CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212819Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212819
Review # 2

Drug Name/Dosage Form	imipenem/cilastatin/relebactam/ Powder for Injection
Strength	500 mg imipenem, 500 mg cilastatin, 250 mg relebactam
Route of Administration	Intravenous/IV
Rx/OTC Dispensed	Rx
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
eCTD 0043	*6/24/2019*	*Labeling/Quality*
eCTD 0039	*5/31/2019*	*Quality*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Mohd Kabir Shahjahan	Suong Tran
Drug Product	George Lunn	Balajee Shanmugam
Process	David Acevedo Santana	Steven Frisbee
Microbiology	Samata Tiwari	Neal Sweeny
Facility	David Acevedo Santana	Steven Frisbee
Biopharmaceutics	N/A	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika E. Englund	
Laboratory (OTR)	N/A	
ORA Lead	Caryn McNab	
Environmental	Refer to DP review	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS and CONSULTS

See Review #1

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. 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 April 15, 2019. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. Summary of Quality Assessments

A. Product Overview

This NDA provides for a single strength of a fixed dose combination of cilastatin, imipenem, and relebactam (500/500/250 mg) as a sterile powder for injection presented in a single-dose vial. See Review #1 for the complete product overview.

1	⇦ **Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	(b) (4)

Duration of Treatment	500/500/250 mg imipenem/cilastatin/relebactam by IV infusion over 30 minutes every 6 hours.
Maximum Daily Dose	2000/2000/1000 mg imipenem/cilastatin/relebactam
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

See Review #1

Comparability Protocol:

See Review #1

Drug Product:
Review #1 described that there were 2 pending IRs, which are discussed below.

The original study for the compatibility with co-administered drugs was submitted to NDA 212819 on 11/16/2018 and studied the product over 4 hours. Only physical compatibility was studied (appearance, turbidity and particulate matter), and in that study one drug was found to be incompatible: propofol. There was no information regarding the chemical compatibility and the following information request was sent on 04/09/2019:

In Section 3.2.P.2.6.5 you conducted a Y-site compatibility study with other injectable drugs and monitored the solutions for appearance, turbidity, and particulate matter. Please also provide the assay values of imipenem, cilastatin, and relebactam and the levels of degradants that are formed in solution.

The applicant responded on 05/03/2019, but did not provide the requested chemical compatibility data. They described that the primary degradation mechanism is due to (b) (4) Note, the current Primaxin labeling does not list the compatibility of the product with other drugs

A comment was included in the PI that CMC does not agree with the listing of the compatible drugs in the labeling without the supporting chemical compatibility data. The compatible drugs listed in the PI should be supported by both physical and chemical compatibility.

The original NDA submission did not include the compatibility data for all of the diluents listed in the labeling. The compatibility data for the product in all diluents was requested during a teleconference with the applicant:

In order to further support the inclusion of these two diluents (5% dextrose + 0.45% sodium chloride and 5% dextrose + 0.225% sodium chloride) in the product labeling and as agreed at the teleconference on 4-April-2019, the applicant will provide in-use compatibility for these two diluents by 1-June-2019.

The applicant provided the requested data on 5/31/2019. (b) (4)

(b) (4)

The applicant responded on 6/24/2019 and described that they reassessed the suitability of the product (b) (4)

This proposal is acceptable from a CMC perspective.

Microbiology:

See Review#1

Process and Facilities:

See Review #1

Biopharmaceutics:
the original Biopharmaceutics review dated 04/09/2019 in Panorama, was based on the notion that the NDA's basis for approval relied only on the Phase 3 pivotal clinical studies using the proposed to-be-marketed drug product. Upon further discussion with the Clinical Team, Biopharmaceutics was informed that the NDA relies also on the two Phase 2 clinical studies (PN003 and PN004), which did not use the proposed to-be-marketed (commercial) drug product. Therefore, the bridging between the drug products used in the Phase 1/2 and Phase 3 Clinical studies is being addressed in this review addendum.

The phase 1 and 2 formulations included (b) (4) The phase 1 and 2 formulations also included (b) (4) The proposed dosing for the to-be-marketed FDC-drug product is justified/supported with the overall PK/clinical data and is being evaluated by the Clinical Pharmacology team. With respect to (b) (4) the Biopharmaceutics perspective, (b) (4) of the proposed FDC-drug product. Moreover, the Clinical Pharmacology team confirmed that the PK in healthy subjects taking co-administration of IMI+formulation C (PN001, PN012, PN003 and PN004) and healthy subject taking formulation D (PN0013 and PN019) are comparable.

This NDA is recommended for approval from a Biopharmaceutics perspective. For further details, refer to the review by Elsbeth Chikhale.

Environmental Assessment:

See Review #1

Labeling:

See Review #1

C. Special Product Quality Labeling Recommendations (NDA only)

See Review #1

D. Final Risk Assessment (see Attachment)

See Review #1

Erika Englund

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BIOPHARMACEUTICS-REVIEW ADDENDUM

Product Background:

NDA: 212819 (505(b)(2))

Drug Product Name / Strength: Cilastatin/Imipenem/Relebactam, 500 mg/500 mg/250 mg Injection (Powder for Solution)

Route of Administration: Intravenous Infusion

Applicant Name: Merck Sharp and Dohme Corp.

