CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209776Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ***Approval***

NDA 209776
Review # 1

Drug Name/Dosage Form	Vabomere™ (meropenem and vaborbactam) for Injection
Strength	2 gram/vial (1 gram of meropenem and 1gram of vaborbactam)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Rempex Pharmaceuticals, a wholly owned subsidiary of The Medicines Company
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	December 29, 2016	All
Amendment (eCTD 004)	January 26, 2017	Facilities
Amendment (eCTD 005)	February 9, 2017	Facilities
Amendment (eCTD 008)	March 7, 2017	Facilities
Amendment (eCTD 010)	March 18, 2017	Drug Product
Amendment (eCTD 013)	March 28, 2017	EA
Amendment (eCTD 018)	April 12, 2017	Drug Substance, Process, Biopharmaceutics
Amendment (eCTD 019)	April 24, 2017	Drug Substance, Drug Product
Amendment (eCTD 022)	May 22, 2017	Drug Substance
Amendment (eCTD 023)	May 25, 2017	Drug Substance, Process
Amendment (eCTD 027)	June 22, 2017	Drug Product
Amendment (eCTD 034)	August 4, 2017	Drug Product
Amendment (eCTD 035)	August 7, 2017	Drug Substance, Drug Product
Amendment (eCTD 036)	August 11, 2017	Drug Substance, Facilities

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Gene Holbert	Benjamin Stevens
Drug Product	George Lunn	Balajee Shanmugam
Process	Christine Falabella	Steven Frisbee
Microbiology	Denise Miller	Bryan Riley
Facilities	Daniel DeCiero	Christina Capacci-Daniel
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	N/A
Laboratory (OTR)	Laura Pogue	N/A
Environmental Assessment	James Laurenson	Michael Furness
Application Technical Lead	Dorota Matecka	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Completed	Comments
(b) (4)	Type II Type II		(b) (4)	Adequate Adequate	*In Panorama*	Refer to reviews by Gene Holbert and Denise Miller
	Type II			Adequate	*See Microbiology Chapter*	
	Type III			Adequate	*As above*	
	Type V			Adequate	*As above*	
	Type V			Adequate	*As above*	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	120040	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Acceptable (*refer to DS and DP reviews*)		
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, meropenem and vaborbactam for injection. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on August 28, 2017. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

The following post-marketing commitment (PMC) has been established for this NDA from the Product Quality perspective:

PMC #3248-6

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.

Protocol Submission:	December 1, 2017
Interim Report:	September 1, 2018
Study Completion:	February 1, 2019
Final Report Submission:	April 1, 2019

II. Summary of Quality Assessments

A. Product Overview

Vabomere™ (meropenem and vaborbactam) for Injection is a combination product consisting of meropenem, a carbapenem-class antibacterial and vaborbactam, a beta-lactamase inhibitor, indicated for the treatment of Complicated Urinary Tract Infections (cUTI), including Pyelonephritis, in patients 18 years and older.

The proposed drug product, Vabomere™ (meropenem and vaborbactam) for Injection, 2 grams, consists of 1 gram of meropenem and 1 gram of vaborbactam supplied as a sterile powder (b) (4) in a glass vial that needs to be reconstituted and further diluted for intravenous infusion. The drug product strength is expressed as the sum of the two components to be consistent with the previously approved products in this class (injectable beta-lactam/beta-lactamase inhibitor combinations).

Proposed Indication(s) including Intended Patient Population	Complicated Urinary Tract Infections (cUTI), including Pyelonephritis, in patients 18 years and older
Duration of Treatment	The recommended dosage is 4 g (meropenem 2 g and vaborbactam 2 g) administered every 8 hours by intravenous (IV) infusion over 3 hours for up to 14 days in patients 18 years of age and older (b) (4) (b) (4) See package insert for the recommended dosage in patients with varying degrees of renal function.
Maximum Daily Dose	As above (see the package insert for details)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The proposed drug product contains two drug substances, meropenem and vaborbactam. Meropenem trihydrate (b) (4) drug substance is prepared by (b) (4) described in DMF Type II (b) (4) held by (b) (4) DMF (b) (4) includes a reference to DMF Type II (b) (4) for the synthesis of meropenem trihydrate (b) (4) drug substance. These DMFs were reviewed in support of the current NDA and found to be adequate (refers to respective reviews in Panorama). Meropenem is a colorless to white or light yellow crystals or crystalline powder soluble in DMF and in 5% K_2HPO_4 solution, sparingly soluble in water and in 5% KH_2PO_4 solution, practically insoluble in alcohol, acetone, methylene chloride and ether. The expiration dating established by the drug substance manufacturer for meropenem trihydrate (b) (4) stored at (b) (4) is (b) (4) months.

The chemistry manufacturing and controls information for vaborbactam drug substance has been provided in the NDA. Vaborbactam drug substance is a white to off-white solid slightly soluble in water; freely soluble in methanol; insoluble in other organic solvents. Vaborbactam (b) (4) drug substance is manufactured in (b) (4) compounds have been found acceptable as starting materials following recommendations for designation of starting materials described in the ICH Q11 Guidance. Vaborbactam was characterized by ultraviolet spectroscopy, infrared spectroscopy, elemental analysis, ^{1}H and ^{13}C NMR, mass spectrometry, DSC, and TGA. The structure assignment is also supported by the results of single crystal X-ray analysis. Analytical data as well as the method of synthesis were found adequate to support the proposed drug substance structure. The vaborbactam specification includes tests and acceptance criteria for appearance, identification, assay, related substances, residual solvents, water content, specific optical rotation, particle size distribution, bulk and tapped density, sterility and bacterial endotoxins. Stability data supports a retest period of (b) (4) months when stored at (b) (4) and packaged in the packaging system described in the application.

