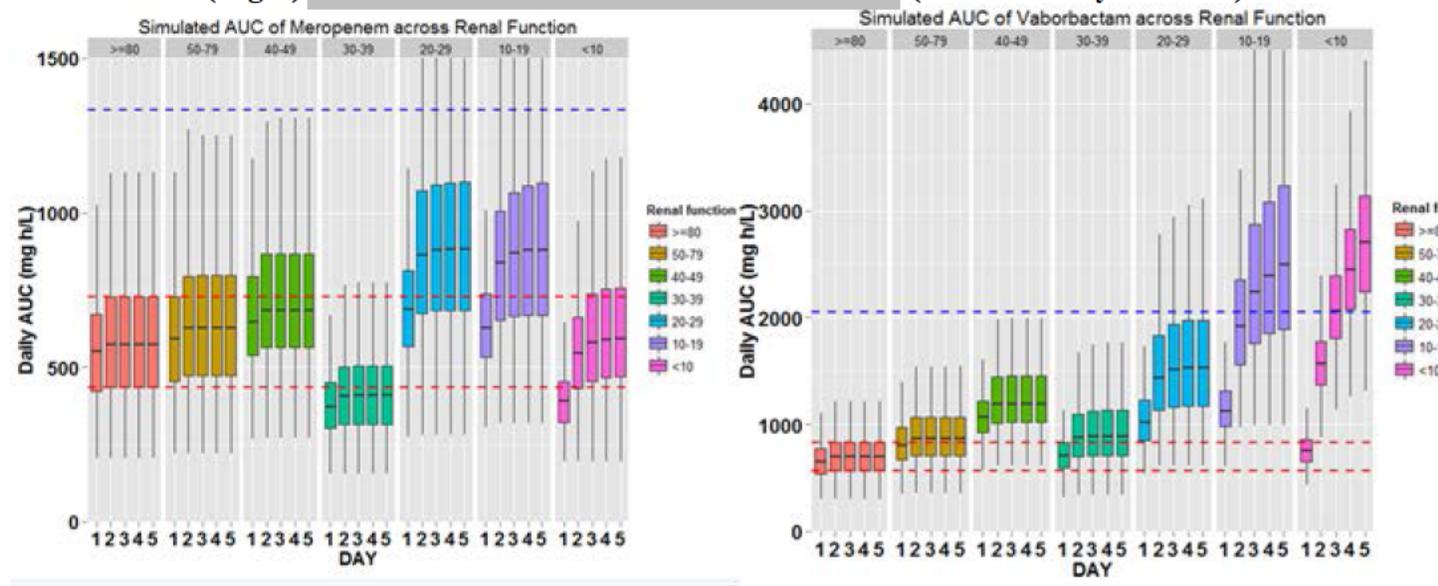
(There were no significant safety findings in Study 506)

Meropenem: 1333 µg•hr/mL

Vaborbactam: 2050 µg•hr/mL

Figure 1 shows the simulated daily AUCs from Day 1 to Day 5 for meropenem and vaborbactam (b)(4). Compared to the AUCs in patients with eGFR ≥80 mL/min/1.73 m<sup>2</sup>, the simulation results show that (a) meropenem AUC in >50% of patients with eGFR 30-39 mL/min/1.73 m<sup>2</sup> are lower than the 25<sup>th</sup> percentile of AUCs among subjects with eGFR ≥80 mL/min/1.73 m<sup>2</sup>; (b) meropenem AUCs in >50% of patients with eGFR 10-29 mL/min/1.73 m<sup>2</sup> are higher than the 75<sup>th</sup> percentile of AUCs among subjects with eGFR ≥80 mL/min/1.73 m<sup>2</sup> with some exposures approaching or exceeding the reference AUC value of 1333 µg•h/mL; (c) for vaborbactam, AUCs from most subjects with eGFR <30 mL/min/1.73 m<sup>2</sup> are higher than the 75<sup>th</sup> percentile of AUCs among subjects with eGFR ≥80 mL/min/1.73 m<sup>2</sup> and are approaching or exceeding the reference AUC value of 2050 µg•h/mL.

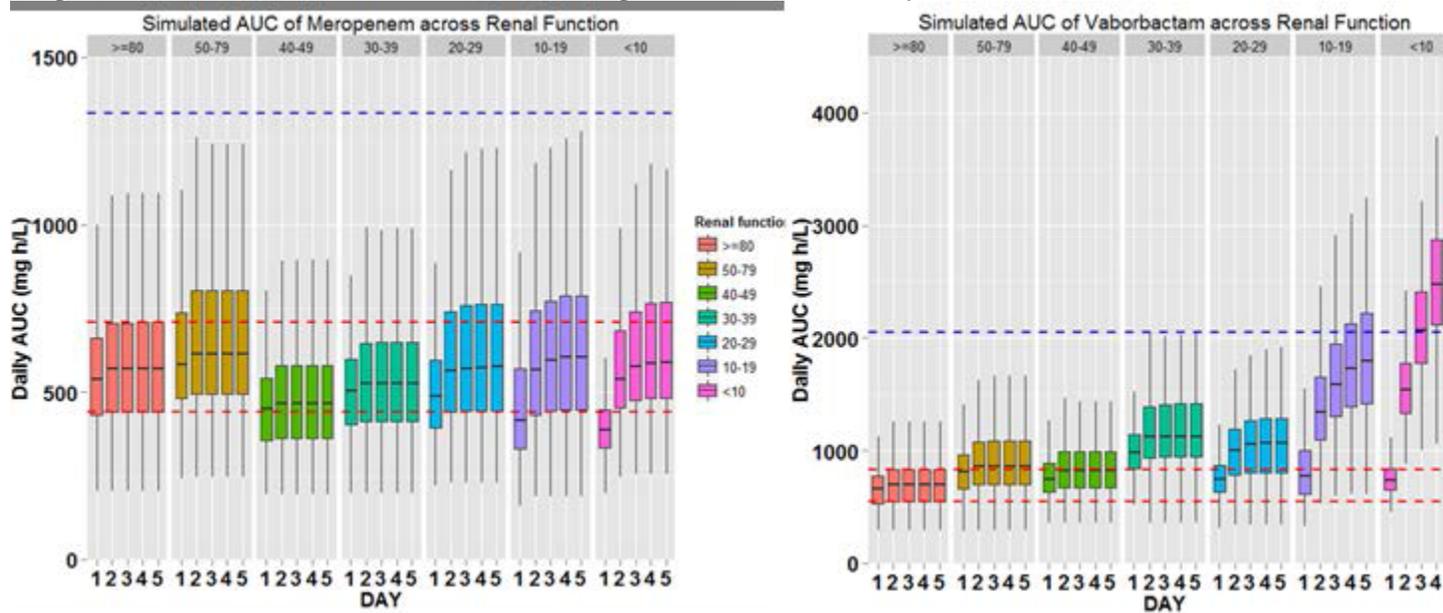
**Figure 1. Simulated Daily AUCs from Day 1 to Day 5 for Meropenem (Left) and Vaborbactam (Right) (Conducted by the FDA)** (b)(4)



Red dashed lines represent the 25<sup>th</sup> and 75<sup>th</sup> percentile of daily AUCs on Day 5 among subjects with eGFR  $\geq$  80 mL/min/1.73 m<sup>2</sup> based on the population PK model. The blue dashed lines represent the reference AUC<sub>0-24,ss</sub> for meropenem (1333  $\mu\text{g}\cdot\text{h}/\text{mL}$ ) and vaborbactam (2050  $\mu\text{g}\cdot\text{h}/\text{mL}$ ).

Additional simulations were conducted to optimize meropenem-vaborbactam dose adjustments for patients with renal impairment. Based on those simulations, the dose adjustments described in Table 1 are recommended. Figure 2 shows the simulated daily AUCs from Day 1 to Day 5 for meropenem and vaborbactam following the administration of the recommended dosing regimens in patients with renal impairment.

**Figure 2. Simulated Daily AUC from Day 1 to 5 for Meropenem (Left) and Vaborbactam (Right) at the FDA’s Recommended Dose Regimens (Conducted by the FDA)**



Red dashed lines represent the 25<sup>th</sup> and 75<sup>th</sup> percentile of daily AUC on Day 5 in subjects with eGFR  $\geq$  80 mL/min/1.73 m<sup>2</sup> based on population PK model. The blue dashed lines represent the reference AUC<sub>0-24,ss</sub> for meropenem (1333  $\mu\text{g}\cdot\text{h}/\text{mL}$ ) and vaborbactam (2050  $\mu\text{g}\cdot\text{h}/\text{mL}$ ).

As shown in Figure 2, the recommended dosing regimens are expected to provide more comparable daily AUCs of meropenem in the renal function groups with eGFR  $<$ 50 mL/min/1.73 m<sup>2</sup> to the group with eGFR  $>$ 80 mL/min/1.73 m<sup>2</sup> than the Applicant’s proposed dosing regimens. For vaborbactam, the simulated AUCs from the groups with eGFR 20-50 mL/min/1.73 m<sup>2</sup> are generally higher than those AUCs in the group with eGFR  $>$ 50 mL/min/1.73 m<sup>2</sup> but still below the reference AUC value of 2050  $\mu\text{g}\cdot\text{h}/\text{mL}$ . However, the simulation results show that our recommended dose adjustment may provide vaborbactam steady state AUCs exceeding the reference AUC value of 2050  $\mu\text{g}\cdot\text{h}/\text{mL}$  to approximately 89% subjects with eGFR  $<$ 15 mL/min/1.73 m<sup>2</sup>.

Since VABOMERE is a fixed combination of meropenem and vaborbactam (1:1), it is not possible to adjust dosing regimens of meropenem and vaborbactam separately for patients with ESRD. In addition, the effect of hemodialysis on meropenem and vaborbactam is quantitatively different although both can be removed by hemodialysis. When VABOMERE is dosed 2 hours after dialysis in patients maintained on hemodialysis, our recommended dose adjustment for this patient population is expected to provide comparable meropenem exposure to patients with eGFR  $<$ 15 mL/min/1.73m<sup>2</sup>, but substantially higher exposure of vaborbactam, relative to

exposure in other patients (Figure 2). On the other hand, when the infusion of VABOMERE is completed 2 hours prior to dialysis in patients maintained on hemodialysis, the increase in vaborbactam exposure is expected to be lower compared to when VABOMERE is dosed 2 hours after dialysis. However, meropenem exposure would be reduced in patients on hemodialysis. Currently, there are insufficient data to determine whether the high vaborbactam exposure when dosed after dialysis would lead to safety concern or whether the lower meropenem exposure when dosed before dialysis would result in compromised efficacy. However, because (a) the proportion of meropenem dose that can be removed by dialysis (i.e., 38% after a single dose administration) is not significantly high and (b) the frequency of dialysis (3 times per week according to common practice) is much less than the VABOMERE dosing frequency in patients maintained on hemodialysis (BID dosing), we anticipate that the reduction of meropenem exposure would not be substantial when VABOMERE is administered before dialysis. Hence, the risk of reduced efficacy of meropenem is anticipated to be low when VABOMERE is administered before dialysis in patients with cUTI including pyelonephritis. Based on the considerations of unknown safety risk due to high vaborbactam exposure when dosing after dialysis and an anticipated low risk of reduced efficacy (i.e., due to lower meropenem exposure) when dosing before dialysis, we recommend VABOMERE be administered before hemodialysis for patients maintained on hemodialysis.

Probability of Target Attainment Analysis

We conducted an independent analysis to assess the probability of target attainment at our recommended dosing regimens. Briefly, using the Applicant’s developed population PK model, a Monte Carlo simulation of meropenem plasma concentrations was conducted in 3540 patients according to the demographics from the two Phase 3 studies and the following renal function groups with eGFR 1)  $\geq 50$  mL/min/1.73m<sup>2</sup>; 2)  $\geq 40$  to 50 mL/min/1.73m<sup>2</sup>; 3)  $\geq 30$  to 40 mL/min/1.73m<sup>2</sup>; 4)  $\geq 20$  to 30 mL/min/1.73m<sup>2</sup>; 5)  $\geq 10$  to 20 mL/min/1.73m<sup>2</sup>; 6)  $< 10$  mL/min/1.73m<sup>2</sup>. A uniform probability distribution of eGFR values was generated in each renal function group. One hundred simulations were performed with the population PK model using NONMEM and the mean PK profile for each subject was calculated using R. Probabilities of PK/PD target attainment by meropenem-vaborbactam MIC range of 0.125 to 128 µg/mL in each renal function group were determined for three meropenem PK/PD targets (i.e., 30, 35, and 45%  $T_{Cf>MIC}/\tau$  which are associated with net-stasis, 1-log<sub>10</sub> and 2- log<sub>10</sub> bacterial reduction effect in animal infection model). Results of probabilities of PK/PD target attainment with 45%  $T_{Cf>MIC}/\tau$  of the meropenem PK/PD target are presented in Table 2. At our recommended dose adjustment, percent probabilities of PK/PD target attainment based on the above-described three PK/PD targets are all >97% across simulated patients in each renal function group at an meropenem-vaborbactam MIC value of 8 µg/mL, the susceptibility breakpoint proposed by the Applicant.

**Table 2. Probability of PK/PD target attainment by meropenem-vaborbactam MIC at the review team recommended dosing regimens based on a 45%  $T_{Cf>MIC}/\tau$  PK/PD target among simulated patients by renal function group (by eGRF, mL/min/1.73m<sup>2</sup>)**

MIC (µg/mL)	eGFR $\geq 50$	eGFR 40-50	eGFR 30-40	eGFR 20-30	eGFR 10-20	eGFR $< 10$
0.12	1	1	1	1	1	1
0.25	1	1	1	1	1	1

0.5	1	1	1	1	1	1
1	1	1	1	1	1	1
2	1	1	1	1	1	1
4	1	1	1	1	1	1
8	1	0.99	0.99	0.99	0.97	0.97
16	0.94	0.75	0.81	0.81	0.75	0.79
32	0.39	0.18	0.24	0.27	0.27	0.28
64	0.03	0.01	0.02	0.03	0.03	0.02

Jane

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JANE A DEAN  
06/28/2017



NDA 209776

## INFORMATION REQUEST

Rempex Pharmaceuticals, a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director Regulatory Affairs  
3033 Science Park Road Suite 200  
San Diego, CA 92121

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 13, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Meropenem and vaborbactam for injection

We also refer to your March 13, 2017 NDA amendment. We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments. We request a written response by **June 22, 2017**, in order to continue our evaluation of your NDA:

We acknowledge your response submitted in the above amendment to our comment regarding the potential impurities that may be extracted from the proposed container closure system into the drug product. Although we agree that the stopper undergoes minimal contact with the reconstituted solution, we remain concerned that undesirable compounds (volatiles and non-volatiles) may emanate from the stopper during prolonged storage of vials and may become adsorbed on the powder contents. Another important factor to consider is the relatively large amount of product in the vial (ca. 2.6 g), which provides a large surface area for the adsorption of leachables. Therefore, we recommend that you conduct extractable/leachable assessment of your commercial container closure system via a post-marketing commitment (PMC) study. We refer you to the USP General Chapters <1663> and <1664> for further guidance regarding the extractable/leachable assessment.

The protocol to be submitted for review as part of the PMC study should describe details of the extractable testing (e.g., the choice of solvents and conditions) and the plan for the leachable evaluation, which should include the batch numbers of the vials that are to be tested, the approximate dates when this testing will be carried out, and the analytical protocols to be used. Your interim report should contain the results of the extractable testing and available leachable data obtained from the stability samples. The final study report should include the leachable data from stability data obtained at the proposed drug product expiration date and a proposal for

inclusion of a leachable test in the drug product specification, if necessary. The results of the PMC study should be submitted for review via a prior-approval (PAS) supplement.

Please indicate your agreement to conducting the following PMC study. Note that the suggested timelines are subject to mutual agreement.

PMC Study:

Conduct extractable/leachable studies on the drug product commercial container-closure system. The results of the extraction studies should be used to monitor the drug product stability samples for potential leachables. The drug product representative stability batches should be tested for leachables through expiry by appropriate analytical techniques as established in a study protocol. The data from these studies along with the final report should be submitted as a prior-approval (PAS) supplement.

PMC Timelines:

Protocol submission: 1-Dec-2017  
Interim Report: 1-Sep-2018  
Study Completion: 1-Feb-2019  
Final Report Submission: 1-April-2019

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



Luz  
Rivera

Digitally signed by Luz Rivera  
Date: 6/20/2017 07:07:04PM  
GUID: 502abbaa000025b89fdb52a977a3d336





NDA 209776

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Rempex Pharmaceuticals  
a wholly owned subsidiary of The Medicines Company  
3013 Science Park Road, 1st Floor  
San Diego, CA 92121

ATTENTION: Starr Shangle  
Senior Director Regulatory Affairs

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated and received December 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Meropenem and Vaborbactam for Injection, 2 g per vial.

We also refer to your correspondence, dated and received April 4, 2017, requesting review of your proposed proprietary name, Vabomere.

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

If any of the proposed product characteristics as stated in your April 4, 2017, 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  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- 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 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 Jane A. Dean, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1202.