REVIEW ADDENDUM:

This Biopharmaceutics Review Addendum replaces the original Biopharmaceutics review for NDA 212819.

It is noted that the recommendation provided in the original Biopharmaceutics review dated 04/09/2019 in Panorama, was based on the notion that the NDA's basis for approval relied only on the Phase 3 pivotal clinical studies using the proposed to-be-marketed drug product. However; upon further discussion with the Clinical Team, Biopharmaceutics was informed that the NDA relies also on the two Phase 2 clinical studies (PN003 and PN004), which did not use the proposed to-be-marketed (commercial) drug product. Therefore, the bridging between the drug products used in the Phase 1/2 and Phase 3 Clinical studies is being addressed in this review addendum.

REVIEW SUMMARY:

Background: The proposed Cilastatin/Imipenem/Relebactam Fixed-Dose Combination (FDC) Injection product received Qualified Infectious Disease Product (QIDP) and Fast Track designations.

***Clinical Pharmacology Studies*:** The clinical pharmacology program consisted of 7 studies in a total of 265 healthy male and female subjects, 232 of whom received relebactam alone (REL, Formulation B or C described in the Table 2 below), Primaxin® co-infused with relebactam (IMI + REL), or cilastatin, imipenem, relebactam as an FDC (IMI/REL) product (study PN019); the remaining subjects received either placebo alone or IMI + placebo. A Population-PK approach was used to evaluate REL and imipenem PK in healthy subjects, renally impaired subjects and patients with active bacterial infection using data from 7 Phase 1 studies (PN001, PN002, PN005, PN007, PN009, PN012 and PN019), two Phase 2 studies (PN003 and PN004) and one Phase 3 study (PN013). Intensive PK sampling was available from the Phase 1 studies, whereas sparse PK sampling was available from the Phase 2 and 3 studies. In total, 624 patients and 231 healthy subjects were studied, with subjects receiving doses in the range of 25 to 1150 mg and 250 to 500 mg for relebactam and imipenem, respectively. In PN001, it was demonstrated that

there was no clinically relevant DDI between REL and cilastatin. Therefore, co-administering IMI with REL as an FDC is expected to have no effect on the PK of cilastatin. Moreover, cilastatin protects imipenem from degradation by enzyme dihydropeptidase in human kidneys, so any clinically meaningful change in cilastatin PK would also manifest as a clinically meaningful change in imipenem PK. Considering this rationale, a Population-PK model for cilastatin was not pursued.

Clinical Studies: Two dose-ranging Phase 2 (PN003 and PN 004) comparator-controlled clinical studies were conducted in patients, using IMI + REL, to support the safety and efficacy of the proposed drug product. In addition, a pivotal, double-blind Phase 3 study (PN0013) using the proposed FDC (IMI/REL) was conducted to support the efficacy and safety of the proposed FDC-drug product.

Table 1:
Phase 2 and 3 Trials

Study Type	Study Number	Title	N
Study Reports and Related Information of Controlled Clinical Studies Pertinent to the Claimed Indication	PN003	A Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone in Patients with Complicated Urinary Tract Infection	302 randomized; 198 treated with IMI + REL
	PN004	A Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone in Patients with Complicated Intra-Abdominal Infection [cIAI]	351 randomized; 231 treated with IMI + REL
	PN013	A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Estimate the Efficacy and Safety of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem/Cilastatin in Subjects with Imipenem-Resistant Bacterial Infection	50 enrolled; 34 treated with IMI/REL

Furthermore, it is noted that the Applicant is also relying, in part, on the FDA's prior findings of safety and effectiveness of the listed drug Primaxin® (imipenem and cilastatin) for Injection (approved under NDA 50587, referred to as IMI). The Applicant claims that the data contained within this NDA combined with the FDA's previous findings of safety and efficacy with Primaxin® (IMI) support the clinical use of the proposed drug product for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in patients 18 years and older with limited or no alternative therapies available caused by gram-negative bacteria.

Proposed FDC-Drug Product: The dosage form of the proposed FDC-drug product is powder for solution, to be administered as intravenous infusion over 30 minutes every 6 hours. The drug product is a clear solution when diluted in normal saline or 5% dextrose solutions. Therefore, there is no need for drug release or dissolution testing.

Bridging of Drug Products Used in Phase 1, 2, and 3 Studies: Table 2 below shows the different formulations of the drug products used in the Clinical Pharmacology and Clinical studies.