The drug product, meropenem and vaborbactam for injection, 1140 mg meropenem trihydrate (equivalent to 1000 mg meropenem), 1000 mg vaborbactam, and 575 mg sodium carbonate in a 50 mL Type I clear glass vial that is sealed with a (b) (4) rubber stopper and an aluminum flip off seal. (b) (4) sodium carbonate is manufactured by (b) (4) under DMF (b) (4) and conforms to the NF specification. The content of a vial is to be reconstituted with 20 mL saline to deliver a withdrawable volume of ca. 21.4 mL. (b) (4)

The drug development was conducted using a two-vial presentation with meropenem and sodium carbonate in one vial and vaborbactam in the other. All clinical trials were conducted with the two-vial presentation. However, for convenience and to avoid medication errors, a single vial presentation was developed for marketing. (b) (4) the commercial drug product presentation is (b) (4) (b) (4) (meropenem trihydrate, vaborbactam and sodium carbonate) filled into glass vials. A (b) (4)% overfill is utilized and studies have been conducted to demonstrate that (b) (4)% of the vial volume could be withdrawn, which will result in the label claim of 1000 mg of each active being dispensed.

The drug product specification contains tests for appearance, identity, reconstitution time, appearance of solution, particulates, pH, (b) (4) uniformity, assay, (b) (4), related substances, elemental impurities, endotoxins, and sterility. Generally, the specification is conventional for this type of product. The related substances are toxicologically qualified and the unspecified impurity limit of (b) (4)% conforms to ICH Q3B. The analytical methods have been described in reasonable detail and the validations are adequate. Satisfactory batch analyses are provided for three registration batches. The individual degradants from meropenem and vaborbactam that are controlled in the drug substances are also controlled in the drug product specification. Two new degradants, (b) (4) have been identified in the drug product. (b) (4) (b) (4) (b) (4) It is tightly controlled at low levels.

The container-closure system consists of 50 mL Type I clear glass vials sealed with a (b) (4) rubber stopper and an aluminum flip off seal. The vial conforms to the 21 CFR requirements and sufficient information is provided in the DMF for the stopper. The applicant has not conducted extractable/leachable studies on the container-closure system. Although the proposed drug product is not a lyophilized product and the stopper undergoes minimal contact with the reconstituted solution, there is a concern that undesirable compounds (volatiles and non-volatiles) may leach out from the stopper during prolonged storage of vials and may become adsorbed on the powder contents. In addition, the relatively large amount of product in the vial (ca. 2.6 g), provides a large surface area for the adsorption of potential leachables. Therefore, at the FDA

recommendation and upon the Applicant agreement, these studies will be conducted post approval via a Post-Marketing Commitment (PMC).

The long-term and accelerated stability data, including the updated stability results submitted in the NDA amendment, as agreed prior to the submission of the NDA, indicate that the proposed drug product is stable under the recommended in the labeling storage conditions. There are no out of specification results and no obvious trends for vials stored at 25°C/60% RH for up to 12 months, 40°C/75% RH for 6 months, and in the light cabinet. The widest range was observed for Impurity A but that appears to be caused by variations in the initial values rather than by trends in the data. In addition, a statistical analysis was performed and provided in the NDA, which projects a shelf life of at least 24 months. Based on the analysis of the stability information provided in the NDA for the proposed drug product, including long term stability data for primary batches (12 months + 9 months + 9 months), the proposed expiration dating period of 24 months with the storage statement: "Store vials at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15-30°C (59-86°F) [see USP, Controlled Room temperature (CRT)]" was found acceptable.

The proposed drug product manufacturing process includes (b) (4) This general manufacturing procedure was used in the manufacture of the three drug product registration batches. The commercial manufacturing process will follow the same procedure (b) (4) as compared to the exhibit batches. During the NDA review several comments regarding the in-process tests and acceptance criteria, and the executed batch records, including process yield reconciliations, were conveyed to and addressed by the Applicant. The overall information regarding the manufacturing process provided in the initial NDA submission and subsequent amendments was found acceptable.

No deficiencies for the proposed drug product, (b) (4) components (b) (4) meropenem trihydrate powder, (b) (4) vaborbactam powder and (b) (4) sodium carbonate) were identified from the product quality microbiology perspective. (b) (4) validation for the (b) (4) manufacturing areas at (b) (4) for meropenem and sodium carbonate were provided in DMFs. The (b) (4) validation of the vaborbactam drug substance and the filling facility were addressed in the NDA. The product quality microbiology information provided in the NDA for the drug product that included container closure integrity, (b) (4) used for the final product, (b) (4) validation, media fill runs, bacterial endotoxin method validation was also found acceptable.

The biopharmaceutics review focused on the evaluation of the in vitro data supporting the bridging between the drug product used in the pivotal clinical studies (a multi-vial configuration) and the commercial drug product (to be supplied as a single vial containing both drugs). The comparative physiochemical characteristics of the infusion solutions (i.e. pH and osmolality) along with the drug products composition, dose, reconstitution and dilution volumes, were found acceptable to support the bridge between the proposed single-vial and the multi-vial drug products.

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) for meropenem and vaborbactam in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. Additional information was requested from the applicant to support the claim for vaborbactam, given the drug is a new molecular entity and a new class of cyclic boronates. The provided information, as well as other information obtained by FDA, was reviewed, and the claim for a categorical exclusion from an EA was found to be acceptable.

The meropenem (b) (4) and vaborbactam (b) (4) drug substances are manufactured by (b) (4) respectively. The manufacture of (b) (4)

The finished drug product manufacture (b) (4)), packaging and testing are performed at Facta Farmaceutici S.p.A., Italy. In addition, several other facilities are involved in the manufacture of meropenem (b) (4) and drug substances testing.

Following a completion of the review of all facilities associated with the NDA and the referenced DMFs, there are no outstanding issues that prevent approval of this NDA. A pre-approval inspection was conducted to support the manufacturing of vaborbactam, the new molecular entity. A re-inspection of the drug product manufacturing facility (Facta) confirmed the desk review of the data reliability package for the current NDA and determined the Warning Letter citations were adequately resolved to find the facility acceptable. Therefore, the overall recommendation of "Approve" was entered for this NDA into Panorama by OPF on August 28, 2017.