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/  
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DANIELLE M HARRIS on behalf of TODD D BRIDGES  
06/14/2017

**From:** Dean, Jane

**Sent:** Tuesday, June 13, 2017 6:06 PM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (meropenem0vaborbactam) - clinical information request re timelines for pediatric studies

Hi, Starr - the clinical reviewer asked me to get the following information from you about your deferred pediatric studies.

For each individual study in your deferral request (for pediatric studies), please provide the dates for:

**Protocol submission date**

**Study completion date**

**Study submission date**

Could you please let me know your turnaround time on this?

Thanks!

Jane

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/s/  
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JANE A DEAN  
06/13/2017

**From:** Dean, Jane  
**Sent:** Thursday, June 08, 2017 2:56 PM  
**To:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (meropenem-vaborbactam) - pharm-tox information request  
**Importance:** High

Hi, Starr – the pharmacology/toxicology has the following information request:

Further review of the results for the embryo-fetal study with vaborbactam in rats (Study No.: 1011-1721) has raised concerns that may affect our understanding of the findings and the current language in Section 8.1 Pregnancy for vaborbactam in the label for your product. Additional information is needed.

1. Please obtain the historical control data for fetal malformations in Sprague-Dawley rats from the contract lab ( [REDACTED] <sup>(b) (4)</sup> ) where Study No.: 1011-1721 was conducted and/or from the supplier for the rats used in Study No.: 1011-1721.

Please let me know what your turn around will be. Thanks!

Jane

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/s/  
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JANE A DEAN  
06/08/2017

**From:** Dean, Jane

**Sent:** Tuesday, May 30, 2017 5:27 PM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (meropenem-vaborbactam) - pharmacology/toxicology information request - please confirm receipt

Hi, Starr – the pharmacology/toxicology reviewer has the following information request:

Further review of the results for the embryo-fetal study with vaborbactam in rabbits (Study No.: 1011-1744) has raised concerns that may affect our understanding of the findings and the current language in Section 8.1 Pregnancy for vaborbactam in the label for your product. Additional information is needed.

1. Please obtain the historical control data for fetal malformations in New Zealand White rabbits from the contract lab ( [REDACTED] <sup>(b) (4)</sup> ) where Study No.: 1011-1744 was conducted and/or from the supplier for the rabbits used in Study No.: 1011-1744.
2. Supernumerary lung lobes were found in rabbits treated with 300 or 1000 mg/kg/day vaborbactam at a higher incidence than in vehicle control rabbits where supernumerary lung lobes were not observed. Please provide a rationale for why supernumerary lung lobes should not be considered a treatment-related malformation.
3. Another finding, supernumerary liver lobes, occurred in 3 litters and 4 fetuses from the vehicle control group, as well as in 3 litters and 5 fetuses from the vaborbactam-treatment groups combined. Please provide a rationale for the relatively high incidence of supernumerary liver lobes that occurred in this study, in comparison with historical control data or other data you might have.

Please let me know what your turnaround time will be – thanks!

Jane

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/s/  
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JANE A DEAN  
05/30/2017

**From:** Dean, Jane  
**Sent:** Friday, May 26, 2017 3:46 PM  
**To:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (meropenem-vaborbactam) - draft labeling

Hi, Starr – below is a table provided by the Pharmacology/Toxicology reviewer to accompany comments that are embedded in the parts of the label I am sending to you. When you revise the label, please acknowledge acceptance of changes and if you don't agree with a suggested change, your proposal and the rationale.

**Table to Accompany the NDA 209776 Product Label as referenced in Comments in Sections 8.1 and 13.**

(b) (4)

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JANE A DEAN  
05/26/2017

**From:** Dean, Jane

**Sent:** Wednesday, May 17, 2017 10:59 AM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (meropenem-vaborbactam) - Pharm-Tox and CMC information request

**Importance:** High

Hi, Starr – the pharmacology/toxicology reviewer along with the CMC reviewer have the following information request:

Toxicology report (b) (4) 1011-0762 does not support the qualification of (b) (4) at the level indicated in Table 3 in Section 3.2.S.4.5 Justification of the Specifications. The Certificate of Analysis for the batch of RPX7009 used in that study (Lot No. 1107427005-A) does not adequately identify the impurities since they are listed only by relative retention time. Provide batch analysis data for Lot No. 1107427005-A that clearly identifies each impurity or provide alternative study and batch data that qualifies (b) (4). Otherwise the specification limit for (b) (4) will need to be reduced to below the Qualification Threshold of (b) (4) % to be consistent with the recommendations of ICH Q3A (R2).

Please let me know what your turnaround time can be.

Thanks!

Jane

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/s/  
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JANE A DEAN  
05/17/2017



NDA 209776

**MID-CYCLE COMMUNICATION**

Rempex Pharmaceuticals, Inc.  
a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director, Regulatory Affairs  
8 Sylvan Way  
Parsippany, NJ 07054

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 29, 2016, received December 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for meropenem and vaborbactam powder for injection, 1000mg/1000mg vial.

We also refer to the teleconference between representatives of your firm and the FDA on April 12, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** April 12, 2017, 1:00pm – 2:00pm

**Application Number:** NDA 209776

**Product Name:** Meropenem-vaborbactam

**Indication:** Treatment of complicated urinary tract infections, including pyelonephritis, in adult patients

**Applicant Name:** Rempex Pharmaceuticals, Inc.

**Meeting Chair:** Sumathi Nambiar, MD, MPH

**Meeting Recorder:** Jane A. Dean, RN, MSN

**FDA ATTENDEES**

**Division of Anti-Infective Products:**

Abimbola Adebowale, PhD	Associate Director of Labeling
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
Carmen DeBellis, RPh, PharmD	Chief, Project Management Staff
Kerian Grande, PhD	Clinical Microbiology Reviewer
Rama Kapoor, MD	Clinical Reviewer
Terry Miller, PhD	Pharmacology/Toxicology Team Leader
Sumathi Nambiar, MD MPH	Director
Joseph Toerner, MD, MPH	Deputy Director for Safety
James Wild, PhD	Pharmacology/Toxicology Reviewer

**Office of Antimicrobial Products:**

John Farley, MD, MPH	Deputy Director
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**Office of Biostatistics:**

Daphne TY Lin, PhD	Deputy Division Director, Biometrics IV
Daniel Rubin, PhD	Statistical Reviewer

**Office of Clinical Pharmacology:**

Seong Jang, PhD	Clinical Pharmacology Team Leader
Xiaohui (Tracey) Wei, PhD	Clinical Pharmacology Reviewer

**Office of Pharmaceutical Quality:**

Elsbeth Chikhale, PhD	Biopharmaceutics Team Leader
Daniel DeCiero, PhD	Product Quality Facilities Reviewer
Christina Falabella, PhD	Product Quality Reviewer
George Lunn, PhD	Product Quality Reviewer

Dorota Matecka, PhD	Product Quality Team Leader (Acting)
Derek Smith, PhD	Branch Chief (Acting), Office of Pharmaceutical Quality
Qi Zhang, PhD	Biopharmaceutics Reviewer

**Office of Scientific investigations:**

Janice Pohlman, MD	Clinical Team Leader
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**Office of Surveillance and Epidemiology:**

Susan Bersoff-Matcha, MD	Medical Officer
Janet Higgins	Regulatory Project Manager
Deborah Myers, RPh, MBA	Safety Evaluator
Til Olickal, PhD, PharmD	Risk Management Analyst
Chih-Ying (Natasha) Pratt, PhD	Epidemiology Team Leader (Acting)

**APPLICANT ATTENDEES**

**Rempex Pharmaceuticals, Inc.:**

Stefanie Andrews	Senior Program Manager
Sabrina Comic-Savic, MD, MPH	Vice President, Quality and Compliance
Isabelle Degeyter, MD	Senior Director, Pharmacovigilance
Mike Dudley, PharmD	Senior Vice President, Chief Scientific Officer
David Griffith	Vice President, Nonclinical Science
Scott Hecker, PhD	Vice President, Chemistry
Loretta Itri, MD	Executive Vice President, Global Health Science & Regulatory
Judy Lee	Senior Director, Chemistry, Manufacturing, and Controls (CMC)
Michelle Linfesty	Senior Director, Program Management
Olga Lomovskaya	Vice President, Biology
Jeff Loutit, MBChB	Senior Vice President, Chief Medical Officer
Mary Ann McElligott	Vice President, CMC
Starr Shangle	Senior Director, Regulatory Affairs
Shu Zhang, ScD	Senior Director, Biostatistics

**Biomedical Advanced Research & Development Authority (BARDA):**

Mark Albrecht, PhD	Project Officer
Sandra Bihary-Waltz	RQA SME, Contractor
Wylie McVay	RQA SME, Contractor
Corrina Pavetto	Clinical SME, Contractor

**Consultant:**

 (b) (4)	CMC Consultant
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## **1.0 INTRODUCTION**

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

## **2.0 SIGNIFICANT ISSUES**

### **Product Quality:**

There are substantive review issues related to manufacturing facility deficiencies. Per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the facilities proposed must comply with the current good manufacturing practice regulations.

During the teleconference, Rempex Pharmaceuticals stated that the previously agreed stability update would be provided within two weeks.

## **3.0 INFORMATION REQUESTS**

We reference our letter, dated February 23, 2017, communicating that we have completed our review of the proposed proprietary name, Carbavance, and concluded that this name is not acceptable.

We acknowledge your submission dated April 4, 2017, with reference to the alternate proposed proprietary name (VABOMERE). The submission is being reviewed at this time. We will notify you if any issue is identified upon review.

We reference the pending information request on April 6, 2017, sent by the Office of Pharmaceutical Quality.

We have received the response to the clinical information request sent March 30, 2017. We will communicate with you if further issues are identified upon review.

We have received the response to the clinical pharmacology information request sent March 30, 2017. We will communicate with you if further issues are identified upon review.

#### **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

There are no major safety concerns identified at this time and there is currently no need for a Risk Evaluation and Mitigation Strategy (REMS) plan.

#### **5.0 ADVISORY COMMITTEE MEETING**

There are no plans at this time for an Advisory Committee meeting.

#### **6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES**

1. Draft labeling will be sent to Rempex by May 29, 2017.
2. Begin Labeling/PMR/PMC discussion with Rempex by June 5, 2017.
3. Late Cycle meeting package will be sent to Rempex by June 14, 2017.
4. The Late Cycle meeting with Rempex is scheduled for June 19, 2017.

#### **Post-Mid-Cycle Communication addendum:**

The Late Cycle meeting with Rempex has been rescheduled for June 23, 2017.

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/s/  
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SUMATHI NAMBIAR  
04/25/2017



NDA 209776

## INFORMATION REQUEST

Rempex Pharmaceuticals, a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director Regulatory Affairs  
3033 Science Park Road Suite 200  
San Diego, CA 92121

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 13, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- meropenem and vaborbactam for injection

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 **Wednesday, April 12, 2017**, in order to continue our evaluation of your NDA. A partial response at that time, with clarification of the timeline for the remaining questions, would also be satisfactory.

### Process:

Please address the following comments regarding your proposed in-process tests and acceptance criteria for your drug product manufacturing process:

1.

2.

(b) (4)

3.

4.

5.

(b) (4)

Drug Substance:

6. Provide additional details for each step in the vaborbactam drug substance manufacturing process such as the reaction scale (range), amounts of starting materials and reagents (range, molar equivalents), solvents (range), temperature (range), time (range), etc. (Section 3.2.S.2)

Biopharmaceutics:

7. Provide a side-by-side comparison table of the quantitative compositions for the formulation before reconstitution and after reconstitution and dilution, for the proposed commercial drug product (single-vial presentation) and the product used in the pivotal clinical studies (multi-vial presentation). In addition, specify any difference in the dose, infusion rate and volume infused.
8. Provide a side-by-side comparison table for the physicochemical characteristics such as pH and osmolality, impurity profiles, and stability information for the proposed commercial drug product (single-vial presentation) and the product used in the pivotal clinical studies (multi-vial presentation) after reconstitution and dilution. The comparative pH and osmolality data should be provided using 1-3 production lots of the proposed reconstituted and diluted commercial drug product and 1-3 lots of the

reconstituted and diluted product used in the pivotal clinical studies. The measurements should be done in triplicate for each lot tested.

9. For any differences in the impurity profiles, stability, physicochemical characteristics, the quantitative compositions, dose, infusion rate and volume infused between the proposed commercial drug product (single-vial presentation) and the product used in the pivotal clinical studies (multi-vial presentation), provide a justification and expected impact on the drug product's safety and efficacy.

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



Luz  
Rivera

Digitally signed by Luz Rivera  
Date: 4/06/2017 08:43:42PM  
GUID: 502abbaa000025b89fdb52a977a3d336



**From:** Dean, Jane  
**Sent:** Friday, March 31, 2017 11:52 AM  
**To:** Andrew Friedman (andrew.friedman@THEMEDCO.com)  
**Cc:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (meropenem-vaborbactam) - clinical information request

Hi, Andrew – the clinical reviewer has the following information request:

While reviewing the information submitted with the NDA, we found some discrepancies in coding and some deficiencies, listed below. We recommend you provide the rationale/explanation /resolutions regarding the following issues in order for us to review your application within the critical time limit.

1. REMPEX-505-703-005-509: The patient had an SAE of death on Day 2. Please provide explanation why this patient is coded as overall assessment of “Indeterminate” and not “Failure.”
2. REMPEX-505-724-009-506: The patient had an AE of lacunar infarct and it is noted that, study treatment was discontinued. Please provide explanation why this patient is assessed as Overall Response “Indeterminate” and not “Failure.”
3. REMPEX-505-112-002-514: Patient is coded correctly by Investigator as “Clinical CURE” at EOIVT and TOC. Please provide microbiology results of baseline urine specimen for the accurate assessment of Overall Response.
4. REMPEX-505-112-006-511: a) Patient is coded correctly by Investigator as “Clinical Improvement” at EOIVT; However, at TOC coded incorrectly as “Indeterminate”, despite of resolution of signs and symptoms, normalized physical examination ( despite meeting pre-specified criteria for clinical Cure); b) Please provide microbiology results of baseline urine specimen, or explanation for non-availability.
5. REMPEX-505-203-002-502: Please provide microbiology results of baseline urine specimen for proper assessment of overall response, or explanation for non-availability.
6. REMPEX-505-203-005-501: Please provide microbiology results of baseline urine specimen for proper assessment of overall response, or explanation for non-availability.
7. REMPEX-505-203-008-507: The patient is coded correctly at EOIVT and TOC as “Clinical Cure.” This patient also had a microbiologic eradication of baseline organism (Klebsiella Pneumoniae). However, Overall Response at EOIVT is assessed as “Indeterminate.” Please provide explanation.
8. REMPEX-505-703-005-506: The patient is coded correctly at EOIVT, and EOT as “Clinical Cure,” however, clinical outcome at TOC is evaluated as “Indeterminate” despite resolution of all signs and symptoms. Overall Response is coded also coded as “Indeterminate.” Please provide explanation and microbiology results of baseline urine specimen.
9. REMPEX-505-705-002-504: The patient is coded correctly at EOIVT as “Clinical Cure,” However, at TOC his clinical outcome is assessed as “Indeterminate,” which is against

meeting pre-specified criteria. Please provide explanation. Please also provide microbiology results of baseline urine specimen or explanation for non-availability.

10. REMPEX-505-804-008-506: The patient's Overall Response is assessed as "Indeterminate" at EOIVT. On day 3, patient developed an AE of generalized body tremor and it is noted that infusion was stopped and therefore, EOT visit was performed that day. Please explain why this patient is not coded as Overall Response of "Failure"
11. REMPEX-505-076-003-510: The patient died due to broncho aspiration. The patient had no assessment performed at TOC visit. Please explain why this patient is coded as Overall Response of "Indeterminate" and not "Failure."
12. REMPEX-505-100-004-501: The patient is assessed as "Clinical Cure" at EOIVT and TOC. The patient had achieved eradication of baseline organism (*E. Cloacae*) however; Overall Response at TOC is assessed as "Indeterminate" despite meeting pre specified criteria of Success. Please provide the explanation.
13. REMPEX-505-203-002-503: The patient had an SAE of "Sudden cardiac death" on day10-11, and therefore TOC visit was not performed. Please explain why this patient is not coded as Overall Response of "Failure."
14. REMPEX-505-300-001-501: The patient is coded correctly as clinical outcome of "Cure" at EOIVT. However, miscoded at TOC as Overall Response of "Indeterminate." There is no examination performed at TOC visit. Microbiologic results consistent with "persistence" of baseline organism (*E. coli* at 5 logs). Please explain why this patient does not qualify for clinical outcome of "Indeterminate" and Overall Response of "Failure" at TOC visit.
15. REMPEX-505-616-006-501: The patient is incorrectly coded at EOIVT as clinical outcome of "Cure" whereas per pre specified criteria, patient should have been coded as "Improvement" based on clinical examination. Subsequently, patient had a moderate AE of "diarrhea" and "generalized weakness," and patient left the hospital. No assessment performed for EOT or TOC. Please explain why this patients' Overall Response at TOC is assessed as "Indeterminate," and not "Failure."
16. REMPEX-505-705-001-502: The patient is correctly coded as clinical outcome of "Cure" at EOIVT. At TOC, patient had an onset of some new clinical symptoms. Please explain why she is coded as clinical outcome of "Indeterminate." Please provide microbiology results of baseline, EOT, and TOC urine specimen.
17. REMPEX-505-112-004-502: The patient's microbiologic outcome at EOIVT is coded as "Recurrence." Please explain how a patient can have recurrence without achieving "eradication" at earlier time points in the study. It is noted that patient had a recent hospitalization for cUTI. Please provide the details of prior hospitalization.
18. REMPEX-505-300-001-518: The patient had clinical assessment performed at day 3 with resolution of fever. Physical examination is noted as "not applicable." No assessment performed on day 3 (which was also considered as EOIVT visit according to documentation in CRF). Please explain why she is coded with Overall Response of "Failure" at EOIVT visit. Please provide microbiology results of baseline urine specimen.

19. REMPEX-505-642-001-506: The patient's clinical outcome is incorrectly assessed as "Improvement" at EOIVT despite having met the pre specified criteria for clinical outcome of "Cure." Microbiologic outcome at EOIVT (based on baseline urine specimen result) is noted as "recurrence." Please explain how a patient can have recurrence without achieving "eradication" at earlier time points in the study. Please provide details of prior medical and hospital records.
20. REMPEX-505-642-002-506: The patient's microbiologic outcome at EOIVT based on baseline urine specimen results is listed as "persistence." Please explain how a patient can have "persistence" of organism in the baseline urine specimen. Please provide details of prior medical and hospital records.
21. REMPEX-505-804-008-505: The patients' clinical outcome at EOIVT visit is incorrectly coded as "Failure." Patient meets pre specified criteria of "Cure." Microbiologic outcome at EOIVT is listed as "Eradication." This patient meets the Overall Response criteria of "Success" at EOIVT. Please explain why patient's Overall Response is coded "Failure" at EOIVT.

Please let me know your expected turnaround time – thanks!

Jane

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/s/  
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JANE A DEAN  
03/31/2017

**From:** Dean, Jane  
**Sent:** Thursday, March 30, 2017 4:13 PM  
**To:** Andrew Friedman (andrew.friedman@THEMEDCO.com)  
**Cc:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (meropenem-vaborbactam) 0 clinical pharmacology information requests

Hi, Andrew – the clinical pharmacology reviewer has the following information requests:

While we are reviewing the Clinical Pharmacology information submitted in this NDA, we found that the following issues were not addressed. We recommend you provide the rationale/explanation regarding the following review issues with additional data analyses, if needed. In addition, we found that many important data variables/datasets are missing in this NDA. Those are critical for us to timely review your proposed dosing regimens. Provide the data variables/datasets listed below in an appropriate format (e.g., table, graph, .xpt files) as soon as possible. If you already submitted some of them, let us know the location of data variables/datasets.

**Query:**

- Provide your rationale for proposing dose regimens according to the range of renal functions categorized by creatinine clearance rather than eGFR (i.e., MDRD).
- Provide reasons that you proposed different dose regimens including dose adjustment for patients with renal impairment from those tested in Phase 3 studies.
- Provide graphical and tabular comparisons of the dosing scenarios together with simulation datasets:
  - A table of meropenem AUC (median and 90% CI) at steady state and Day 1 grouped by creatinine clearance (<10, 10-20, 20-30, 30-40, 40-50, and >50 mL/min) for the proposed dosing, the regimen evaluated in Study 505 and 506, and the currently labeled meropenem regimen
  - A table of vaborbactam AUC (median and 90% CI) at steady state and Day 1 grouped by creatinine clearance (<10, 10-20, 20-30, 30-40, 40-50, and >50 mL/min) for the proposed dosing and the regimen evaluated in Study 505 and 506
  - Graphs of meropenem AUC (median and 90% CI) versus creatinine clearance for the proposed dosing versus the dosing evaluated in Study 505 and 506 and the labeled meropenem dosing. The predicted AUC for the two regimens should be overlaid with a maximum CrCL of 100 mL/min. Provided separate figures based on Day 1 AUC and steady state AUC
  - A graph of vaborbactam AUC (median and 90% CI) versus creatinine clearance for the proposed dosing versus the dosing evaluated in Study 505

and 506. The predicted AUC for the two regimens should be overlaid with a maximum CrCL of 100 mL/min. Provided separate figures based on Day 1 AUC and steady state AUC

**Information Request:**

Please provide the following data listings as .xpt file (if you did not submit) as well as readable tables:

- Study 501
  - List of individual data of plasma concentration versus time for meropenem, meropenem metabolite, and vaborbactam stratified by dosing cohorts in a readable format.
  - List of individual PK parameters (e.g.,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $CL_t$ ,  $CL_R$ ,  $CL_{NR}$ ,  $C_{max}$ ,  $f_e$ ,  $K_{el}$ ,  $t_{1/2}$ ,  $T_{max}$ ,  $A_e$ ) for meropenem, meropenem metabolite, and vaborbactam stratified by dosing cohorts.
  
- Study 504
  - List of individual data of plasma concentration versus time for meropenem, meropenem metabolite, and vaborbactam stratified by renal function groups in a readable format.
  - List of individual PK parameters (e.g.,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $CL_t$ ,  $CL_t\_WTKG$ ,  $CL_R$ ,  $CL_{NR}$ ,  $C_{max}$ ,  $f_e$ ,  $K_{el}$ ,  $t_{1/2}$ ,  $T_{max}$ ,  $A_e$ ,  $V_{ss}$ ,  $V_z$ ) along with individual values of eGFR, CLcr, BSA, and normalized CLcr for meropenem, meropenem metabolite, and vaborbactam stratified by renal function groups.
  
- Studies 505 and 506/Study 00373-1 (Pop-PK)
  - List of individual data of plasma concentration versus time for meropenem, meropenem metabolite, and vaborbactam stratified by renal function groups in a readable format.

Please confirm receipt of this IR and your turnaround time. Thanks!

Jane

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/s/  
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JANE A DEAN  
03/30/2017

**From:** Dean, Jane  
**Sent:** Wednesday, March 29, 2017 10:16 AM  
**To:** Andrew Friedman (andrew.friedman@THEMEDCO.com)  
**Cc:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (meropenem-vaborbactam) - clinical information request

Hi, Andrew – the clinical reviewer has the following information request:

**Please send eCRFs for following subject IDs at your earliest convenience:**

**USUBJID:**

<b>REMPEX-505-112-006-511</b>
<b>REMPEX-505-203-005-501</b>
<b>REMPEX-505-203-008-507</b>
<b>REMPEX-505-604-005-505</b>
<b>REMPEX-505-703-005-506</b>
<b>REMPEX-505-705-002-504</b>

<b>REMPEX-505-100-004-501</b>
<b>REMPEX-505-300-001-501</b>
<b>REMPEX-505-300-001-507</b>
<b>REMPEX-505-705-001-502</b>

Jane

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/s/  
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JANE A DEAN  
03/29/2017



**METHOD VERIFICATION  
MATERIALS RECEIVED**

NDA 209776

March 27, 2017

Starr Shangle  
starr.shangle@themedco.com  
Rempex  
8 Sylvan Way  
Parsippany, NJ 07054

Dear Starr Shangle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Carbavance (meropenem and vaborbactam) powder for injection and to our March 1, 2017, letter requesting sample materials for method verification testing.

We acknowledge receipt on March 23, 2017, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

**Laura C. Pogue**

-S

Digitally signed by Laura C. Pogue -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Laura C. Pogue -  
S, 0.9.2342.19200300.100.1.1=2000606027  
Date: 2017.03.27 07:29:28 -05'00'

Laura C. Pogue, Ph.D.  
MVP Coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**From:** Dean, Jane

**Sent:** Monday, March 13, 2017 12:37 PM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (meropenem-vaborbactam) - clinical information request - rapid turn around time needed please

**Importance:** High

Starr, I just received this urgent request from the clinical reviewer to obtain the following information and she is asking for a turnaround time of "as soon as possible" – can you please let me know when you can submit this information?

**Re: Analysis data set Adam for ISS Folder**

Please convert Unique Subject IDs for studies 501, 504 and 503 in ISS data sets to similar format as in studies 505 and 506 (REMPEX-505-076-001-501, REMPEX-506-840-023-602), and send us those data sets as soon as possible

Thanks!!

Jane

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/s/  
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JANE A DEAN  
03/13/2017

**From:** Dean, Jane

**Sent:** Thursday, March 02, 2017 9:02 AM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (meropenem-vaborbactam) - clinical information request

Hi, Starr – the clinical reviewer has the following information request:

**For variables : “MAXTEMP” and “ICUDAYS”,** values are “missing” for large number of patients in Study 505 data sets. Can you provide us with the dataset which includes all missing values.

Please confirm receipt and let me know what your turnaround time can be. Thanks!

Jane

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/s/  
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JANE A DEAN  
03/02/2017



## REQUEST FOR METHOD VERIFICATION MATERIALS

NDA 209776

March 1, 2017

Starr Shangle  
starr.shangle@themedco.com  
Rempex  
8 Sylvan Way  
Parsippany, NJ 07054

Dear Starr Shangle:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Carbavance (meropenem and vaborbactam) powder for injection.

We will be performing method verification studies on Carbavance (meropenem and vaborbactam) powder for injection as described in NDA 209776.

In order to perform the necessary testing, we request the following sample materials and equipment:

### Method, current version

- 1) Identification, Assay, and Related Substances in Vaborbactam
- 2) Determination of Related Substance in the Meropenem-Vaborbactam for Injection

### Chemicals, Samples and Reference Standards

- 1) Vaborbactam Drug Substance (2 x 1g)
- 2) Vaborbactam Reference Standard (2 x 1g)
- 3) RPX7009 IMP Reference Standard (*Please comment if this is the same as the Vaborbactam Reference standard. There is confusion regarding the "IMP" in the naming of the standard. If it is not the same, please include 1 g of material*)
- 4) Meropenem Reference Standard (2 x 1g)
- 5) Carbavance Drug Product (50 vials)



6) Please include 200 mg of each of the following individual impurities:

Components Related to Drug Substance	Components Related to Drug Product
(b) (4)	

**Equipment**

1) (b) (4)

**Please include the MSDSs and the Certificates of Analysis for the sample and reference materials as well as impurities if available.**

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: MVP Sample Custodian  
645 S Newstead  
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155) or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

**Laura C. Pogue**

-S

Laura C Pogue, Ph.D.  
MVP Coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Digitally signed by Laura C. Pogue -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Laura C. Pogue -  
S, 0.9.2342.19200300.100.1.1=2000606027  
Date: 2017.03.01 10:20:15 -06'00'

**From:** Dean, Jane

**Sent:** Tuesday, February 28, 2017 9:46 AM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (meropenem-vaborbactam) - clinica information request

Hi, Starr – the clinical reviewer has the following information request. Please confirm receipt of this and let me know your turnaround time for providing a response. Thanks!!

For Study-505, you have submitted *Charlson comorbidity scoring in the format of  $\leq 2$  and  $\geq 3$*  . Can you provide us the data set which includes severity scoring in the range of 0 – 6.

Jane

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/s/  
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JANE A DEAN  
02/28/2017



NDA 209776

**INFORMATION REQUEST**

Rempex Pharmaceuticals, a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director Regulatory Affairs  
3033 Science Park Road Suite 200  
San Diego, CA 92121

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 13, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- meropenem-vaborbactam

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a written response by **Monday March 13, 2017**, in order to continue our evaluation of your NDA.

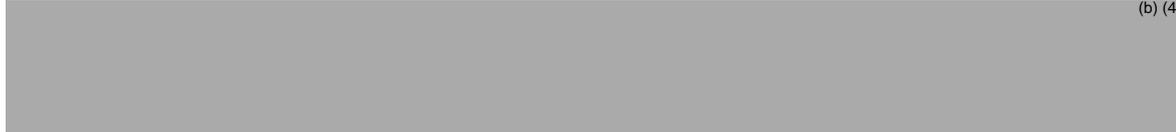
**Drug Product**

1. In Section P.2.5 you describe the Blue Dye test. Please provide the results of this testing.

2.  (b) (4)

3. Please describe the ICP-MS method used to carry out the elemental impurities testing and provide validation data to show that the LOQ for each element can be met.

4. Please describe the system suitability criteria for the related substances HPLC method. The system suitability criteria should include at least one critical resolution. Please provide data to show that this critical resolution is maintained during robustness testing.

5.  (b) (4)

6. In the batch analyses the results for the Uniformity of Dosage Units testing is “Conforms”. Please provide the numerical data that underlie these results.
7. Your proposal [REDACTED] (b) (4) is not acceptable. Please commit to continuing this testing or instituting another test [REDACTED] (b) (4).
8. Please confirm that the components of the container-closure system conform to the relevant 21 CFR food additive regulations.
9. Please provide data to show that impurities are not extracted from the container-closure system under realistic conditions of use, including after constitution.
10. At a number of time points during the stability testing you state “Sterility, Bacterial Endotoxins and Particulate Matter are conducted at these time points and met the requirements”. Please provide the numerical data that support these statements for the endotoxins and particulates.

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



Luz  
Rivera

Digitally signed by Luz Rivera  
Date: 2/27/2017 02:27:02PM  
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NDA 209776

**FILING COMMUNICATION -  
NO FILING REVIEW ISSUES IDENTIFIED**

Rempex Pharmaceuticals, Inc.  
a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director, Regulatory Affairs  
8 Sylvan Way  
Parsippany, NJ 07054

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 29, 2016, received December 29, 2016, submitted under section 505(b) and pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for meropenem and vaborbactam powder for injection, 1000mg/1000mg vial.

We also refer to your amendment dated December 29, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is August 29, 2017. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 12, 2017.

In addition, the planned date for our internal mid-cycle review meeting is March 31, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

### **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 [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- 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.

During our preliminary review of your submitted labeling, we have identified the following labeling issue and have the following comment:

1. The length of **HIGHLIGHTS** (HL) must be one-half page or less unless a waiver has been granted in a previous submission.

We request that you resubmit labeling (in Microsoft Word format) that addresses this issue by March 13, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. See the following link to the SRPI:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf>.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

## **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). 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), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

## **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

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/  
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SUMATHI NAMBIAR  
02/15/2017

**From:** Dean, Jane  
**Sent:** Friday, February 10, 2017 12:09 PM  
**To:** 'Starr Shangle'  
**Cc:** Andrew Friedman  
**Subject:** RE: NDA 209776 (meropenem-vaborbactam) - QT-IRT information request

Starr, here's the response I just received from the QT/IRT folks in response to your question below:

“After the ADAM adegpc.xpt dataset is transposed to a wide-structure dataset, we only see the post-dose observations with baselines and deltas. The baseline observations are not included as separate rows. Although they have no concentrations, we still need them to run E-14 analyses”.

Hope this helps!

Jane

---

**From:** Starr Shangle [<mailto:starr.shangle@THEMEDCO.com>]  
**Sent:** Thursday, February 09, 2017 6:05 PM  
**To:** Dean, Jane  
**Cc:** Andrew Friedman  
**Subject:** RE: NDA 209776 (meropenem-vaborbactam) - QT-IRT information request

Hi Jane,

Our statistician has a question on the 2. b. of the Information Request below:

2. *Update and re-submit the following dataset for the Study 505:*
  - b. *adegpc.xpt: currently observations of baseline were excluded, please include them*

Here is her question:

The baseline value for each ECG parameter, for each subject included in this analysis, is included in the ADEGPC dataset (see variable BASE). Baseline concentrations for meropenem and vaborbactam are missing for all observations at baseline because predose concentrations were presumed to be zero and were not collected. We would appreciate clarity on exactly what the Agency is requesting.

Thanks so much,  
Starr

---

**From:** Dean, Jane [<mailto:Jane.Dean@fda.hhs.gov>]  
**Sent:** Thursday, February 09, 2017 8:30 AM  
**To:** Starr Shangle <[starr.shangle@THEMEDCO.com](mailto:starr.shangle@THEMEDCO.com)>  
**Subject:** NDA 209776 (meropenem-vaborbactam) - QT-IRT information request  
**Importance:** High

Hi, Starr – the QT/IRT reviewers have the following information request. Can you please let me know when you can provide the information they need? Thanks!

1. Upload the available ECG waveforms with annotations from 6 studies (402, 501, 502, 503, 504, 505 and 506) to the ECG warehouse at [www.ecgwarehouse.com](http://www.ecgwarehouse.com)
2. Update and re-submit the following dataset for the Study 505:
  - a. adeg.xpt: only about half of the observations were populated (60732/118660), and 290 subjects were present
  - b. adegpc.xpt: currently observations of baseline were excluded, please include them

Jane

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/s/  
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JANE A DEAN  
02/10/2017

**From:** Dean, Jane

**Sent:** Thursday, February 09, 2017 11:58 AM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (meropenem-vaborbactam) - additional clinical information request related to the IR sent 2-8-17

Hi, Starr! The clinical reviewer has the additional information request related to the one sent yesterday:

Please send us CRFs ( in addition to what was requested earlier), for all patients who discontinued the study treatment and discontinued the study

Thanks!