C. Special Product Quality Labeling Recommendations (see labeling review)

D. Final Risk Assessment (see Attachment I)

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Microbiology

CHAPTER V: Biopharmaceutics

CHAPTER VI: Facilities

CHAPTER VII: Labeling

CHAPTER VIII: Environmental Assessment

ATTACHMENT I: Risk Assessment

CHAPTER I: Drug Substance

Steven Frisbee

Digitally signed by Steven Frisbee
Date: 6/12/2017 03:49:50PM
GUID: 54b0011d0005b2d52216cec7d7d58953

Christine Falabella

Digitally signed by Christine Falabella
Date: 6/12/2017 03:53:25PM
GUID: 53b44f29000133dc0402c48649d4d56a

MICROBIOLOGY

Product Background: The product is a sterile powder (b) (4) of two antibiotics and an excipient. Each of the antibiotics and the excipient is (b) (4) The components are then (b) (4)

NDA: 209-776

Drug Product Name / Strength: meropenum-vaborbactam for injection
1000 mg/1000 mg per vial
Route of Administration: Intravenous

Applicant Name: Rempex Pharmaceuticals (wholly owned subsidiary of The Medicines Company)

Manufacturing Sites:

(b) (4)

Facta Farmaceutical S.p.A. Italy: (b) (4)

Method of Sterilization: (b) (4)

Review Summary: ADEQUATE

The drug product is a (b) (4) meropenum powder, (b) (4) vaborbactam powder and (b) (4) sodium carbonate. (b) (4) validation for the (b) (4) manufacturing areas at (b) (4) validation for the meropenum and the excipient sodium carbonate were provided in DMFs. The (b) (4) validation of the vaborbactam and the finish/fill facility were addressed in this NDA application. There were not any deficiencies noted in the information provided.

List Submissions being reviewed:

Original Submission: 29 December 2016

Highlight Key Outstanding Issues from Last Cycle: NA

Concise Description Outstanding Issues Remaining: None

Referenced Drug Master Files (DMF):

(b) (4)

23 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Denise Miller

Digitally signed by Denise Miller
Date: 5/11/2017 08:16:48AM
GUID: 508da7280002a5d546459b998253d1aa

Bryan Riley

Digitally signed by Bryan Riley
Date: 5/12/2017 09:04:29AM
GUID: 503450f200004f5816a1d3ae902b5e91

BIOPHARMACEUTICS

Product Background:

NDA: 209776

Drug Product Name / Strength: Tradename® (meropenem and vaborbactam) for injection, 1000 mg/1000 mg per vial

Route of Administration: intravenous

Applicant Name: Rempex Pharmaceuticals, a wholly owned subsidiary of The Medicines Company

Review Summary:

Submission: Rempex Pharmaceuticals submitted Original NDA 209776 for Tradename® (meropenem and vaborbactam) for Injection indicated for the treatment of complicated urinary tract infections, including pyelonephritis. This NDA is being submitted under Section 505(b)(2) of the FD&C Act as it partially relies on the Agency's previous findings of safety and effectiveness for meropenem. The listed drug product (LD) is MERREM® (meropenem for Injection, 500 mg/vial and 1000 mg/vial, NDA 050706, AstraZeneca UK Ltd.). Vaborbactam is a novel beta-lactamase inhibitor and is a new molecular entity (NME).

Review Objective: Evaluation of the in vitro data supporting the bridging of formulations between the pivotal clinical (multi-vial) and the commercial drug product (single-vial).

Reviewer's Assessment: The provided in vitro comparison data for the formulation compositions, dose, reconstitution and dilution volume, and physiochemical characteristics (i.e. pH and osmolality) for infusion support the bridge between the proposed single-vial and the clinical multi-vial drug products. The proposed commercial single-vial drug product is expected to be bioequivalent to the clinical multi-vial drug product.

Conclusion and Recommendations: From the Biopharmaceutics perspective, NDA 209776, Carbavance (meropenem and vaborbactam) for injection, 1000 mg/1000 mg per vial is recommended for **APPROVAL**.

List Submissions being reviewed (table):

eCTD #	Received date	Document
0001	12/29/2016	Original Submission
0018	4/12/2016	Quality/Response to Information Request

Highlight Key Outstanding Issues from Last Cycle:

N/A, this is the first review cycle.

Concise Description Outstanding Issues Remaining:

None.

BCS Designation

Reviewer's Assessment: N/A

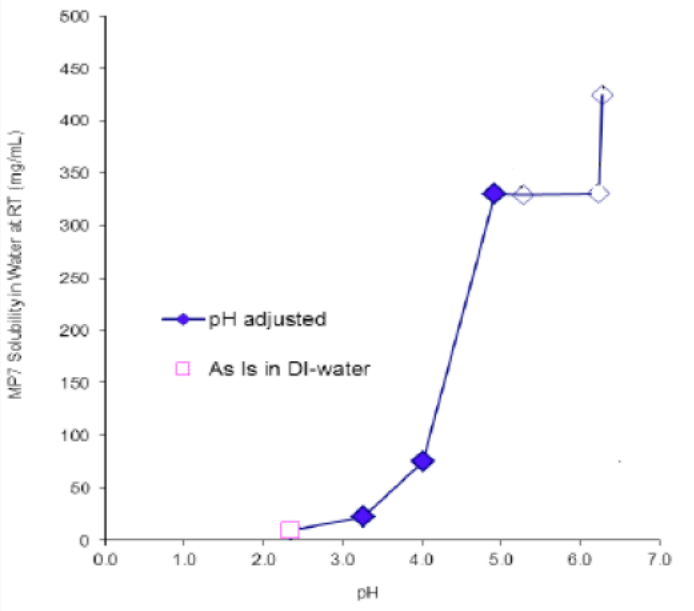
BCS Class designation is not applicable to non-orally administrated drug product.