Jane

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/s/  
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JANE A DEAN  
02/09/2017

**From:** Dean, Jane  
**Sent:** Thursday, February 09, 2017 11:30 AM  
**To:** starr.shangle@themedco.com  
**Subject:** NDA 209776 (meropenem-vaborbactam) - QT-IRT information request  
**Importance:** High

Hi, Starr – the QT/IRT reviewers have the following information request. Can you please let me know when you can provide the information they need? Thanks!

1. Upload the available ECG waveforms with annotations from 6 studies (402, 501, 502, 503, 504, 505 and 506) to the ECG warehouse at [www.ecgwrehouse.com](http://www.ecgwrehouse.com)
2. Update and re-submit the following dataset for the Study 505:
  - a. adeg.xpt: only about half of the observations were populated (60732/118660), and 290 subjects were present
  - b. adegpc.xpt: currently observations of baseline were excluded, please include them

Jane

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/s/  
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JANE A DEAN  
02/09/2017

**From:** Dean, Jane

**Sent:** Wednesday, February 08, 2017 2:28 PM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (meropenem-vaborbactam) - clinical information request

Hi, Starr – the clinical reviewer has asked for a copy of the following:

We need CRFs for following USUBJID:

***REMPEX-505-300-001-518***

***REMPEX-505-642-001-506***

***REMPEX-505-642-002-506***

***REMPEX-505-840-014-503***

Thanks!!

Jane

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/s/  
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JANE A DEAN  
02/08/2017

## Kinsley, Steven

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**From:** Kinsley, Steven  
**Sent:** Friday, February 03, 2017 1:04 PM  
**To:** 'starr.shangle@themedco.com'  
**Cc:** Rivera, Luz E (CDER); Dean, Jane  
**Subject:** NDA 209776 Information Request  
**Attachments:** NDA 209776 Information Request.pdf

Dear Ms. Shangle,

Please find the attached Information Request for NDA 209776. If you have any questions, please 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](mailto:Steven.Kinsley@fda.hhs.gov)





NDA 209776

## INFORMATION REQUEST

Rempex Pharmaceuticals, a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director Regulatory Affairs  
3033 Science Park Road Suite 200  
San Diego, CA 92121

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 29, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- meropenem-vaborbactam

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a written response by February 10, 2017 in order to continue our evaluation of your NDA.

1. In the cover letter of your submission (Sequence 004) dated 26 Jan 2017, you have indicated that you recently became aware of the Warning Letter (WL 320-17-17) issued on January 13, 2017 to the drug product manufacturer (FACTA Farmaceutici SpA). You further indicated that you (i.e., the Applicant) have reached an agreement with FACTA Farmaceutici SpA to conduct an independent review and contracted (b) (4) to assess and help address the FDA's concerns. We recommend you to continue to communicate with your contract manufacturers to ensure they work with the appropriate Office(s) to resolve any outstanding inspectional issues. Please provide a copy of the protocol that will be followed by (b) (4) and a summary of the expected scope of their assessment.

Given your review, please provide an assessment of the impact of the citations listed in the Warning Letter (WL 320-17-17) on the product, process, and data submitted in NDA 209776. If you determine that these citations do not impact NDA 209776, please provide the justification and evidence that has resulted in that conclusion.

2. It is noted that you have provided details on the DMFs and manufacturers for (b) (4) Meropenem in Module 2 of your application submission. Please provide an updated 356h form listing all sites involved in the manufacture of the drug

substance  
Meropenem.

(b) (4) for

Sincerely,

Steven  
Kinsley -S

Digitally signed by Steven Kinsley -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Steven Kinsley -  
S,  
0.9.2342.19200300.100.1.1=2001720189  
Date: 2017.02.03 13:07:58 -05'00'

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



NDA 209776

## INFORMATION REQUEST

Rempex Pharmaceuticals, a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director Regulatory Affairs  
3033 Science Park Road Suite 200  
San Diego, CA 92121

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for meropenem-vaborbactam, (b) (4), 1000mg/1000mg per vial.

We also refer to your December 29, 2016 submission, containing your new drug application.

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

### **FACILITIES:**

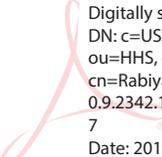
1. At the time of submission, all facilities must be ready for inspection. Additionally, per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the facilities proposed must comply with the current good manufacturing practice regulations. Please confirm that you are in contact with your manufacturing and testing facilities, and that you are aware of any inspections or 483's that have been issued.
2. Update Module 3.2.S.2.1 and Module 3.2.P.3.1 to include all facilities involved in the manufacture and testing of all drug substances and drug products associated with this application. Please provide an updated 356h form to ensure consistency between facilities and responsibilities listed in Module 3.2.S.2.1, Module 3.2.P.3.1, and those listed on the 356h form.

If you have any questions, please contact, Quality Assessment Lead (Acting), at (301) 796 4013, or [luz.e.rivera@fda.hhs.gov](mailto:luz.e.rivera@fda.hhs.gov) . Please respond **ASAP**.

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=200155500  
7  
Date: 2017.01.24 17:43:03 -05'00'

**From:** Dean, Jane

**Sent:** Tuesday, January 17, 2017 12:37 PM

**To:** starr.shangle@themedco.com

**Subject:** NDA 209776 (Meropenem–Vaborbactam) - statistics reviewer information request

Hi, Starr - the statistics reviewer has the following information request:

“Please clarify why the Study 505 sample size of 550 subjects in the ITT population differed from the planned enrollment of approximately 500 subjects.”

Jane

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/s/  
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JANE A DEAN  
01/17/2017



NDA 209776

**NDA ACKNOWLEDGMENT**

Rempex Pharmaceuticals, Inc.  
a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director, Regulatory Affairs  
8 Sylvan Way  
Parsippany, NJ 07054

Dear Ms. Shangle:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Carbavance (meropenem-vaborbactam) powder, 1000mg vial

Date of Application: December 29, 2016

Date of Receipt: December 29, 2016

Our Reference Number: NDA 209776

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 27, 2017, in accordance with 21 CFR 314.101(a)

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of 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](mailto: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, at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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JANE A DEAN  
12/30/2016



IND 120040

**MEETING MINUTES**

Rempex Pharmaceuticals, Inc.  
A Subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director, Regulatory Affairs  
3033 Science Park Road, Suite 200  
San Diego, CA 92121

Dear Ms. Shangle:

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

We also refer to the meeting between representatives of your firm and the FDA on November 3, 2016. The purpose of the meeting was to discuss filing a New Drug Application (NDA).

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

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager at (301) 796-1202.

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

Enclosure:  
Meeting Minutes



## MEMORANDUM OF MEETING MINUTES

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

**Meeting Date and Time:** November 3, 2016, 1:00pm – 2:00pm  
**Meeting Location:** Building 22, Conference Room 1313  
10903 New Hampshire Avenue  
Silver Spring, MD 20903-0002

**Application Number:** IND 120040  
**Product Name:** Meropenem-vaborbactam  
**Indication:** Treatment of complicated urinary tract infections (cUTI), including pyelonephritis, in patients 18 years and older  
**Sponsor/Applicant Name:** Rempex Pharmaceuticals, Inc.

**Meeting Chair:** Sumathi Nambiar, MD, MPH  
**Meeting Recorder:** Jane A. Dean, RN, MSN

### FDA ATTENDEES

#### Division of Anti-Infective Products:

Shukal Bala, PhD	Clinical Microbiology Reviewer
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
Carmen DeBellis, RPh, PharmD	Chief, Project Management Staff
Tamara Feldblyum, MS, PhD	Clinical Microbiology Team Leader (Acting)
Kerian Grande Roche, PhD	Clinical Microbiology Reviewer
Dmitri Iarikov, MD, PhD	Clinical Team Leader
Seong Jang, PhD	Clinical Pharmacology Team Leader
Rama Kapoor, MD	Clinical Reviewer
George Lunn, PhD	Product Quality Reviewer
MAJ William McCalmont, PhD	Pharmacology/Toxicology Fellow
Terry Miller, PhD	Pharmacology/Toxicology Team Leader (Acting)
Sumathi Nambiar, MD MPH	Director
Daniel Rubin, PhD	Statistical Reviewer
Joseph Toerner, MD, MPH	Deputy Director for Safety
James Wild, PhD	Pharmacology/Toxicology Reviewer
Katherine Windsor, PhD	Product Quality Reviewer
Zhixia (Grace) Yan, PhD	Clinical Pharmacology Reviewer

## **SPONSOR ATTENDEES**

### **Rempex Pharmaceuticals, Inc.:**

Elizabeth Alexander, MD	Director, Clinical Development
Cynthia Dinella, PharmD	Regulatory Consultant
Mike Dudley, PharmD	Senior Vice President, Chief Scientific Officer
Andrew Friedman, PharmD	Senior Vice President, Regulatory Affairs
David Griffith	Vice President, Nonclinical Service
Loretta Itri, MD	Executive Vice President, Global Health Science & Regulatory
Judy Lee	Senior Director, Chemistry, Manufacturing & Controls
Olga Lomovskaya	Vice President, Biology
Jeff Loutit, MBChB	Vice President, Chief Medical Officer
Starr Shangle	Senior Director, Regulatory Affairs

### **Biomedical Advanced Research and Development Authority (BARDA):**

Mark Albrecht, PhD  
Michael Elisseou, PhD

## **1.0 BACKGROUND**

Rempex Pharmaceuticals, Inc., hereafter referred to as Rempex, submitted a Pre-New Drug Application (Pre-NDA) meeting request on September 1, 2016. The meeting was granted and scheduled for November 3, 2016. The purpose of the meeting as described in the October 4, 2016, briefing document was “to communicate the high-level safety and efficacy results from the completed Phase 3 study, Study 505, and from an interim analysis using a data cut-off date of 31 March 2016 for the ongoing, supportive, Phase 3 study, Study 506”. In addition, Rempex is “seeking agreement with the Food and Drug Administration (FDA) that the statistically significant and clinically meaningful results for Study 505 and available safety data from Studies 505 and 506 support proceeding to an NDA filing using the 505(b)(2) regulatory pathway”.

The Division sent Preliminary Comments to Rempex on October 26, 2016 (see Attachment 1). On November 2, 2016, Rempex sent their responses to the comments and identified which questions they wanted to focus on during the meeting (see Attachment 2).

## **2. DISCUSSION**

The meeting began with introductions. It was then turned over to Rempex who expressed appreciation to the Division for the meeting and sending preliminary responses.

Question 7 dealt with the Chemistry, Manufacturing and Control filing strategy. Rempex confirmed they would be including in the NDA the information requested in the preliminary responses. Specifically it was agreed that the additional stability data can be submitted as a minor application component within 4 months after the submission of the original application as per the FDA pre-meeting feedback provided by the Agency on 19 August 2016 and the

preliminary responses of October 26, 2016. It was also noted that the commercial product will be a vial containing 1 g of vaborbactam and 1 g of meropenem.

The Agency thanked the Sponsor for submission of the Clinical Study Report for Study 505. The Agency noted that one review issue in assessing the statistically significant difference found between meropenem-vaborbactam and piperacillin-tazobactam for the primary analysis may be to further analyze subjects with missing or indeterminate clinical or microbiological outcomes. Additional comments related to pharmacology/toxicology included the following clarifications:

From the preliminary comments:

**Pharmacology/Toxicology:** Note that your NDA submission should include a comprehensive summary of the nonclinical toxicology and pharmacokinetic information available for meropenem, vaborbactam, and the drug combination, using information from the meropenem product label, literature reports, and data generated by you in addition to or inclusive of the data summarized in Table 15 of the meeting package. Provide all final study reports and any referenced literature in your NDA.

The Sponsor posed two questions/comments with reference to the Pharmacology/Toxicology preliminary comment noted above and Table 15 in the meeting package.

1. The Sponsor asked if the Agency was in agreement with the list of studies and sources for nonclinical information for meropenem and vaborbactam as summarized in Table 15. The FDA responded that the intention behind including the Pharmacology/Toxicology preliminary comment was to make the Sponsor aware that all of the available nonclinical study information for the two compounds whether derived from new studies conducted for the IND, information from the Merrem product label or derived from the literature should be included in the NDA submission.
2. The Sponsor referred to a previous written communication from the FDA dating from a March 28, 2014 meeting with the Sponsor where the following recommendation from the FDA was submitted: "A pre-postnatal study for meropenem is recommended. Alternatively, the addition of a meropenem treatment group in the pre-postnatal study planned for RPX7009 may be acceptable." With reference to this previous recommendation, the Sponsor asked if the pre-postnatal study with meropenem was still necessary in light of new clinical postnatal data for meropenem and new juvenile toxicity data for meropenem. The FDA replied that a nonclinical pre-postnatal study for meropenem was still necessary. In response, the Sponsor asked if pre-postnatal information described in a publically available Merrem Product Monograph by AstraZeneca Canada Inc. would provide sufficient information. The FDA replied that it might, but a final determination would be a review decision dependent on the depth of information included in the monograph.

**Post-Meeting Comment:** Upon reviewing the pre-postnatal study information in the Product Monograph for Merrem by AstraZeneca Canada Inc., it does not appear that the summary information included in the monograph is sufficiently comprehensive to allow review and

evaluation. In order to be included in the product label, nonclinical study information must be sufficiently comprehensive to allow review. Ideally the information should derive from rigorous GLP-study(ies), include sufficient information about methods and results as to allow evaluation and review, and be clearly linked to originating laboratory facilities and personnel thus allowing verification. We recommend that you either obtain right of reference from AstraZeneca for the meropenem pre-postnatal study and submit the complete study report for review, or as recommended in our written comments for the March 28<sup>th</sup>, 2014 meeting, conduct a nonclinical pre-postnatal study with meropenem.

### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

The content of a complete application was discussed. Per agreements under the Prescription Drug User Fee Act (PDUFA) V, agreement on submission of an application component after the submission of the original application must be documented. Rempex confirmed with the Division their understanding and agreement to submit stability data within 120 days after the NDA is submitted (see Attachment 3).

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- 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 related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy

registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

**MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

## **505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any

published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues identified that required further discussion.

## 5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Division will provide meeting minutes within 30 days.	FDA	December 3, 2016
Rempex will provide advance notice of the timing for the submission of their NDA	Sponsor	No later than December 30, 2016

## 6.0 ATTACHMENTS AND HANDOUTS

**Attachment 1:** Preliminary responses to meeting questions sent via email on October 26, 2016 to Rempex

**Attachment 2:** Responses sent via email from Rempex on November 2, 2016

**Attachment 3:** Copy of preliminary responses sent to the sponsor by Office of Pharmaceutical Quality on August 18, 2016

## **ATTACHMENT 1**

**From:** Dean, Jane  
**Sent:** Wednesday, October 26, 2016 9:42 AM  
**To:** starr.shangle@themedco.com  
**Subject:** IND 120040 (meropenem-vaborbactam) - preliminary responses to meeting questions for 11-3-16

Hi, Starr – attached below are the preliminary responses to your meeting questions. Please be advised that any new information or data not contained in your meeting package and presented in response to these comments will not be considered for official comment at the scheduled meeting. The information may be very briefly presented, but must be provided as a submission to the application subsequent to this meeting to allow an opportunity for appropriate review and comment.

In preparation for our upcoming meeting, please be advised that the official advice and recommendations of this division will be communicated during the formal dialogue of our upcoming meeting. Any conversations before or after the official meeting will not reflect the decisions or agreements of the division and thus will not be reflected in the official meeting minutes. If follow-up or clarification on a particular issue is required, those issues should be discussed during the meeting or can be pursued through the formal meetings process in a subsequent meeting or teleconference.

If you wish to change this meeting to a telecon, please contact your Project Manager. If you wish to cancel this meeting, the following responses will become part of the administrative record. Submit your cancellation by letter to your application and contact your Project Manager.

If you wish to discuss another application, the official meeting process should be followed as outlined in the May 2009 *“Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants”*.

**Question 1: Does the Agency agree that Study 505 has demonstrated the efficacy of meropenem 2 g-vaborbactam 2 g for the treatment of cUTI, including pyelonephritis?**

**FDA Response:** The results provided from Study 505 seem to support the efficacy of meropenem 2 g-vaborbactam 2 g in the treatment of cUTI. However, the review of the complete study report is needed for a conclusion about the efficacy of the drug for treatment of cUTI.

**Question 2: Does the Agency have any comments on the safety results from Study 505?**

**FDA Response:** The review of the complete study report is needed to conclude whether submitted safety data are adequate to characterize the safety profile of meropenem-vaborbactam. If safety concerns are identified upon review of the application, additional safety data may be needed.

**Question 3:** Does the Division agree that the single trial, Study 505, combined with the Division's previous findings of safety and effectiveness for meropenem are sufficient to support an NDA filing for meropenem-vaborbactam for the full indication of the treatment of cUTI, including pyelonephritis?

**FDA Response:** Provided that the review of Study 505 supports the safety and efficacy of meropenem-vaborbactam for the treatment of cUTI, Study 505 combined with the Agency's previous findings of safety and effectiveness for meropenem may be sufficient to support an NDA submission for meropenem-vaborbactam for the treatment of cUTI without a limited use statement.

**Question 4:** Does the Agency agree, based on the data available at the time of the Pre-NDA Meeting, that a REMS and Medication Guide are not necessary to include with the meropenem-vaborbactam NDA?

**FDA Response:** The decision regarding the need for a REMS for meropenem-vaborbactam will be made upon reviewing the NDA. With regard to the Medication Guide, given that meropenem-vaborbactam will be administered intravenously and mainly in the inpatient setting, a Medication Guide may not be needed. However, a final decision can only be made upon the review of the NDA.

**Question 5:** Would the Agency comment on the potential for an Anti-Infective Drugs Advisory Committee meeting for meropenem-vaborbactam for the initial indication in cUTI, including pyelonephritis?

**FDA Response:** It is premature to comment on the need for an Anti-Microbial Drugs Advisory Committee meeting for meropenem-vaborbactam. The decision as to whether the meeting is needed will be made upon review of the NDA.

**Question 6: Does the Agency agree that the proposed datasets and planned analysis are sufficient to support approval of disk interpretive criteria to be included in the label, provided that the error rates meet existing criteria?**

**FDA Response:** Overall, your plan appears reasonable, however, in addition to CLSI M23 (2016) please refer to Appendix A of the guidance document, “ Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis and Presentation”. The number of wild-type isolates versus those with resistance mechanisms should be presented; additionally, the specific resistance phenotypes and the geographic region of origin of the isolate should be specified. In general, we prefer that the error rates for MIC and disk correlation be within the guidelines established by CLSI M23 for acceptable discrepancy rates. If these guidelines cannot be met, then a rationale should be provided for review.

**Question 7: Does the Agency have any additional comments on the filing strategy outlined for the drug substance and drug product CMC information?**

**FDA Response:** In general your proposal is acceptable. In the NDA you should include the following information concerning the meropenem drug substance.

- A list of all sites involved in manufacturing and testing the drug substance.
- Information usually contained in 3.2.S.1, as an aid to the reviewer.
- The drug substance specification applied by the finished product manufacturer for testing meropenem on receipt. We remind you that the meropenem drug substance specification applied by the finished product manufacturer should include any appropriate product-specific tests and acceptance criteria (e.g., particle size) that may not be included in the drug substance specification of the meropenem DMF.
- Batch data for at least three batches of meropenem analyzed by the finished product manufacturer.

Information on the reference standard used by the finished product manufacturer. In addition you should be able to show that you have a knowledge of any drug substance issues that may affect drug product performance. Therefore:

- If the drug substance is accepted “based on identity testing and a review of the manufacturers CoA” then the specification and analytical methods used by the DMF holder should be included in the drug substance section.
- If process impurities from the drug substance are ignored during the testing of the drug product then the specification and analytical methods used by the DMF holder should be included in the drug substance section.
- If the drug substance requires special storage, stability data should be included in the drug substance section.
- Any drug substance parameter that might affect drug product performance should be addressed in the drug substance section. This would certainly include particle size and polymorphic form if they are relevant. It might also include residual solvents. There is at least a theoretical possibility that a Class 3 solvent such as ethanol being present at levels varying from 0 to 5000 ppm could affect manufacturability. These items could conceivably be discussed in P.2.2.1.

**Question 8: Does the Agency agree the additional stability data can be submitted as a minor application component within 4 months after the submission of the original application as per the FDA pre-meeting feedback provided by the Agency on 19 August 2016?**

**FDA Response:** We agree that the additional stability data can be submitted, as agreed, within 4 months after the submission of the NDA (e.g., if the NDA is submitted on December 30, 2016, then the stability update will need to be submitted no later than April 30, 2017). However, if the stability data update is submitted later than 4 months after the NDA submission we would regard this as a major amendment that could cause delay in taking an action on your NDA.

The adequacy of the drug substance and the drug product stability data is an NDA review decision.

#### **Additional Comments:**

##### **Clinical Microbiology**

- Refer to the Microbiology guidance referenced in response to Question 6 above, including Appendix E, for criteria to consider when developing the lists of bacteria for inclusion in section 12.4 Microbiology of the labeling.

- In the NDA, provide all studies for meropenem and vaborbactam that support the mechanism of action, activity in vitro and in animal models of infection, potential for development of resistance, mechanism of resistance. Any studies supporting an interaction of meropenem and vaborbactam with other antimicrobials should also be included.
- All nonclinical studies supporting the contribution of meropenem and vaborbactam alone as well as in combination should be included.
- Details of all the microbiological methods used in the clinical trial should be included in the NDA. Also, the name(s) of the laboratories where testing of clinical specimens was performed should be included.

**Pharmacology/Toxicology:** Note that your NDA submission should include a comprehensive summary of the nonclinical toxicology and pharmacokinetic information available for meropenem, vaborbactam, and the drug combination, using information from the meropenem product label, literature reports, and data generated by you in addition to or inclusive of the data summarized in Table 15 of the meeting package. Provide all final study reports and any referenced literature in your NDA.

**Clinical Pharmacology:** Include PK/PD target attainment analysis data (i.e., population pharmacokinetic model and codes for simulations) for both meropenem and vaborbactam in the NDA. We recommend that you conduct these analyses in patients with renal impairment as well.

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

## **ATTACHMENT 2**

# MEROPENEM-VABORBACTAM PRE-NDA MEETING

Meeting Date: November 3, 2016

We appreciate FDA's preliminary comments. For tomorrow's meeting, we would like to focus discussions on the Agency's feedback to Question 7 along with their Additional Comments regarding Pharmacology/Toxicology at the meeting. Please find our clarifications/responses to the Agency's Meeting Preliminary Feedback below.

## **Question 7: CMC Filing Strategy**

Meropenem 2 g-vaborbactam 2 g is a combination product with two drug substances: meropenem and vaborbactam. The CMC information for meropenem drug substance will be provided by a Letter of Authorization to reference the Type II Drug Master File # (b) (4) from (b) (4), the manufacturer. The CMC information for vaborbactam drug substance and the single vial drug product will be provided in Module 3 of the NDA.

**Question 7:** Does the Agency have any additional comments on the filing strategy outlined for the drug substance and drug product CMC information?

**FDA Response:** *In general your proposal is acceptable. In the NDA you should include the following information concerning the meropenem drug substance.*

## **Rempex Response:**

A list of all sites involved in the manufacture and testing of both meropenem and vaborbactam drug substances as well as meropenem-vaborbactam for Injection finished product is summarized in Table 1. This information will also be provided for easy reference in the Reviewer's Guide of the NDA.

Table 1: List of Sites for the Manufacturing of Drug Substances and Drug Product

	Drug Substance	Drug Product
	(b) (4)	(b) (4) Final Filled Vials*
Manufacturing and Testing Site	(b) (4)	Facta Farmaceutici, S.p.A. Zona Industriale Sant'Atto, 64100 San Nicolò a Tordino (TE), Italy

- *A list of all sites involved in manufacturing and testing the drug substance.*
- *Information usually contained in 3.2.S.1, as an aid to the reviewer.*

## **Rempex Response:**

As requested, a list of all sites involved in the manufacture and testing of meropenem and vaborbactam drug substances will be provided in 3.2.S.1 of the NDA.

**MEROPENEM-VABORBACTAM PRE-NDA MEETING**

**Meeting Date: November 3, 2016**

- *The drug substance specification applied by the finished product manufacturer for testing meropenem on receipt. We remind you that the meropenem drug substance specification applied by the finished product manufacturer should include any appropriate product-specific tests and acceptance criteria (e.g., particle size) that may not be included in the drug substance specification of the meropenem DMF.*

**Rempex Response:**

[REDACTED] (b) (4)

The specification for meropenem drug substance, including our product-specific tests and acceptance criteria, will be provided in the NDA.

- *Batch data for at least three batches of meropenem analyzed by the finished product manufacturer.*

**Rempex Response:**

Batch analysis data from the three meropenem batches used in the manufacture of the meropenem-vaborbactam for Injection registration batches will be provided in the NDA.

- *Information on the reference standard used by the finished product manufacturer.*

**Rempex Response:**

Information on the reference standards used by the finished product manufacturer will be provided in the NDA.

*In addition you should be able to show that you have a knowledge of any drug substance issues that may affect drug product performance. Therefore:*

- *If the drug substance is accepted “based on identity testing and a review of the manufacturers CoA” then the specification and analytical methods used by the DMF holder should be included in the drug substance section.*

**Rempex Response:**

[REDACTED] (b) (4)  
[REDACTED], and will be included in the NDA.

## MEROPENEM-VABORBACTAM PRE-NDA MEETING

Meeting Date: November 3, 2016

- *If process impurities from the drug substance are ignored during the testing of the drug product then the specification and analytical methods used by the DMF holder should be included in the drug substance section.*

### **Rempex Response:**

(b) (4)  
The specification and analytical methods for both meropenem and vaborbactam drug substances will be included in the NDA.

- *If the drug substance requires special storage, stability data should be included in the drug substance section.*

### **Rempex Response:**

No special storage is required for the drug substance.

- *Any drug substance parameter that might affect drug product performance should be addressed in the drug substance section. This would certainly include particle size and polymorphic form if they are relevant. It might also include residual solvents. There is at least a theoretical possibility that a Class 3 solvent such as ethanol being present at levels varying from 0 to 5000 ppm could affect manufacturability. These items could conceivably be discussed in 3.2.P.2.2.1.*

### **Rempex Response:**

We will identify the drug substance parameters that might affect drug product performance in the NDA.

# MEROPENEM-VABORBACTAM PRE-NDA MEETING

Meeting Date: November 3, 2016

## FDA Response:

***Additional Comments Pharmacology/Toxicology:*** Note that your NDA submission should include a comprehensive summary of the nonclinical toxicology and pharmacokinetic information available for meropenem, vaborbactam, and the drug combination, using information from the meropenem product label, literature reports, and data generated by you in addition to or inclusive of the data summarized in Table 15 of the meeting package. Provide all final study reports and any referenced literature in your NDA.

## **Rempex Response:**

We would like to further clarify items in Table 15 from the Pre-Meeting Briefing Package, reproduced below.

**Table 15: Data Planned to Be Submitted in the NDA to Satisfy the 505(b)(2) Regulation**

Clinical	Meropenem-Vaborbactam	Vaborbactam	Meropenem
Clinical Data	Safety and effectiveness data generated by Sponsor	Safety data generated by Sponsor	Reliance on FDA's previous findings of safety and effectiveness
<b>Nonclinical</b>			
<b>Safety pharmacology</b>			
Respiratory	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Cardiovascular	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Central nervous system	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
<b>PK</b>			
PK (mouse, rat, dog)	Data generated by Sponsor	Data generated by Sponsor	Data generated by Sponsor
TK (Rat, Dog)	Data generated by Sponsor	Data generated by Sponsor	Data generated by Sponsor
Protein Binding	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Phase 1 and Phase 2 metabolism	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
CYP inhibition/induction	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Other transporters	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
<b>Toxicology</b>			
<b>Genotoxicity</b>			
Ames	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Chromosome aberration test	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Mouse Micronucleus	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
<b>Single-Dose Toxicity</b>			
Mouse	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Rat	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
<b>Repeat-Dose Toxicity</b>			
28-day rat	Data generated by Sponsor	Data generated by Sponsor	Data generated by Sponsor
28-day dog	Data generated by Sponsor	Data generated by Sponsor	Data generated by Sponsor
<b>Reproductive Toxicology</b>			
Male fertility	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Female fertility	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Embryo-fetal development in rats	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Embryo-fetal development in rabbits	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
Pre- and postnatal development in rats	ND	Data generated by Sponsor	Reliance on FDA's previous findings of safety
<b>Juvenile Toxicology</b>			
Rat	Data generated by Sponsor	Data generated by Sponsor	Data generated by Sponsor

FDA = Food and Drug Administration; ND = not determined; NDA = New Drug Application; PK = pharmacokinetics; TK = toxicokinetics;

## **ATTACHMENT 3**



IND 120040

**MEETING PRELIMINARY COMMENTS**

Rempex Pharmaceuticals, Inc.  
Attention: Starr Shangle, Director Regulatory Affairs  
3033 Science Park Road  
Suite 200  
San Diego, CA 92121

Dear Ms. Shangle:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Carbavance® (meropenem/RPX7009).

We also refer to your May 19, 2016, correspondence, requesting a meeting to discuss:

- Updated stability information on (b) (4) vaborbactam drug substance and meropenem-vaborbactam single-vial drug product
- Rempex's responses to the FDA Post-meeting Comments from the March 10, 2016 Type C meeting minutes

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** C  
**Meeting Category:** Guidance

**Meeting Date and Time:** August 23, 2016, 12:00 PM – 1:00 PM, EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1421  
Silver Spring, Maryland 20903

**Application Number:** IND 120040  
**Product Name:** Carbavance® (meropenem/RPX7009)  
**Indication:** Treatment of complicated urinary tract infections (cUTI) including pyelonephritis  
**Sponsor/Applicant Name:** Rempex Pharmaceuticals

**FDA ATTENDEES (tentative)**

**Office of Pharmaceutical Quality (OPQ)**

Balajee Shanmugam, Ph.D. Acting Branch Chief  
George Lunn, Ph.D. Drug Product Reviewer  
Katherine Windsor, Ph.D. Drug Substance Reviewer  
Dorota Matecka, Ph.D. CMC Lead  
Navdeep Bhandari, Pharm.D. Regulatory Health Project Manager

**Division of Anti-Infective Products (DAIP)**

Sumathi Nambiar, MD, MPH Director  
Dmitri Iarikov, MD, Ph.D. Clinical Team Leader  
Rama Kapoor, MD Medical Officer  
Susmita Samanta Safety Regulatory Project Manager

**Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 23, 2016, 12:00 PM - 1:00 PM, EST between Rempex Pharmaceuticals and the Office of Pharmaceutical Quality. 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the

meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

## 1.0 BACKGROUND

A Type C meeting briefing package was submitted June 24, 2016, for an August 23, 2016, CMC Meeting for Rempex Pharmaceuticals.

## 2.0 Questions

### Question 1

*Does the agency agree that the currently available stability data as described below and the stability data proposed to be provided in the eventual NDA and during review can support registration of the drug product?*

#### **Agency Response:**

Given the potential for Carbavance to meet an unmet medical need, we agree with the proposed amount of stability data for the drug substance and the drug product to be included in the initial NDA submission and updated during the NDA review, as outlined in Tables 1 and 2 of your background package (pages 5 and 6), respectively.

The adequacy of the drug substance and the drug product stability data is an NDA review decision. If the time lines proposed in Tables 1 and 2 are followed, the updated stability data will need to be submitted no later than 4 months after the NDA submission (e.g., if the NDA is submitted on December 1, 2016, then the stability update will need to be submitted no later than April 1, 2017). If the stability data update is submitted later than 4 months after the NDA submission we would regard this as a major amendment that could cause delay in taking an action on your NDA.

Supportive stability data for the drug substance, i.e., [REDACTED] (b) (4) [REDACTED] should also be provided, as you have outlined in the February 4, 2016 meeting package.

Please provide updated release and shelf-life specifications for the drug product and clarify if sterility, endotoxins, and particulates for reconstituted solution are included in the stability specification.

## **Question 2**

*Rempex provides below responses to the FDA questions contained in the FDA Meeting Minutes (dated April 8, 2016) and FDA's subsequent General Advice Letter (dated April 21, 2016) from the March 10, 2016 Type C meeting. Does the agency have any additional comments regarding the impurity (b) (4) and the proposed in-use stability program to support the single-vial drug product NDA?*

### **Agency Response:**

The protocol for the in-use stability testing, i.e., testing the stability of prepared infusions, seems reasonable although the acceptance criteria will be an NDA review decision. The acceptance criteria for the degradants (including those from meropenem) should be qualified toxicologically.

It is not entirely clear to us how much in-use testing will be conducted. We recommend that in-use testing be conducted for each of the three single-vial registration batches at every time point of storage at the long term conditions. At each test point solutions should be stored refrigerated and at ambient conditions and should be made up in saline and 5% dextrose (if 5% dextrose is to be described in the labeling). The concentrations of vaborbactam and meropenem should be at the outer limits of the ranges being proposed in the labeling.

Although the testing protocols, acceptance criteria, results, etc. for the in-use testing are an NDA review decision it does not appear to us, after review of Table 3, Table 4, and Appendix 5, that the data support the use of the prepared infusion solution for (b) (4) 4 hours after preparation when stored at ambient conditions. We have in the past seen reference to a 3 hour infusion for your proposed drug product. Note that your in-use stability data should support the time and storage conditions statements for the reconstituted and further diluted solutions proposed in the package insert.

The detailed information concerning the formation of the impurity (b) (4) and method development should be included in the NDA.