Solubility:

Meropenem: The drug substance Meropenem trihydrate is a free acid. It is soluble in water as a sodium salt. (b) (4)

Vaborbactam: The drug substance Vaborbactam is a free acid. It is slightly soluble in water and freely soluble in water in a pH-dependent manner (i.e., > 350 mg/ml above pH 5, **Figure 1**).

Figure 1: Vabobactam Solubility Profile at Various pH



Note: Open diamonds indicate samples were not at equilibrium

Permeability:

Meropenem: Not reported

Vaborbactam: Not reported.

Dissolution: N/A

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: N/A

{Assess method development, method robustness, and criteria; modeling approach}

The proposed dosage form is a powder for injection to be reconstituted and further diluted to yield a solution for intravenous administration; therefore, there is no need for dissolution testing.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: N/A

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: N/A

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: N/A

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: N/A

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: N/A

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: N/A

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: N/A

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: N/A

Bridging of Formulations

Reviewer's Assessment: Acceptable

The product used in the clinical trials is the multi-vial presentation of meropenem and vaborbactam. The multi-vial drug product is comprised of individual vials of meropenem for Injection (1000 mg/vial) and vaborbactam for Injection (500 and 1000 mg/vial). Meropenem for Injection was supplied by several commercial sources (Table 1). Vaborbactam for Injection vials were supplied by various contract-manufacturing organizations (Table 2).

Table 1: Batches of Meropenem for Injection Used in Clinical Trials

Meropenem for Injection Lot Number	Strength (mg/vial)	Drug Product Manufacturer	Clinical Study Number
13062D	1000	Astra Zeneca	501
0016D31	1000	APP[1]	503
0023D31	1000	APP	504
0049D3	1000	Facta Farmaceutici[2]	505, 506
0001D5	1000	Facta Farmaceutici	505, 506

1. APP sells Meropenem for Injection commercially in the US. Batches purchased from APP were manufactured by (b) (4) (b) (4)
2. Manufactured solely for clinical use, but released against Facta Farmaceutici, S.p.A commercial specifications

Notes: Clinical Study 501, Study 503, and Study 504 are Phase I studies. Study 505 and Study 506 are Phase III studies.

Table 2: Batches of Vaborbactam for Injection Used in Clinical Trials

Vaborbactam for Injection Lot Number	Strength (mg/vial)	Drug Product Manufacturer	Vaborbactam Manufacturer	Vaborbactam Lot Number	Clinical Study Number
1-FIN-1521	500	(b) (4)		1207MP702	402
CL3-001	500			1212MP702	402, 501
CL3-402	500			RP01L104A0	501, 503, 504
CL4-017	500			LTRE7A1001	505, 506
CL4-024	1000			LTRE7A1001	505, 506
CL4-373	1000			LTRE7A1001	Not used
CL5-001	1000			LTRE7A2004	505, 506
CL5-002	1000			LTRE7A2005	505, 506
CL5-003	1000			LTRE7A2006	Not used

1. (b) (4)
2.

The proposed commercial drug product for Meropenem-Vaborbactam for Injection is a single vial combination drug product, [redacted] (meropenem trihydrate and vaborbactam) and the excipient sodium carbonate. The quantitative composition of the commercial drug product in the single vial is shown in **Table 3**.

The Applicant reported that the pH of the reconstituted single-vial product is about 7.9 and the osmolalities when diluted to 8 mg/mL and 2 mg/mL are approximately 430 mOsmol/kg and 318 mOsmol/L respectively.

Table 3: Composition of Meropenem-Vaborbactam for Injection

Component	Reference to Standard	Function	Labeled Content Per Vial*
Meropenem Trihydrate	USP, Ph.Eur., Sterile	Active Ingredient	1140 mg**
Vaborbactam	In-house, Sterile	Active Ingredient	1000 mg
Sodium Carbonate	NF, Ph.Eur, Sterile	[redacted]	575 mg
[redacted]			

Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia, NF = National Formulary
* There is a [redacted]% overfill per vial ([redacted] mg of each meropenem and vaborbactam) to allow for delivery of the labeled content.
** Meropenem drug substance is provided as trihydrate. 1140 mg of meropenem trihydrate is equivalent to 1000 mg of meropenem anhydrous. With [redacted]% overfill, [redacted] mg of meropenem anhydrous is equivalent to [redacted] mg of meropenem trihydrate.

There are no in vivo comparative BA data between the proposed commercial drug product (single-vial) versus the product used in the pivotal clinical studies (multi-vial). In Submission 018 (dated 04/12/2017) in response to the IR (dated 04/06/2017; Refer to the below List of Deficiencies), the Applicant provided the in vitro comparative data between the single-vial vs. multi-vial drug products with respect to the quantitative compositions (before reconstitution), dose, reconstitution and dilution volume, and physiochemical characteristics (i.e. pH and osmolality) of the infusion solution (**Tables 4-6**).

As shown in **Table 4**, the proposed single-vial formulation differs from the clinical multi-vial formulation [redacted] The multi-vial formulation for Vaborbactam uses [redacted].

Both the proposed single-vial and the clinical multi-vial products contain same amount of the active ingredients, same dose per infusion, and are diluted to the same final concentration 8 mg/mL for infusion for each of meropenem and vaborbactam (**Table 5**). The infusion volume and the infusion time are the same between the single-vial and multi-vial products.