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/s/  
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NAVDEEP BHANDARI  
08/19/2016

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUMATHI NAMBIAR  
11/30/2016



IND 120040

**MEETING MINUTES**

Rempex Pharmaceuticals, Inc.  
Attention: Starr Shangle, Director Regulatory Affairs  
3033 Science Park Road  
Suite 200  
San Diego, CA 92121

Dear Ms. Shangle:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Carbavance® (meropenem/RPX7009).

We also refer to the meeting between representatives of your firm and the FDA on March 10, 2016. The purpose of the meeting was to discuss:

- The planned NDA stability data package intended to support the proposed retest period for API and shelf-life for the drug product, and
- The planned approach for controlling and setting specifications for two degradation products identified during the development of a new analytical method.

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 C  
**Meeting Category:** Guidance

**Meeting Date and Time:** March 10, 2016, 10:00 AM – 11:00 AM, EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room 1419  
Silver Spring, Maryland 20903

**Application Number:** IND 120040  
**Product Name:** Carbavance® (meropenem/RPX7009)  
**Indication:** Treatment of complicated urinary tract infections (cUTI) including pyelonephritis  
**Sponsor/Applicant Name:** Rempex Pharmaceuticals

**Meeting Chair:** Balajee Shanmugam  
**Meeting Recorder:** Navdeep Bhandari

### FDA ATTENDEES

#### Office of Pharmaceutical Quality (OPQ)

Balajee Shanmugam, Ph.D.	Acting Branch Chief
Dorota Matecka, Ph.D.	CMC Lead
Katherine Windsor, Ph.D.	Drug Substance Reviewer
Navdeep Bhandari, Pharm.D	Regulatory Health Project Manager
Neal Sweeney, Ph.D.	Microbiology Reviewer

#### Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, MD, MPH	Director
Dmitri Iarikov, MD, Ph.D.	Clinical Team Leader
Rama Kapoor, MD	Medical Officer
James Wild, Ph.D.	Pharmacology/Toxicology Reviewer
Susmita Samanta	Safety Regulatory Project Manager

### SPONSOR ATTENDEES

John Roth, PhD	Vice President, Regulatory Affairs
Jeff Loutit, MBChB	Vice President, Chief Medical Officer

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Type C CMC Meeting

Scott Hecker, PhD

David Griffith

Judy Lee, PhD

Starr Shangle

 (b) (4)

Michael Elisseou, PhD

Louise Latriano, PhD

Vice President, Chemistry

Vice President, Non-Clinical Science

Senior Director, CMC Regulatory

Director, Regulatory Affairs

CMC Consultant

BARDA Representative

BARDA Representative

Meeting Minutes  
Type C CMC Meeting

## 1.0 BACKGROUND

A Type B meeting briefing package was submitted February 4, 2016, for a March 8, 2016, CMC meeting with (b) (4).

## 2.0 DISCUSSION

The Agency sent preliminary responses on March 6, 2016, to the Sponsor. The Sponsor asked to discuss questions 1, 2, and 3. Additional information was provided by the Sponsor on March 9, 2016 (attached below).

### 2.0 Questions

#### Question 1

*Does the agency agree that the amount of stability data to be provided at the NDA submission and during review would be sufficient to support the proposed (b) (4) months retest period for RPX7009 (b) (4) drug substance upon initial approval?*

**Agency Response:** An appropriate retest period for RPX7009 (b) (4) drug substance will be assigned based on evaluation of the data available at the time of review. Given the potential for Carbavance to meet an unmet medical need, we are willing to accept less than the ICH Q1A recommended amount of stability data for (b) (4) RPX7009 to file the NDA. We recommend that the third registration batch of (b) (4) API be manufactured and placed on a stability program prior to NDA filing with the release data submitted in the NDA. Updated stability data for the registration batches will need to be provided during the NDA review in accordance with mutual agreements to be discussed and reached at the meeting. Supportive stability data (b) (4) (b) (4) should also be provided, as you have outlined in the meeting package.

#### Meeting Discussion:

The Sponsor clarified that Drug Substance information (for both RPX7009 and meropenem, both manufactured by (b) (4)) will be included in the NDA, in Module 3. The Sponsor also indicated ongoing discussions with the CMO (b) (4) (b) (4) but the timeline on the availability of the release data for this batch is unknown. The Sponsor will update the FDA (at a planned Summer 2016 meeting) prior to the pre-NDA meeting (August or September 2016) on the timing of release and the amount of stability data that is likely to be available for this third batch at the time of NDA filing. The summer meeting will also allow for an update on any stability data available for the first two drug substance registration batches, as well as updated drug product stability data (see Question 2 Discussion below).

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## **Question 2**

*For the single vial drug product containing (b) (4) meropenem and (b) (4) RPX7009, does the agency agree that the amount of stability data to be provided in the submission and during review would be sufficient to support the proposed (b) (4) month shelf-life at initial approval?*

**Agency Response:** The drug product expiration dating is an NDA review decision and will be based on the assessment of the overall information submitted in the NDA. Considering the potential for Carbavance to meet an unmet medical need, we are willing to accept less than the ICH Q1A recommended amount of stability data for the proposed commercial drug product at the NDA filing, and subsequent stability updates during the NDA review to be discussed at the meeting. In preparation for this discussion, please provide the exact batch size and describe the differences between the formulations, manufacturing processes, and container-closure systems used for each batch described in Table 2. Also, describe the container-closure used for the multi-vial product and provide information on stability of the RPX7009 drug product in the multi-vial packaging configuration.

In addition, please provide details of the formulations (including batch sizes), manufacturing processes, and container-closure systems used in the studies described in Appendices V-VIII. Describe the relationship between the formulations, manufacturing processes, and container-closure systems used for these studies and the proposed commercial formulation and container-closure system.

Similarly, please provide details of the formulations (including batch sizes), manufacturing processes, container-closure systems, and reconstitution processes used in the in-use studies described in Appendix IX. Also, provide the assay values for meropenem and RPX7009 for each data point for the studies described in Appendix IX. We note a significant increase in the meropenem related impurities reported in these studies.

Please refer to the response to Question 3 for additional recommendations and information that should be provided in the NDA to support the stability and expiration dating for the proposed commercial drug product, (b) (4) components supplied in one vial.

## **Meeting Discussion:**

The Sponsor provided additional information on the batches described in the background package. The Sponsor confirmed the commercial single vial presentation is 1g/1g and the registration batches will be manufactured at commercial scale. The Agency indicated that the shelf-life will be supported mainly from stability data on the registration batches since the lab scale provides very limited data and cannot be considered to be supportive due to a very small batch size.

The Agency reiterated the importance of having 6-month stability data available from the second and third registration batches at NDA submission. Given that stability data may be limited at

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NDA submission, the Agency recommended that the Sponsor add an additional testing point at 5-month time point in the stability protocol if the 6-month data will not be available at the time of NDA submission. Furthermore, the Sponsor indicated that in-use stability will be generated under long-term and accelerated conditions to support the label claim. The Sponsor's proposed to provide an update on the drug substance and drug product stability prior to the Pre-NDA meeting. The FDA expressed willingness to meet and also review the updated information so an agreement on an acceptable stability package can be reached at the Pre-NDA meeting. The FDA noted that as this product will receive a priority review and will be reviewed under The Program, all agreements for data submission after the NDA is submitted will have to be agreed to at the pre-NDA meeting.

On the observed level of impurities, the Agency expressed concern on the possibility of the interactions of the (b) (4) components combined in a single vial that is the proposed commercial configuration. The Agency also clarified that the comment in the Preliminary Meeting Response (regarding an increase in meropenem-related impurities) reported in Appendix 9 was related to the relatively high level of Impurity A (b) (4) (%) and total impurities.

### **Question 3**

*Two new degradation products, (b) (4) and (b) (4) were first observed using the new HPLC-UV method during pilot in-use studies with both the multi-vial and single vial configurations, and have been qualified in a 28-day repeat dose toxicology study in rat. Does the agency agree with the proposed limits for (b) (4) and (b) (4) for the purpose of establishing drug product shelf-life and in-use period for the single vial configuration?*

**Agency Response:** The proposed threshold limits for the two new degradations products, (b) (4) and (b) (4) appear to be qualified by the impurity NOAEL values obtained in the 28-Day Toxicology Study in Rats (Study No.: (b) (4) Study #1015-0201). A final determination will be dependent on evaluation of complete data included in the final study report. Please describe the calculations used to determine the impurity NOAEL values including the percent impurity in the dose solution associated with the parent-compound NOAEL in the 28-Day Toxicology Study. The final study report can be submitted with the NDA or prior to submission of the NDA to allow for earlier evaluation and confirmation of the qualification calculations and the proposed limits for (b) (4) and (b) (4)

We recommend that you carry out in-use studies for samples in the stability program at each time point for all three registration batches. Such studies should include tests such as: description, assay (for each active ingredient), impurities/degradation products, pH, particulate matter, sterility and other quality attributes as necessary. The in-use studies should be carried out for both the reconstituted and further diluted product (using all reconstitution and dilution agents listed in the package insert) at the temperature conditions (e.g., refrigerated, room temperature) and for periods in excess of the maximum hold time specified in the package insert.

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In addition, provide results of the stress stability studies and discuss conditions and factors that may facilitate interaction among the components of the proposed drug product, (b) (4) components supplied in one vial, and accelerate formation of (b) (4) and other potential degradation products.

### **Meeting Discussion:**

The Agency felt that the NOEL calculation appears acceptable, but that impurity qualifications will be based on review of final data. The Sponsor will submit a final 28-day toxicology study report to the IND by the end of April.

The Sponsor recognized that the Agency has concerns regarding the (b) (4) impurity and will provide in use data to support the hypothesis that the impurity (b) (4) (b) (4). The Agency noted that data provided in the background package indicates some levels of (b) (4) (e.g., (b) (4) % reported in Appendix V) present in the proposed drug product ( (b) (4) ). The Sponsor explained that these results are due to the formation of (b) (4) during chromatographic analysis of the drug product sample. The Sponsor agreed to provide further explanation and information for these results. The Sponsor also committed to providing in the NDA the in-use stability data for the three single-vial registration batches and one multi-vial batch. In addition, the Sponsor will provide a list of the physical and chemical tests to be included in the in-use stability studies. The Agency indicated that a microbial challenge study would be needed to support labeling storage recommendations for the drug product reconstituted and further diluted solutions for (b) (4) 4 hours at room temperature or (b) (4) hour under refrigeration. The Sponsor agreed to conduct the appropriate studies.

### **Post-meeting Comments:**

In preparation for the follow-up meeting, please address the following comments:

1. Provide results of the in-use stability testing (using a new HPLC method) for the infusion solutions of the drug product batches (a multi-vial configuration) used in the clinical studies.
2. Provide a description of the new HPLC analytical procedure (including a sample preparation) to be used for the analysis of impurities/degradation products in the proposed drug product.
3. Please indicate if different drug substance batches are used in the manufacture of the drug product registration stability batches.

**REMPEX'S RESPONSE TO FDA'S PRELIMINARY COMMENTS**  
**Carbavance**  
**(MEROPENEM/RPX7009)**

**Meeting Date: March 10, 2016**

We appreciate FDA's preliminary comments, and flexibility in being willing to accept less than the ICH Q1A recommended stability data given the potential for Carbavance to address an unmet medical need. Please find our clarifications/responses to the Agency's Meeting Preliminary Comments below. For tomorrow's meeting, we plan to focus the discussion on the following topics:

Questions 1 and 2:

- Discussion with the Agency on the provision of updated stability data (drug substance and drug product) during the review period.

Question 2:

- Discussion and clarification on the Agency's comment that "a significant increase in the meropenem related impurities were reported in these [pilot in-use] studies."

Question 3:

- Discussion regarding the in-use stability program.

**Question 1**

*Does the agency agree that the amount of stability data to be provided at the NDA submission and during review would be sufficient to support the proposed (b) (4) months retest period for RPX7009 (b) (4) drug substance upon initial approval?*

**Agency Pre-Meeting Response:**

**An appropriate retest period for RPX7009 (b) (4) drug substance will be assigned based on evaluation of the data available at the time of review. Given the potential for Carbavance to meet an unmet medical need, we are willing to accept less than the ICH Q1A recommended amount of stability data for (b) (4) RPX7009 to file the NDA. We recommend that the third registration batch of (b) (4) API be manufactured and placed on a stability program prior to NDA filing with the release data submitted in the NDA. Updated stability data for the registration batches will need to be provided during the NDA review in accordance with mutual agreements to be discussed and reached at the meeting. Supportive stability data for the (b) (4) (b) (4) should also be provided, as you have outlined in the meeting package.**

**Rempex Response:**

In response to the Agency's comment, (b) (4)

(b) (4) While our goal is to include this data in the NDA filing per the Agency's request, we anticipate gaining additional clarity with regard to scheduling in the coming months and plan to update FDA in a subsequent meeting.

Supportive stability data

(b) (4)

(as outlined in the meeting package) will be provided in the NDA.

## **Question 2**

For the single vial drug product containing (b) (4) meropenem and (b) (4) RPX7009, does the agency agree that the amount of stability data to be provided in the submission and during review would be sufficient to support the proposed (b) (4) month shelf-life at initial approval?

### **Agency Pre-Meeting Response:**

The drug product expiration dating is an NDA review decision and will be based on the assessment of the overall information submitted in the NDA. Considering the potential for Carbavance to meet an unmet medical need, we are willing to accept less than the ICH Q1A recommended amount of stability data for the proposed commercial drug product at the NDA filing, and subsequent stability updates during the NDA review to be discussed at the meeting. In preparation for this discussion, please provide the exact batch size and describe the differences between the formulations, manufacturing processes, and container-closure systems used for each batch described in Table 2. Also, describe the container-closure used for the multivial product and provide information on stability of the RPX7009 drug product in the multi-vial packaging configuration.

In addition, please provide details of the formulations (including batch sizes), manufacturing processes, and container-closure systems used in the studies described in Appendices V-VIII.

Describe the relationship between the formulations, manufacturing processes, and container closure systems used for these studies and the proposed commercial formulation and container closure system.

### **Rempex Response:**

The batch size, formulation composition, manufacturing processes (b) (4), scales for each operation, and container closure system used for each batch is described in Table 2 of the Briefing Package for the March 10th meeting (SN0070) are provided below in Table 1.

The components and ratio thereof for the product formulation are (b) (4) presented in Table 1. (b) (4) used for the registration batches. Lab batches 1 and 2 were (b) (4) used for the registration batches.

**Table 1: Details of Single Vial Drug Product Batches**

Drug Product Batch	Composition/Vial	(b) (4)	Container/Closure System
Lab Batch 1 <sup>1</sup>	RPX7009: 1000 mg Meropenem: 1000 mg Sodium Carbonate: 575 mg		50 mL Type 1 glass vial 20 mm (b) (4) stopper 20 mm Flip-off aluminum seal (b) (4)
Lab Batch 2 <sup>2</sup>	RPX7009: (b) (4) Meropenem: (b) (4) Sodium Carbonate: (b) (4)		
Registration Batch 1	RPX7009: 1000 mg		
Registration Batch 2	Meropenem: 1000 mg		
Registration Batch 3	Sodium Carbonate: 575 mg		

1. Stability data presented in Appendices V and VI of the Briefing Document for March 10, 2016 meeting.

2. Stability data presented in Appendices VII and VIII of the Briefing Document for March 10, 2016 meeting.

The container closure systems used for the multi-vial and single vial Carbavance drug products are provided in Table 2. With the exception of the vial size, the container closure system for the multi-vial drug product is the same as that used for all single vial batches.

**Table 2: Container Closure Systems for Carbavance Drug Products**

Presentation	Drug Product	Vial	Stopper	Seal
Multi-vial	RPX7009 for Injection for Multi-vial presentation	20 mL, Type 1 glass vial	20 mm (b) (4) rubber stopper	20 mm Flip-off aluminum seal (b) (4)
	Meropenem for Injection	30 mL, Type 1 glass vial		
Single vial	Carbavance for injection	50 mL, Type 1 glass vial		

Batch information for (b) (4) RPX7009 for Injection drug product in the multi-vial packaging configuration on stability is provided in Table 3, also was also provided in the Briefing Package from the September 30, 2015, Type C meeting (SN0052). Stability data available for all batches are provided in Attachment 1.

**Table 3: Batch Information for Six Stability Batches of (b) (4) RPX7009 for Injection**

Lot Number	Batch Size Kg	Mfg Date	Stability Data Available as of March 2016	
			Accelerated	Long-term
CL4-017	(b) (4)	April 2014	6 months	18 months
CL4-024	(b) (4)	April 2014	6 months	18 months
CL4-373	(b) (4)	November 2014	6 months	12 months
CL5-001	(b) (4)	February 2015	6 months	9 months
CL5-002	(b) (4)	March 2015	6 months	9 months
CL5-003	(b) (4)	March 2015	6 months	9 months

**Agency Pre-Meeting Response:**

Similarly, please provide details of the formulations (including batch sizes), manufacturing processes, container-closure systems, and reconstitution processes used in the in-use studies described in Appendix IX. Also, provide the assay values for meropenem and RPX7009 for each data point for the studies described in Appendix IX. We note a significant increase in the meropenem related impurities reported in these studies.