Table 4: Comparison of the Proposed Commercial Drug Product (Single-Vial Presentation) vs. the Drug Product used in Pivotal Clinical Studies (Multi-Vial) – Before Reconstitution

Per Vial	Single-Vial	Multi-Vial	
	Meropenem-Vaborbactam for Injection	Meropenem for Injection	Vaborbactam for Injection
Meropenem (mg)	1000	1000	NA
Vaborbactam (mg)	1000	NA	1000
Sodium Carbonate (mg)	575	(b) (4)	NA
(b) (4)			

Table 5: Comparison of the Proposed Commercial Drug Product (Single-Vial) vs. the Drug Product used in Pivotal Clinical Studies (Multi-Vial) – After Reconstitution and Dilution

	Single-Vial	Multi-Vial	
	Meropenem-Vaborbactam for Injection	Meropenem for Injection	Vaborbactam for Injection
Dose per Infusion	2000 mg meropenem 2000 mg vaborbactam	2000 mg meropenem	2000 mg vaborbactam
Reconstitution Volume	20 mL/vial	20 mL/vial	10 mL/vial
Infusion volume	250 mL		
Infusion Time	3 hours		
Concentration for Infusion	8 mg/mL each of meropenem and vaborbactam		

(b) (4)

The pH data provided in **Table 6** from 3 lots of the proposed single-vial products confirmed that the pH after reconstituted and dilution is in the range of 7.77-7.98, which is similar to that of the reconstituted and diluted multi-vial products (7.78-7.80).

It should be noted that there is a difference between the osmolality of drug product solution obtained after reconstitution and dilution using the single vials (429-439 mOsm/Kg) vs. the multi-vial (389-394 mOsm/Kg), which is expected based on the differing amounts of the excipient, sodium carbonate. In general, the normal osmolality range for IV infusions is in the

range of the average serum osmolality 298 mOsmol/Kg ± 50 mOsm/Kg. Both the multi-vial and single-vial drug products are approximately 50 mOsm higher than the physiological osmolality and are hypertonic. However, since the osmolality for both products is lower than 500 mOsmol/Kg that might be a cause of infusion phlebitis, the difference in osmolality between the the single vial and multi-vial product (< 50 mOsm) is not a concern when considering the safety of the proposed drug product.

Table 6: Comparison of pH, Osmolality and Impurity Profiles of reconstituted diluted Meropenem-Vaborbactam solutions, Single-Vial vs. Multi-Vial

	Reconstituted and Diluted with Saline at 8 mg/mL (Pivotal Clinical Concentration)								
Product Presentation		Multi-vial		Single-vial					
Lot Numbers		0001 D5/ CL5-002		0001 D6		0002 D6		0003 D6	
		Tested after storage at 25°C/60%RH (Months)							
Tests	**Acceptance Criteria**	**0**	**3**	**0**	**3**	**0**	**3**	**0**	**3**
pH	Report Results	7.78	7.80	7.98	7.95	7.88	7.85	7.85	7.77
Osmolality (mOsmol/Kg)	Report Results	389	394	431	439	432	439	429	438
Impurities									
Meropenem Impurity A	(b) (4)								
Meropenem Impurity B									
(b) (4)									
Unknown									
(b) (4)									
Total Impurities									

N.D. = not detected

Considering that the infusion volume, infusion rate, concentrations of meropenem and vaborbactam are the same for the single-vial presentation and multi-vial presentation, and based on the provided comparative data for pH and osmolality between the single-vial and multi-vial formulations, the difference in the excipient sodium carbonate vs (b) (4) is unlikely to significantly affect the BA/BE of the proposed single-vial drug products.

Therefore, overall, the comparative data provided by the Applicant support the bridge between the proposed single-vial and the clinical multi-vial drug products. From the Biopharmaceutics

perspective, the proposed commercial single-vial drug product is expected to be bioequivalent to the clinical multi-vial drug product.

Notes: Defer to Drug Product Reviewer for the adequacy of the impurity and stability data.

Biowaiver Request

Reviewer's Assessment:

The Applicant conducted clinical pharmacokinetic (PK) studies to characterize the proposed combination drug product using the multi-vial presentation comprised of individual vials of meropenem and vaborbactam (See **Table 1** and **Table 2**). The OCP review team will review the human PK data.

Comparative bioavailability (BA) data between the proposed commercial single-vial combination drug product versus the the clinical multi-vial combination product are not provided nor required because an acceptable bridge was established between the single-vial and multi-vial drug products (see the above section "Bridging of Formulation"). Therefore, a biowaiver request is not submitted, nor required.

R Regional Information

Comparability Protocols

Reviewer's Assessment: N/A

N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

N/A

Lifecycle Management Considerations

List of Deficiencies:

IR dated April 6, 2017:

- Provide a side-by-side comparison table of the quantitative compositions for the formulation before reconstitution and also 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.

- Provide a side-by-side comparison table for the physicochemical characteristics such as pH, 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 at least 3 production lots of the proposed reconstituted and diluted commercial drug product and 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.

- 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.

The Applicant has provided acceptable responses (amendment dated 04/12/2017) to the above information requests.

Recommendations:

From the Biopharmaceutics perspective, NDA 209776, Carbavance (meropenem and vaborbactam) for injection, 1000 mg/1000 mg per vial is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

Qi Zhang Ph.D., 05/15/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
I concur with Dr. Zhang's assessment and recommendation
Elsbeth Chikhale, Ph.D., 5/21/2017

Qi
Zhang

Digitally signed by Qi Zhang
Date: 5/22/2017 10:00:51AM
GUID: 547e178000007695c91eb10380b07939

Elsbeth
Chikhale

Digitally signed by Elsbeth Chikhale
Date: 5/23/2017 11:19:03AM
GUID: 50743ccc000031928b54eba1769a5df9

FACILITIES

Product Background: First Review

The drug product is indicated for the treatment of patients with complicated urinary tract infections, including pyelonephritis

NDA: 209776

Drug Product Name / Strength: Meropenem Vaborbactam Powder for Injection (1000mg/1000mg per vial)

Route of Administration: Intravenous

Applicant Name: Rempex Pharmaceuticals a wholly owned subsidiary of The Medicines Company

Review Summary:

Following review of the inspection documentation and application documents, the manufacturing facilities for NDA 209776 are **acceptable**.