Please refer to the response to Question 3 for additional recommendations and information that should be provided in the NDA to support the stability and expiration dating for the proposed commercial drug product, (b) (4) components supplied in one vial.

**Rempex Response:**

Regarding the Agency’s request for RPX7009 and meropenem assay data for the in-use studies described in Appendix IX, they were not collected. The objective of these pilot studies was to evaluate a new analytical method and to assess potential new impurity formation of the drug combination in solution. As a result of these pilot studies, the impurities (b) (4) and (b) (4) were observed.

The study simulating the single vial configuration was conducted by adding the individual components (meropenem, RPX7009 and sodium carbonate) to a beaker followed by addition of normal saline at a volume sufficient to achieve the target concentration (8 mg/mL of each component). After mixing and dissolution, the beaker was placed at 25°C and sampled over time and tested for impurity profile only.

The study simulating the multi-vial configuration was conducted by reconstituting individual vials of meropenem and RPX7009 (b) (4) and adding them to a beaker followed by addition of normal saline at a volume sufficient to achieve the target concentration (8 mg/mL of each component). After mixing, the beaker was placed at 25°C and sampled over time and tested for impurity profile only.

Formal “in-use” studies will be conducted on both drug product configurations (refer to response to Q3).

Regarding the Agency's comment on the increase in the meropenem-related impurities reported in Appendix IX, we would like to discuss and gain clarification on this comment during the meeting.

**Question 3**

Two new degradation products, (b) (4) and (b) (4) were first observed using the new HPLC-UV method during pilot in-use studies with both the multi-vial and single vial configurations, and have been qualified in a 28-day repeat dose toxicology study in rat. Does the agency agree with the proposed limits for (b) (4) and (b) (4) for the purpose of establishing drug product shelf-life and in-use period for the single vial configuration?

**Agency Pre-Meeting Response:**

The proposed threshold limits for the two new degradations products, (b) (4) and (b) (4) appear to be qualified by the impurity NOAEL values obtained in the 28-Day Toxicology Study in Rats (Study No.: (b) (4) Study #1015-0201). A final determination will be dependent on evaluation of complete data included in the final study report. Please describe the calculations used to determine the impurity NOAEL values including the percent impurity in the dose solution associated with the parent-compound NOAEL in the 28-Day Toxicology Study. The final study report can be submitted with the NDA or prior to submission of the NDA to allow for earlier evaluation and confirmation of the qualification calculations and the proposed limits for (b) (4) and (b) (4)

**Rempex Response:**

We plan to submit the final 28-day toxicology report for (b) (4) Study #1015-0201 by the end of April.

The impurity NOAEL information (Table 4) is updated from the one provided in the Briefing Package for the March 10<sup>th</sup> meeting. The dose solution analysis was finalized and the table now includes data from all four dosing solution analyses as well as all four known meropenem-related impurities in Carbavance. The impurity NOAEL is calculated by determining the dose of the impurity in the dose solutions at the NOAEL of meropenem in Carbavance (in this study, the NOAEL for meropenem was 500 mg/kg/day in combination with RPX7009 at 1000 mg/kg, the highest dose tested). For example, the concentration of meropenem in the dose solution at the NOAEL dose was determined to be 25 mg/mL by HPLC. Meropenem impurity A was found to be (b) (4)% by area in the same dose solution. Therefore, the % Impurity Qualified in the drug product (DP) at (b) (4)g per day is calculated using the following equations:

- 1) Impurity A concentration in the dose solution:  
% Impurity x meropenem concentration = Impurity Concentration;

$$(b) (4) \text{ mg/mL.}$$

- 2) Impurity A Dose in mg/kg:  
Dose solution concentration (mg/mL) x Dose volume (mL/kg);

$$(b) (4) \text{ mg/kg.}$$

- 3) Impurity A NOAEL in mg/kg:  
Impurity A Dose (mg/kg) at parent NOAEL

(b) (4)

- 4) Impurity A NOAEL Human Equivalent Dose (HED) in mg/day:  
 Impurity NOAEL X Human Weight (60 kg) / Human to Animal Weight Factor (6.2 for the rat)

(b) (4) mg/day

- 5) % of Impurity Qualified in DP when meropenem 6 g/ RPX7009 6 g administered per day:

Impurity A NOAEL HED/Carbavance Daily Dose in man (mg) x 100

(b) (4) %

**Table 4: Calculation of the Human Equivalent NOAEL Dose for Meropenem and Meropenem Related Impurities Potentially Present in the Clinical Trial Materials Based on Dose Solution Analysis**

Impurity	Average Impurity Concentration in Dose Solution (mg/mL)	Average Impurity Dose (mg/kg/day) <sup>a</sup>	Impurity NOAEL (mg/kg/day)	Impurity NOAEL HED (mg/day) <sup>b</sup>	% of Impurity Qualified in DP when meropenem 6g/ RPX7009 6g administered per day <sup>c</sup>
Meropenem Impurity A					(b) (4)
Meropenem Impurity B					
(b) (4)					
(b) (4)					

a) Impurity Dose = Dose Solution Concentration x Dose Volume (mL/kg)

b) NOAEL HED = Impurity NOAEL x Human Weight (60kg) / Human to Animal Weight Factor (6.2 Rat; 1.8 Dog)

c) % Qualification = NOAEL HED/Daily Dose x 100

1 (b) (4) Study 1015-0201

**Agency Pre-Meeting Response:**

**We recommend that you carry out in-use studies for samples in the stability program at each time point for all three registration batches. Such studies should include tests such as: description, assay (for each active ingredient), impurities/degradation products, pH, particulate matter, sterility and other quality attributes as necessary. The in-use studies should be carried out for both the reconstituted and further diluted product (using all reconstitution and dilution agents listed in the package insert) at the temperature conditions (e.g., refrigerated, room temperature) and for periods in excess of the maximum hold time specified in the package insert.**

**In addition, provide results of the stress stability studies and discuss conditions and factors that may facilitate interaction among the components of the proposed drug product,** (b) (4)

components supplied in one vial, and accelerate formation of (b) (4) and other potential degradation products.

**Rempex Response:**

As recommended by the Agency, the sponsor commits to carry out in-use studies on the three single vial registration batches at each ICH stability time point to support drug product approval. The study will include the appropriate physical and chemical tests and will be conducted with both D5W and 0.9% sodium chloride solution for both reconstituted and further diluted product at both refrigerated and room temperature conditions for periods in excess of the maximum hold time specified in the package insert.

The in-use studies will be conducted at a separate site ( (b) (4) ). The methods are currently being validated and we plan to start the in-use studies in April 2016 on the first registration batch. In-use stability studies will be performed on one batch of multi-vial drug product to establish comparability. The timeline for the availability of all in-use stability data for both the single and multi-vial drug products is summarized in Table 5.

**Table 5: Timeline for “In-use” Stability Data Availability for Drug Product**

Product Configuration	Batch	Manufacturing Date	In-Use Stability Start Date	In-Use Stability Data Available (in months) at Indicated Date		
				Dec 2016	Feb 2017	May 2017
Single Vial	Registration Batch 1	Jan 2016	April 2016	0, 3, 6	9	12
	Registration Batch 2	May 2016	July 2016	0, 3	6	9
	Registration Batch 3	May 2016	July 2016	0, 3	6	9
Multi-Vial	1 Batch	May 2015	April 2016	3, 6	9	12

We commit to provide results of the stress studies on single vial Carbavance drug product and discuss conditions and factors that may facilitate interaction among the components in the NDA filing.

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/s/  
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NAVDEEP BHANDARI  
04/08/2016



IND 120040

**MEETING MINUTES**

Rempex Pharmaceuticals, Inc.  
Attention: Elizabeth Morgan  
VP Clinical and RA/QA Operations  
11535 Sorrento Valley Road  
San Diego, CA 92121

Dear Ms. Morgan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Carbavance™ (Meropenem/RPX7009).

We also refer to the meeting between representatives of your firm and the FDA on July 3, 2014. The purpose of the meeting was to discuss 1) the designation of starting materials and the control strategies for impurities and stereochemistry, 2) the design of the microbial challenge study for drug product, particularly the selection of challenge organisms, and 3) additional recommendations to support the drug substance and drug product as part of a future NDA for Meropenem (RPX2014) /RPX7009.

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}*

Navi Bhandari, Pharm.D  
Regulatory Health Project Manager  
Office of Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** EOP2

**Meeting Date and Time:** July 3, 2014 1:00 – 2:00 pm, EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1415  
Silver Spring, Maryland 20903

**Application Number:** IND 120040  
**Product Name:** Carbavance™ (Meropenem/RPX7009)  
**Indication:** Treatment of complicated urinary tract infection (cUTI) (b) (4)  
[REDACTED]

**Sponsor/Applicant Name:** Rempex Pharmaceuticals

**Meeting Chair:** Rapti D. Madurawe, Ph.D.  
**Meeting Recorder:** Navdeep Bhandari, Pharm.D.

**FDA ATTENDEES**

Rapti D. Madurawe, Ph.D.	Branch Chief
Dorota Matecka, Ph.D.	CMC Lead
James Wild, Ph.D.	Pharmacology/Toxicology Reviewer
Dmitri Iarikov, M.D.	Medical Officer
Navdeep Bhandari, Pharm.D	Regulatory Health Project Manager
Shrikant Pagay, Ph.D.	Chemistry Reviewer
John Alexander, M.D.	Lead Medical Officer
John Metcalfe, Ph.D.	Microbiology Reviewer

**SPONSOR ATTENDEES**

Michael Dudley, PharmD	Sr. VP and Chief Scientific Officer Rempex/MDCO
Scott Hecker, PhD	VP, Chemistry Rempex/MDCO
David Griffith	VP, Nonclinical Rempex/MDCO
(b) (4)	CMC Consultant
(b) (4)	Quality Assurance Consultant
Judy Lee	CMC Regulatory Affairs MDCO
(b) (4)	Regulatory Consultant
Melissa Stundick, PhD	Project Officer BARDA

IND 120040  
Meeting Minutes  
Type B EOP2 Meeting

ONDQA  
Division of Anti-Infective Products

Murti Vemuri, PhD  
John Grosso, PhD  
Michael Elisseou, PhD  
Elizabeth Morgan

CMC SME, Contractor BARDA  
CMC SME, Contractor BARDA  
Regulatory and Quality Affairs SME Contractor  
VP Clinical and RA/QA Operations

APPEARS THIS WAY ON ORIGINAL

## 1.0 BACKGROUND

A Type B meeting briefing package was submitted June 2, 2014, for a July 3, 2014, End-of-Phase 2 CMC Meeting for Carbavance™ (Meropenem [RPX2014] /RPX7009).

## 2.0 DISCUSSION

This meeting's focus was to provide proposed plans for CMC topics relative to this IND, and gain input from the Agency on 1) the designation of starting materials and the control strategies for impurities and stereochemistry, 2) the design of the microbial challenge study for drug product, particularly the selection of challenge organisms, and 3) additional recommendations to support the drug substance and drug product as part of a future NDA for Carbavance™ (Meropenem/RPX7009).

The Agency sent preliminary responses on June 27, 2014 to the Sponsor. The Sponsor asked to focus on questions 1, 3, 4 and 5. A slide deck was provided by the Sponsor on July 3, 2014 (attached below).

## 3.0 QUESTIONS

**Question 1:** Does the Division agree with the Rempex proposal to designate (b) (4) and (b) (4) ( (b) (4) ) as the starting materials (justification provided in Section 10.1.6)?

**Agency Response:** We agree with the proposal to designate (b) (4) as a starting material. With regards to (b) (4) ( (b) (4) ) no agreement is made at this time.

(b) (4)

The adequacy of (b) (4) as a starting material will be evaluated during the NDA review.

**Discussion:** The FDA expressed a concern that the currently proposed starting material, (b) (4)

(b) (4)

(b) (4) **The Agency reiterated that the adequacy of designation (b) (4) as a starting material will be assessed during the NDA review based on the overall information and data submitted.**

**Question 2:** Does the Division agree with the proposed (b) (4) and (b) (4) (b) (4) starting material control strategies (Section 10.1.6)?

**Agency Response:** *The general approach appears reasonable. All specifications for the starting materials will be evaluated for acceptability during NDA review.*

**Discussion:** **There was no specific discussion on this question.**

**Question 3:** Does the Division agree with the proposed control strategy for RPX7009, including stereochemistry and impurity qualification (Sections 10.1.3 and 10.1.4)?

**Agency Response:** *Your non-clinical approach to impurity qualification appears reasonable. The qualification levels of both impurities and degradants will be an NDA review issue.*

*The proposed control strategy for impurities and stereochemistry control will be evaluated during NDA review. Describe in the NDA, critical quality attributes of the drug substance, the manufacturing process parameters, any in-process tests and controls used, and a discussion of critical process parameters that impact drug substance quality, including stereoisomeric purity.*

*Provide data from several batches for the stereoisomeric impurity levels to support the proposed drug substance specifications.*

**Discussion:** **The Sponsor stated that they would submit data on the stereoisomeric impurity levels from at least six batches to support the proposed drug substance specifications. These batches will include registration and validation batches, as well as**

**development batches. The Agency agreed that that the proposed number of batches is reasonable.**

**The Sponsor inquired if they could submit for review the process validation protocols. The Agency responded that validation protocols are normally reviewed on-site by the Office of Regulatory Affairs and Office of Compliance and not by the review Division.**

**Question 4:** Based on the data and information presented in the briefing package, does the Division have any additional comments or recommendations regarding the drug substance for ultimate NDA filing?

***Agency Response:** Please conduct a one time in-use stability study (stability of reconstituted vial of RPX7009 and stability of RPX7009 plus meropenem in the infusion bag) over drug product shelf life for three registration stability batches and submit the available data in the NDA. It may also be useful to ascertain at annual time points in a one-time study that no stereoisomeric conversion occurs over stability. This information could be used to justify the proposed release and stability specifications.*

**Discussion:** The Sponsor agreed to conduct a one-time in-use stability study (i.e., stability of reconstituted vial of RPX7009 and stability of RPX7009 plus meropenem in the infusion bag) over drug product shelf life for three registration stability batches and submit the available data in the NDA.

**The Sponsor also agreed to conduct a one-time study with one registration batch of the drug substance to confirm that no stereoisomeric conversion occurs over stability. The Agency indicated that similar one time study may be needed for the drug product adding that a follow up recommendation would be provided as a post-meeting comment.**

**Post-meeting Comment:**

*Please test the stereoisomeric purity of the three drug product registration stability batches (annual time points recommended) to demonstrate that no stereoisomeric conversion occurs over drug product storage. If no conversion is observed, the data may be used to justify the exclusion of a test for stereoisomeric purity in the drug product specification.*

**Question 5:**

(b) (4)

Does the Agency agree with this approach?

**Question 6:** Does the Division agree with Rempex's selection of the challenge organisms and study design for the in use microbiology stability study to support the proposed hang time as outlined in Section 11 of the briefing package?

**Agency Response:** *Yes, we agree.*

**Discussion:** **There was no specific discussion on this question.**

**Question 7:** Based on the data and information presented in the briefing package, does the Division have any additional comments or recommendations regarding the drug product for ultimate NDA filing?