List Submissions being reviewed (table):

Reviewed Submissions		
Description	SD # (Sequence)	Date
Original Submission	2 (0001)	29-DEC-2016
Submission of 3rd Party Data Audit Protocol	5 (0006)	9-FEB-2017
Submission of 3rd Party Data Audit Report	9 (0008)	7-MAR-2017
Updates to Vaborbactam Manufacturing Process	36 (0035)	11-AUG-2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

3.2.S.2 Manufacture

11 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Derek Smith

Digitally signed by Derek Smith
Date: 8/28/2017 01:17:11PM
GUID: 508da7480002bfe5d5fe14a12da3599d

Labeling Review
NDA 209776

Review Of Common Technical Document-Quality (Ctd-Q) Module 1

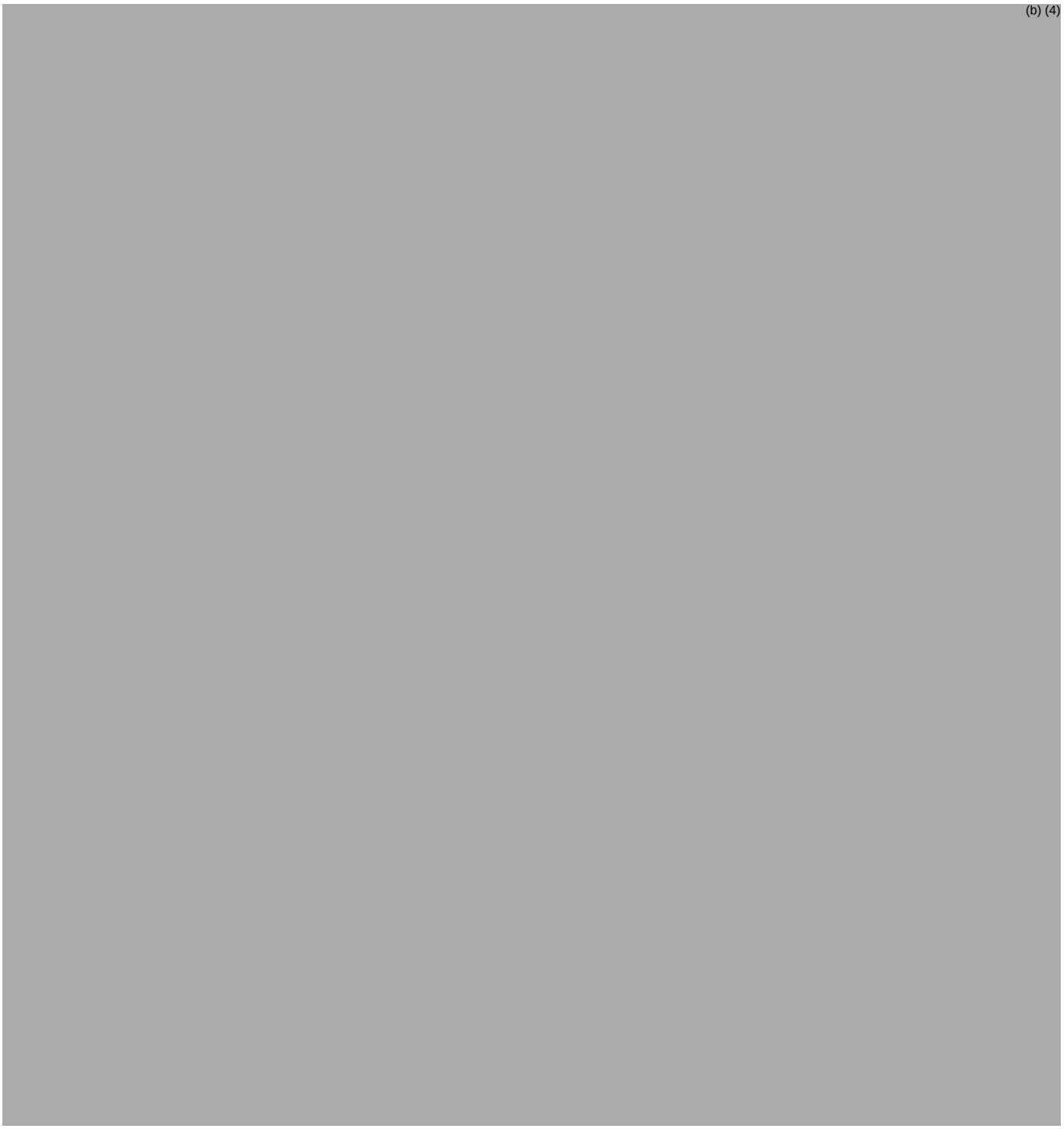
Labeling & Package Insert

A. Carton and Container Label

The carton is as follows.

(b) (4)

An enlarged section of the carton is as follows.



Comments: Adequate. The applicant has been informed (e-mail from Jane Dean 8/14/17) that the container label should state "Single Dose Only" rather than "(b) (4)". Additionally the carton, in conformity with the container label, should contain the statements:

For Intravenous Infusion Only
Single Dose Only
Discard Unused Portion After Use

The storage statement is correct. As amended the carton and container label are acceptable from the CMC point of view.

B. Package Insert

The CMC sections of the Package Insert are as follows.

Section	Contents	Comments
Section 2.3	Preparation and Administration of VABOMERE for Intravenous Infusion	Indicate that the entire reconstituted volume should be withdrawn. Provide a table (Table 2) describing the volumes used to prepare various doses.
Section 3	Dosage Forms and Strengths	Add "and sealed with a rubber stopper and an aluminum overseal".
Section 11	Description	Acceptable
Section 16	How Supplied/Storage and Handling	Acceptable. The Storage Statement is: "Store vials at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°-30°C (59°-86°F) [see USP, Controlled Room temperature (CRT)]".

The label recommendations (Section 2.3) that the constituted solution be further diluted with saline immediately and that infusion of the diluted solution should be completed within 4 hours when stored at room temperature, or within 22 hours when refrigerated are supported by data. This has been emphasized in the label with the phrase "must be **completed**". These comments were conveyed to the clinical review team.

As amended Section 2.3 is as follows.

2.3 Preparation and Administration of VABOMERE for Intravenous Infusion

Preparation

VABOMERE is supplied as a dry powder in a single-dose vial that must be constituted and further diluted prior to intravenous infusion as outlined below. VABOMERE does not contain preservatives. Aseptic technique must be used for constitution and dilution.

1. To prepare the required dose for intravenous infusion, constitute the appropriate number of vials, as determined from Table 2 below. Withdraw 20 mL of 0.9% Sodium Chloride Injection, USP, from an infusion bag and constitute each vial of VABOMERE.

2. Mix gently to dissolve. The constituted VABOMERE solution will have an approximate meropenem concentration of 0.05 gram/mL and an approximate vaborbactam concentration of 0.05 gram/mL. The final volume is approximately 21.3 mL. The constituted solution is not for direct injection.
3. The constituted solution must be diluted further, immediately, in a 0.9% Sodium Chloride Injection, USP infusion bag before intravenous infusion. The intravenous infusion of the diluted solution **must be completed** within 4 hours if stored at room temperature or 22 hours if stored refrigerated at 2°C to 8°C (36°F to 46°F).
4. To dilute the constituted solution, withdraw the full or partial constituted vial contents from each vial and add it back into the infusion bag in accordance with Table 2 below. After dilution, the final infusion concentration of meropenem and vaborbactam will be approximately between 2 mg/mL and 8 mg/mL.

Table 1: Preparation of VABOMERE Doses

VABOMERE (meropenem and vaborbactam) Dose	**Number of Vials to Constitute for Further Dilution**	**Volume to Withdraw from Each Constituted Vial for Further Dilution**	**Volume of infusion bag**
4 grams (2 grams-2 grams)	2 vials	Entire contents (approximately 21 mL)	250-1000 mL
2 grams (1 gram-1 gram)	1 vial	Entire contents (approximately 21 mL)	125-500 mL
1 gram (0.5 gram-0.5 gram)	1 vial	10.5 mL (discard unused portion)	70-250 mL

Visually inspect the diluted VABOMERE solution for particulate matter and discoloration prior to administration (the color of the VABOMERE infusion solution for administration ranges from clear to light yellow). Discard unused portion after use.

Comments: Adequate. Comments have been conveyed to the clinical review team and have been accepted. The term “Single Dose” is used throughout the Package Insert. The storage statement is correct. As amended the Package Insert is acceptable from a CMC point of view.

George Lunn

Digitally signed by George Lunn
Date: 8/16/2017 08:59:33AM
GUID: 508da72000029f40833369b0a181e8b3

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 8/16/2017 10:25:26AM
GUID: 50758d5000003c1b1962e036ea11002c

ENVIRONMENTAL ANALYSIS

Summary: The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) for meropenem and vaborbactam in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. Additional information was requested from the applicant to support the claim for vaborbactam, given the drug is a new molecular entity and a new class of cyclic boronates. The provided information, as well as other information obtained by FDA, was reviewed, and the claim for a categorical exclusion from an EA was found to be acceptable.

R Regional Information

Environmental Analysis

The applicant provided a claim for a categorical exclusion from an EA for meropenem and vaborbactam in accordance with 21 CFR Part 25.31(b). Specifically, the applicant claimed that the peak expected introduction concentration (EIC) of the combination across five years, (b) (4) ppb, is lower than the 1 ppb categorical exclusion value. This peak was calculated from the combined amount for both active ingredients, however, while FDA needs to assess individual ingredient amounts separately. Furthermore, vaborbactam is the first of a novel class of drugs, and it has an EIC that might be close to the exclusion's cutoff of 1 ppb, which generally triggers additional scrutiny at FDA. Therefore, to support the statement of no extraordinary circumstances per 21 CFR 25.15, FDA asked the applicant to provide the following additional information about vaborbactam, to the extent possible: (1) a summary of any available aquatic toxicity data, predicted no-effects concentrations (PNECs), etc. for vaborbactam or similar substances (e.g., other cyclic boronates and/or substances with similar modes of action); and (2) a discussion of vaborbactam's potential for aquatic effects, taking into account this toxicity data, the EIC, and any other relevant and available information or environmental risk assessments.

A summary of applicant responses to FDA is as follows.

1. The individual active ingredient use amounts at the peak (5th) year are (b) (4) kg for meropenam (EIC = (b) (4) µg/L) and (b) (4) kg for vaborbactam (EIC = (b) (4) µg/L).
2. The estimated [or expected] environmental concentration (EEC) in surface water for vaborbactam is (b) (4) µg/L (i.e., the aquatic EIC of (b) (4) µg/L divided by 10 to account for dilution with surface water).
3. No aquatic toxicity data for vaborbactam are available. However:
    a. Predicted no effect concentration (PNEC) data are available for similar substances (i.e., avibactam [PNEC= (b) (4) µg/L], tazobactam [PNEC = (b) (4) µg/L]);

b. In absence of experimentally-derived aquatic toxicity data, ECOSAR v1.113 was used to estimate the aquatic toxicity of vaborbactam, with the lowest modeled chronic value of (b) (4) mg/L, for fish, based on the Amides-acid ECOSAR Class, and an estimated PNEC of (b) (4) µg/L using an assessment factor (AF) of 10;
c. The EEC for vaborbactam is more than three orders of magnitude lower than the lowest PNEC derived from ECOSAR data and other beta-lactamase inhibitor drugs; and
d. Vaborbactam has an estimated log octanol-water partition coefficient (log K_{ow}) of (b) (4), indicating a very low potential for bioaccumulation.