**Agency Response:** *We recommend that the initial NDA submission contains 6-month accelerated and at least 12-months long-term stability data for 3 registration batches of the drug product (RPX7009) meeting ICH Q1A(R2) "Selection of Batches" criteria, and the batches are manufactured using the equipment of the same design and operating principles as the commercial manufacturing equipment and process.*

**Discussion:** There was no specific discussion on this question.

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/s/  
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DOROTA M MATECKA  
08/01/2014

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 209776

**LATE-CYCLE MEETING MINUTES**

Rempex Pharmaceuticals, Inc.  
a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director, Regulatory Affairs  
8 Sylvan Way  
Parsippany, NJ 07054

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 29, 2016, received December 29, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for meropenem and vaborbactam powder for injection, 1000mg/1000mg vial.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 23, 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 Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

Dmitri Iarikov, MD, PhD  
Cross-Discipline Team Leader  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** June 23, 2017, 11:00am – 12:00pm  
**Meeting Location:** Conference Room 6305, Building 22  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

**Application Number:** NDA 209776  
**Product Name:** VABOMERE (Meropenem-vaborbactam)  
**Indication:** complicated Urinary Tract Infections (cUTI) including  
Pyelonephritis  
**Applicant Name:** Rempex Pharmaceuticals, Inc. a wholly owned subsidiary of The  
Medicines Company

**FDA ATTENDEES (tentative)**

**Division of Anti-Infective Products:**

Abimbola Adebowale, PhD	Associate Director of Labeling
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
Carmen DeBellas, PharmD, RPh	Chief, Project Management Staff
Kerian Grande, PhD	Clinical Microbiology Reviewer
Dmitri Iarikov, MD, PhD	Acting Deputy Director
Rama Kapoor, MD	Clinical Reviewer
Terry Miller, PhD	Pharmacology/Toxicology Team Leader
Sumathi Nambiar, MD MPH	Director
Joseph Toerner, MD, MPH	Deputy Director for Safety
James Wild, PhD	Pharmacology/Toxicology Reviewer

**Office of Biostatistics:**

Daniel Rubin, PhD	Statistical Reviewer
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**Office of Clinical Pharmacology:**

Seong Jang, PhD	Clinical Pharmacology Team Leader
Xiaohui (Tracey) Wei, PhD	Clinical Pharmacology Reviewer

**Office of Pharmaceutical Quality:**

Daniel DeCiero, PhD	Product Quality Facilities Reviewer
George Lunn, PhD	Product Quality Reviewer
Dorota Matecka, PhD	CMC Lead
Derek Smith, PhD	Branch Chief (Acting), Office of Pharmaceutical Quality

**Office of Surveillance and Epidemiology:**

Janet Higgins	Regulatory Project Manager
Deborah Myers, RPh, MBA	Safety Evaluator
Til Olickal, PhD, PharmD	Risk Management Analyst

**APPLICANT ATTENDEES**

**Rempex Pharmaceuticals, Inc.:**

Stefanie Andrews	Senior Program Manager
Walter Cespedes	Vice President Quality Assurance
Sabrina Comic-Savic, MD, MPH	Vice President Quality and Compliance
Mike Dudley, PharmD	Senior Vice President, Chief Scientific Officer
David Griffith	Vice President, Nonclinical Science
Scott Hecker, PhD	Vice President, Chemistry
Loretta Itri, MD	Executive Vice President Global Health Science & Regulatory
Michelle Linfesty	Senior Director, Program Management
Jeff Loutit, MBChB	Senior Vice President, Chief Medical Officer
Mary Ann McElligott	Vice President, CMC
Starr Shangle	Senior Director, Regulatory Affairs
Shu Zhang, ScD	Senior Director, Biostatistics

**Consultant:**

 (b) (4) CMC Consultant

**Biomedical Advanced Research and Development Authority:**

Mark Albrecht, PhD	Project Officer
Sandra Bihary-Waltz	Regulatory/Quality Assurance Subject Matter Expert
Louise Latriano, PhD	Toxicology/PK Subject Matter Expert
Wylie McVay	Regulatory/Quality Assurance Subject Matter Expert

**1.0 BACKGROUND**

NDA 209776 was submitted on December 29, 2016 for meropenem-vaborbactam.

Proposed indication: complicated Urinary Tract Infections (cUTI) including Pyelonephritis

PDUFA goal date: August 29, 2017

FDA issued a Background Package in preparation for this meeting on June 14, 2017.

**2.0 DISCUSSION**

1. Introductory Comments – 5 minutes (Dmitri Iarikov)  
Welcome, Introductions, Ground rules, Objectives of the meeting

## 2. Discussion of Substantive Review Issues

Each issue was introduced by FDA and followed by a discussion.

**Discussion:** The Division provided the following information on product quality and clinical pharmacology:

### a. Product quality

There are substantive review issues related to manufacturing facility deficiencies. Per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the facilities proposed must comply with the current good manufacturing practice regulations.

### b. Clinical pharmacology

We recommend that the dosing regimen of VABOMERE in patients with renal impairment be adjusted based on eGFR calculated by MDRD equation (b) (4)   for the following reasons:

(a) eGFR was used in Study 504 to categorize subjects with different degrees of renal impairment (mild, moderate, severe, and end stage renal disease)

(b) eGFR was used to determine the effect of renal function on CL in the population PK models for both meropenem and vaborbactam and the relationship of eGFR to CL was used to simulate the exposure of meropenem and vaborbactam for determination of dose adjustment in subjects with renal impairment.

In addition, we conducted analyses to determine the optimized dose adjustment of VABOMERE in order to provide exposures of meropenem and vaborbactam in patients with  $eGFR < 50 \text{ mL/min/1.73m}^2$  comparable to exposures in patients with  $eGFR \geq 50 \text{ mL/min/1.73m}^2$ . Accordingly, we recommend the dose adjustment of VABOMERE in patients with renal impairment as presented in Table 1.

Because the contribution of renal clearance to total body clearance is greater for vaborbactam compared to meropenem, vaborbactam demonstrated a significantly higher degree of accumulation in subjects with ESRD ( $eGFR < 15 \text{ mL/min/1.73 m}^2$ ) compared to meropenem. In addition, the effect of hemodialysis on meropenem and vaborbactam is quantitatively different, although both can be removed by hemodialysis. Based on the proportion of meropenem dose removed by dialysis (i.e., 38% after a single dose administration) and the frequency of dialysis (3 times per week according to common practice) relative to frequency of VABOMERE twice daily dosing in patients maintained on hemodialysis, we anticipate that the reduction of meropenem exposure would not be substantial when VABOMERE is administered

before dialysis. Therefore, considering unknown safety risk of high vaborbactam exposure and a relatively minor probability of low meropenem exposure, we recommend VABOMERE be administered before hemodialysis.

**Table 1. FDA Recommended VABOMERE Dose Adjustments in Patients with Renal Impairment**

Estimated Glomerular Filtration Rate eGFR <sup>a</sup> (mL/min/ 1.73m <sup>2</sup> )	Recommended Dosage Regimen for VABOMERE (meropenem and vaborbactam) <sup>b,c,d</sup>	Dosing Interval
≥50	VABOMERE 4 grams (2 grams-2 grams)	Every 8 hours
≥30-49	VABOMERE 4 grams (2 grams-2 grams)	Every 12 hours
≥15-29	VABOMERE 2 grams (1 gram-1 gram)	Every 12 hours
<15	VABOMERE 1 gram (0.5 gram-0.5 gram)	Every 12 hours

<sup>a</sup> Estimated GFR (eGFR) is based on a Modification of Diet in Renal Disease (MDRD) formula.;

<sup>b</sup> All doses of VABOMERE are administered intravenously over 3 hours.;

<sup>c</sup> Both meropenem and vaborbactam can be removed by hemodialysis. For patients maintained on hemodialysis, administer VABOMERE before hemodialysis.;

<sup>d</sup> The total duration of treatment is for up to 14 days.

**Discussion:** The applicant stated that they would like to review the renal dosing analyses done by the Agency and if further discussion is required, the Division noted that a follow up teleconference with the applicant could be scheduled.

### 3. Discussion of Minor Review Issues

**Discussion:** There were no minor review issues that required further discussion.

### 4. Additional Applicant Data

**Discussion:** There was no additional applicant data that required further discussion.

### 5. Information (IR)

**Discussion:** Pharmacology/toxicology sent an IR June 8, 2017 requesting to obtain the historical control data for fetal malformations in Sprague-Dawley rats from the contract lab ( (b) (4) ) where Study No.: 1011-1721 was conducted and/or from the supplier for the rats used in Study No.: 1011-1721.

### 6. Postmarketing Requirements/Postmarketing Commitments (PMR/PMC)

**Discussion:**

- **Clinical Microbiology PMR:** Conduct US surveillance studies for five years from the date of marketing to determine if resistance to VABOMERE has developed in those organisms specific to the indications in the label.
- **TQT study PMR:** Conduct a TQT study for this product as a PMR to exclude QT prolongation effects. Please refer to minutes of the September 30, 2015 meeting where a PMR for a TQT study was discussed.
- **Product Quality PMC:** Perform extractable/leachable study on the commercial container closure system.

7. Major labeling issues

**Discussion:** Labeling will be discussed during the remaining time in the review cycle.

8. Review Plans

**Discussion:** Action Goal Date is August 29, 2017.

9. Wrap-up and Action Items

**Discussion:** 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.

## 5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Agency will provide the meeting minutes within 30 days.	FDA	July 23, 2017
The Agency will share their analyses that support the renal dosing recommendations; if further discussion is required, a follow up teleconference with the applicant could be scheduled.	FDA	July 14, 2017

## 6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts used for this meeting.

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/s/  
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DMITRI IARIKOV  
07/17/2017



NDA 209776

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Rempex Pharmaceuticals, Inc.  
a wholly owned subsidiary of The Medicines Company  
Attention: Starr Shangle  
Senior Director, Regulatory Affairs  
8 Sylvan Way  
Parsippany, NJ 07054

Dear Ms. Shangle:

Please refer to your New Drug Application (NDA) dated December 29, 2016, received December 29, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for meropenem and vaborbactam powder for injection, 1000mg/1000mg vial.

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 23, 2017. Attached is our background package, including our agenda, for this meeting.

Please email a list of your attendees to [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov), at least one week prior to the meeting.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

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

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** June 23, 2017, 11:00am – 12:00pm  
**Meeting Location:** Conference Room 6305, Building 22  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

**Application Number:** NDA 209776  
**Product Name:** meropenem-vaborbactam  
**Indication:** complicated Urinary Tract Infections (cUTI)  
**Applicant Name:** Rempex Pharmaceuticals, Inc. a wholly owned subsidiary of The Medicines Company

### **FDA ATTENDEES (tentative)**

#### **Division of Anti-Infective Products:**

Abimbola Adebawale, PhD	Associate Director of Labeling
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
Carmen DeBellis, RPh, PharmD	Chief, Project Management Staff
Kerian Grande, PhD	Clinical Microbiology Reviewer
Rama Kapoor, MD	Clinical Reviewer
Terry Miller, PhD	Pharmacology/Toxicology Team Leader
Sumathi Nambiar, MD MPH	Director
Joseph Toerner, MD, MPH	Deputy Director for Safety
James Wild, PhD	Pharmacology/Toxicology Reviewer

#### **Office of Antimicrobial Products:**

John Farley, MD, MPH	Deputy Director
----------------------	-----------------

#### **Office of Biostatistics:**

Daphne TY Lin, PhD	Deputy Division Director, Biometrics IV
Daniel Rubin, PhD	Statistical Reviewer

#### **Office of Clinical Pharmacology:**

Seong Jang, PhD	Clinical Pharmacology Team Leader
Xiaohui (Tracey) Wei, PhD	Clinical Pharmacology Reviewer

#### **Office of Pharmaceutical Quality:**

Elsbeth Chikhale, PhD	Biopharmaceutics Team Leader
Daniel DeCiero, PhD	Product Quality Facilities Reviewer
Christina Falabella, PhD	Product Quality Reviewer
George Lunn, PhD	Product Quality Reviewer
Dorota Matecka, PhD	CMC Lead
Derek Smith, PhD	Branch Chief (Acting), Office of Pharmaceutical Quality
Qi Zhang, PhD	Biopharmaceutics Reviewer

**Office of Scientific investigations:**

Janice Pohlman, MD Clinical Team Leader

**Office of Surveillance and Epidemiology:**

Susan Bersoff-Matcha, MD Medical Officer  
Janet Higgins Regulatory Project Manager  
Deborah Myers, RPh, MBA Safety Evaluator  
Til Olickal, PhD, PharmD Risk Management Analyst  
Chih-Ying (Natasha) Pratt, PhD Epidemiology Team Leader (Acting)

**SPONSOR ATTENDEES (tentative)**

**Rempex Phamraceuticals:**

Stefanie Andrews Senior Program Manager  
Sabrina Comic-Savic, MD, MPH Vice President Quality and Compliance  
Isabelle Degeyter, MD Senior Director Pharmacovigilance  
Mike Dudley, PharmD Senior Vice President, Chief Scientific Officer  
David Griffith Vice President, Nonclinical Science  
Scott Hecker, PhD Vice President, Chemistry  
Loretta Itri, MD Executive Vice President Global Health Science &  
Regulatory  
Judy Lee Senior Director, Chemistry, Manufacturing, and Controls  
(CMC)  
Michelle Linfesty Senior Director, Program Management  
Olga Lomovskaya Vice President, Biology  
Jeff Loutit, MBChB Senior Vice President, Chief Medical Officer  
Mary Ann McElligott Vice President, CMC  
Starr Shangle Senior Director, Regulatory Affairs  
Shu Zhang, ScD Senior Director, Biostatistics

**Consultant:**

 (b) (4) CMC Consultant

**Biomedical Advanced Research and Development Authority (BARDA):**

Mark Albrecht, PhD Project Officer  
Sandra Bihary-Waltz Regulatory/Quality Assurance Subject Matter Expert,  
Contractor  
Wylie McVay Regulatory/Quality Assurance Subject Matter Expert,  
Contractor

**INTRODUCTION**

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not

yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

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

## **BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE**

### **1. Discipline Review Letters**

No Discipline Review letters have been issued to date.

### **2. Substantive Review Issues**

#### **Product Quality**

There are substantive review issues related to manufacturing facility deficiencies. Per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the facilities proposed must comply with the current good manufacturing practice regulations.

#### **Clinical Pharmacology**

We recommend that the dosing regimen of VABOMERE in patients with renal impairment be adjusted based on eGFR calculated by MDRD equation (b) (4) for the following reasons:

(a) eGFR was used in Study 504 to categorize subjects with different degrees of renal impairment (mild, moderate, severe, and end stage renal disease)

(b) eGFR was used to determine the effect of renal function on CL in the population PK models for both meropenem and vaborbactam and the relationship of eGFR to CL was used to simulate the exposure of meropenem and vaborbactam for determination of dose adjustment in subjects with renal impairment.

In addition, we conducted analyses to determine the optimized dose adjustment of VABOMERE in order to provide exposures of meropenem and vaborbactam in patients with eGFR < 50 mL/min/1.73m<sup>2</sup> comparable to exposures in patients with eGFR ≥ 50 mL/min/1.73m<sup>2</sup>.

Accordingly, we recommend the dose adjustment of VABOMERE in patients with renal impairment as presented in Table 1.

Because the contribution of renal clearance to total body clearance is greater for vaborbactam compared to meropenem, vaborbactam demonstrated a significantly higher degree of accumulation in subjects with ESRD (eGFR <15 ml/min/1.73 m<sup>2</sup>) compared to meropenem. In addition, the effect of hemodialysis on meropenem and vaborbactam is quantitatively different, although both can be removed by hemodialysis. Based on the proportion of meropenem dose removed by dialysis (i.e., 38% after a single dose administration) and the frequency of dialysis (3 times per week according to common practice) relative to frequency of VABOMERE twice daily dosing in patients maintained on hemodialysis, we anticipate that the reduction of meropenem exposure would not be substantial when VABOMERE is administered before dialysis. Therefore, considering unknown safety risk of high vaborbactam exposure and a relatively minor probability of low meropenem exposure, we recommend VABOMERE be administered before hemodialysis.

**Table 1. FDA Recommended VABOMERE Dose Adjustments in Patients with Renal Impairment**

<b>Estimated Glomerular Filtration Rate eGFR<sup>a</sup> (mL/min/ 1.73m<sup>2</sup>)</b>	<b>Recommended Dosage Regimen for VABOMERE (meropenem and vaborbactam)<sup>b,c,d</sup></b>	<b>Dosing Interval</b>
≥50	VABOMERE 4 grams (2 grams-2 grams)	Every 8 hours
≥30-49	VABOMERE 4 grams (2 grams-2 grams)	Every 12 hours
≥15-29	VABOMERE 2 grams (1 gram-1 gram)	Every 12 hours
<15	VABOMERE 1 gram (0.5 gram-0.5 gram)	Every 12 hours

<sup>a</sup> Estimated GFR (eGFR) is based on a Modification of Diet in Renal Disease (MDRD) formula.;

<sup>b</sup> All doses of TRADENAME are administered intravenously over 3 hours.;

<sup>c</sup> Both meropenem and vaborbactam can be removed by hemodialysis. For patients maintained on hemodialysis, administer VABOMERE before hemodialysis.;

<sup>d</sup> The total duration of treatment is for up to 14 days.

## 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 (RPM/CDTL) (Dmitri Iarikov)  
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 30 minutes. Each issue will be introduced by FDA and followed by a discussion.
  - a. Product quality – 10 minutes
  - b. Clinical pharmacology – 20 minutes
3. Discussion of Minor Review Issues – none
4. Additional Applicant Data – 5 minutes (Applicant)
5. Information (IR) – 5 minutes

Pharmacology/toxicology IR from June 8, 2017 requesting to obtain the historical control data for fetal malformations in Sprague-Dawley rats from the contract lab ( [REDACTED] <sup>(b) (4)</sup> [REDACTED] ) where Study No.: 1011-1721 was conducted and/or from the supplier for the rats used in Study No.: 1011-1721.

6. Postmarketing Requirements/Postmarketing Commitments (PMR/PMC) – 5 minutes

**Clinical Microbiology PMR:** Conduct US surveillance studies for five years from the date of marketing to determine if resistance to VABOMERE has developed in those organisms specific to the indications in the label.

**TQT study PMR:** Conduct a TQT study for this product as a PMR to exclude QT prolongation effects. Please refer to minutes of the September 30, 2015 meeting where a PMR for a TQT study was discussed.

**Product Quality PMC:** Perform extractable/leachable study on the commercial container closure system.

7. Major labeling issues – Labeling will be discussed during the remaining time in the review cycle.
8. Review Plans – 5 minutes
9. Wrap-up and Action Items – 5 minutes

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUMATHI NAMBIAR  
06/14/2017