In summary, the applicant states that while experimentally-derived aquatic toxicity data are not currently available for vaborbactam, model predictions for vaborbactam and publicly available aquatic toxicity data for other beta-lactamase inhibitor drugs indicate that the surface water PNEC for vaborbactam is expected to be above the categorical exclusion surface water cutoff of (b) (4) µg/L and the EIC and EEC, confirming that vaborbactam is not reasonably expected to pose serious harm to the environment at the expected level of exposure in accordance with 21 CFR §25.21.

Reviewer's Assessment:

The claims for categorical exclusions from EAs per 21 CFR Part 25.31(b) are appropriate for the anticipated amounts of each drug to be used (b) (4) µg/L EICs), the calculations appear accurate, and adequate statements of no extraordinary circumstances per 21 CFR 25.15 are present.

The exclusion claim for meropenam is acceptable in part due to the likelihood that little or no increase in use is expected from approval of this application, which is relevant to the additional categorical exclusion at 21 CFR Part 25.31(a).

For vaborbactam, additional data provided by the applicant support the claim for the categorical exclusion, with the possible exception of the 10-fold dilution factor used to develop an EEC. This dilution factor is not relevant in the increasing number of municipalities for which most or all of the effluent from a sewage treatment plant form the primary flow of the receiving stream or river. Nevertheless, using the EIC (i.e., the EEC without this dilution factor) still results in more than a two order of magnitude difference from the lowest PNEC. Given these PNECs are uncertain with regard to relevance with an actual PNEC specifically for vaborbactam, FDA also utilized a fish plasma model (FPM) to screen for aquatic risk, per Huggett et al. (2003). The FPM showed that based on an expected introduction concentration (EIC) of (b) (4) µg/L, a therapeutic concentration of (b) (4) µg/mL (Cmax from p. 16 of module 2.5, Clinical Overiew), and a log D of (b) (4) (pH (b) (4); from www.chemicalize.com), the effect ratio (ER) > (b) (4) which is >> (b) (4), the threshold below which Huggett et al. (2003) recommends the need for additional information. Therefore, given the results of the FPM, the results from the comparison of the EIC with PNECs from related drugs, and the conservative assumptions

inherent with the use of the EIC in these calculations (no metabolism, degradation, or dilution), FDA sees no evidence of extraordinary circumstances. The claim for a categorical exclusion from an EA for vaborbactam is acceptable.

Reference: Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

Primary EA Reviewer Name and Date: James P. Laurenson, 5/16/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Scott Furness, 5/19/2017

APPEARS THIS WAY ON ORIGINAL

James Laurenson

Digitally signed by James Laurenson
Date: 5/16/2017 05:01:32PM
GUID: 51dc6bdb0000c62de59b85452e59746f

Michael Furness

Digitally signed by Michael Furness
Date: 5/17/2017 03:43:59PM
GUID: 502e8c7600003dd8331cf6eebf43697a

ATTACHMENT I: Final Risk Assessments

From Initial Risk Identification			Review Assessment		
From Initial Risk Identification	**Review Assessment**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay /Stability	Formulation Raw materials Process parameters Scale/equipment Site	L		Acceptable	
Uniformity of Dose	Formulation Process parameters Scale/equipment Site	M		Acceptable	
Reconstitution time	Formulation Raw materials Process parameters Scale/equipment Site	L	Data demonstrate tight range for stability batches	Acceptable	
Extractables and leachables	Formulation Container closure	M	PMC study to conduct E/L assessment	Acceptable	*Leachable data from stability batches should be evaluated*
Endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	M		Acceptable	
Sterility	Formulation Raw materials	H		Acceptable	

	Process parameters Scale/equipment Site				
Particulate matter	Formulation Raw materials Process parameters Scale/equipment Site	M	The drug product meets <788>	Acceptable	

This NDA is recommended for Approval from the Product Quality perspective.

Dorota M. Matecka -S

Digitally signed by Dorota M Matecka -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300123291, cn=Dorota M Matecka -S
Date: 2017.08.28 16:00:58 -04'00'

On behalf of OPQ Team
Dorota Matecka, Ph.D. ATL for NDA 209776

FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: June 19, 2017

To: George Lunn, CMC Reviewer
Dorota Matecka, CMC Lead

Through: Hongping Ye, Ph.D., Acting Lab Chief, Branch II, CDER/OPQ/OTR/DPA

From: Daniel J. Mans, Ph.D., Chemist, CDER/OPQ/OTR/DPA
Nisarga Phatak, Ph.D., ORISE Fellow, CDER/OPQ/OTR/DPA
Laura Pogue, Ph.D., Method Verification Coordinator, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 209776: Carbavance (meropenem and vaborbactam) powder for injection

The following methods were evaluated and are *not acceptable* for quality control and regulatory purposes:

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

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the methods:

Note: As a result of failing results for several system suitability criteria for both methods, DPA performed a check analysis by a second analyst on a separate HPLC system. After obtaining failing system suitability results for the Drug Substance method once again, it was determined there was no need to use additional resources for a check analysis of the Drug Product method as it was confirmed to be a method issue and not an analyst or system issue. In addition, without successful system suitability results, results for the actual drug substance and drug product are invalid and therefore, not included in this report.

Original analyst worksheets can be viewed using this ECMS link:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f881123813

Summary of Results

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

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 DPA that it was identified as (b) (4). DPA suggests that the RRTs be more closely evaluated.

4. The original reviewer request for this work was in reference to (b) (4) and (b) (4) The reviewer stated that the firm claims these two impurities were formed during the sample preparation step of analysis and therefore, they created a new method in which they were not present. This is not the case. The method tested DOES see these two impurities but they are BELOW the limit set by the firm.

David Keire

Digitally signed by David Keire
Date: 6/19/2017 07:37:14PM
GUID: 508da7360002b1349aadf16617d62a00

APPEARS THIS WAY ON ORIGINAL