Table 2:
Formulations Used in Clinical Trials and Proposed Commercial Formulation

Ingredient	Amount (mg)/Vial				
	Commercial Formulation of IMI (Phase 1 and 2)	Formulation B (Phase 1)	Formulation C (Phase 1 and 2)	Formulation D (Phase 3 and PN019)	Proposed Commercial Formulation
Imipenem[a]	(b) (4)			500	500
Cilastatin[b]				500	500
Sodium bicarbonate				20	20
Relebactam[c]				250	250
					(b) (4)

The proposed to-be-marketed/commercial FDC-drug product has the same formulation as formulation D, used in a Phase 1 study (PN019), the pivotal Phase 3 clinical trial (PN013) (b) (4) However, to support the approval of this NDA, the Applicant is also relying on the data from two Phase 2 clinical studies (PN003 and PN004), which used the listed drug Primaxin® (imipenem and cilastatin) for Injection, co-administered with formulation C. The products (2 vials referred to as IMI+REL) used in the two Phase 2 studies

(PN003 and PN004), differ from the proposed (1 vial) FDC drug product (b) (4) (b) (4) (b) (4) The proposed dosing for the to-be-marketed FDC-drug product is justified/supported with the overall PK/clinical data and is being evaluated by the Clinical Pharmacology team.

With respect to the difference in excipients between the Phase1/2 and Phase 3 product-formulations, from the Biopharmaceutics perspective, (b) (4) (b) (4) (b) (4) is not expected to have an impact on the PK (distribution, metabolism, and elimination), safety, and/or efficacy of the proposed FDC-drug product. Moreover, the Clinical Pharmacology team confirmed that the PK in healthy subjects taking co-administration of IMI+formulation C (PN001, PN012, PN003 and PN004) and healthy subject taking formulation D (PN0013 and PN019) are comparable. For specific information, refer to Attachment 1 of this review, which includes the pharmacokinetic bridging report, authored by Dr. Eliford Kitabi, Clinical Pharmacology Reviewer, DPM, OCP.

(b) (4)

In conclusion, Biopharmaceutics considers that the overall information/data provided in this NDA, support the bridge between the drug products used in the Phase 2 and Phase 3 PK/Clinical studies, as well as the bridge between the proposed and listed drug products.

RECOMMENDATION:

NDA 212819 for Cilastatin/Imipenem/Relebactam, 500 mg/500 mg/250 mg Injection (Powder for Solution for parental IV Infusion) is recommended for **APPROVAL** from a Biopharmaceutics perspective.

Biopharmaceutics Team Lead Name and Date: Elsbeth Chikhale, Ph.D., 6/14/2019

Biopharmaceutics Branch Chief Name and Date: Angelica Dorantes, Ph.D., 6/14/2019

ATTACHMENT 1

Includes;

Clinical Pharmacology Bridging Assessment Report

"***Pharmacokinetic Bridging Between Co-Formulation and Separate Formulations of Imipenem and Relebactam***"

Authored by
Dr. Eliford Kitabi, Clinical Pharmacology Reviewer, DPM, OCP

Pharmacokinetic bridging between co-formulation and separate formulations of imipenem and relebactam

Review question:

1. Are the imipenem and relebactam PK parameters comparable between co-formulation and separate formulations of imipenem and relebactam after single dose infusions in humans?

Data:

Pharmacokinetic profiles after the first dose of the co-formulation of imipenem/relebactam were available from a phase 1 study (PN-019) and a phase 3 study (PN-013). Similarly, first-dose PK profiles after co-administration of separate formulations of imipenem and relebactam were available from phase 1 studies (PN-001, PN-002, PN-005, and PN-012) and two phase 2 studies (PN-003 and PN-004). However, while subjects in studies PN-012, PN-013 and PN-019 received relebactam 250mg, no subjects received relebactam 250 mg in studies PN-002, and PN-005; these studies were removed from the analysis. Subjects in studies PN-001 and PN-012 who received relebactam 125mg were also excluded from the analysis. Samples in study PN-019 obtained after co-administration with probenecid were also removed from the analysis. The number of analysed subjects from each study are given in table 2.

Results:

Figures 1 and 2 show concentration-time profiles for imipenem and relebactam respectively for each individual subject in studies PN-001, PN-012 and PN-019. By comparing imipenem intensive profiles betweeen co-formulation and separate formulations, the two modes of administrations have comparable PK profiles. Similarly, relebactam profiles are comparable between the modes of administrations. Figures 1 and 2 show sparse imipenem and relebactam concentrations over-time respectively from the phase 2 studies (PN-003, and PN-004) and a phase 3 study (PN-013). The figure shows that the imipenem and relebactam concentrations are comparable between co-formulation and separate-formulation modes of administration. Sparse data profiles from PN-013 seem to be consistent with the intensively sampled data, except for some outliers.

Table 1 shows geometric mean and corresponding 95% confidence interval of imipenem and relebactam concentrations, 30 minutes after start of infusion (Cmax). There is no difference in imipenem and relebactam Cmax between the co-formulation and the separate formulations.

Conclusion:

Co-formulation and separate formulations of imipenem and relebactam provides comparable Cmax of imipenem and relebactam. The intensive and sparsely sampled PK profiles are also comparable.

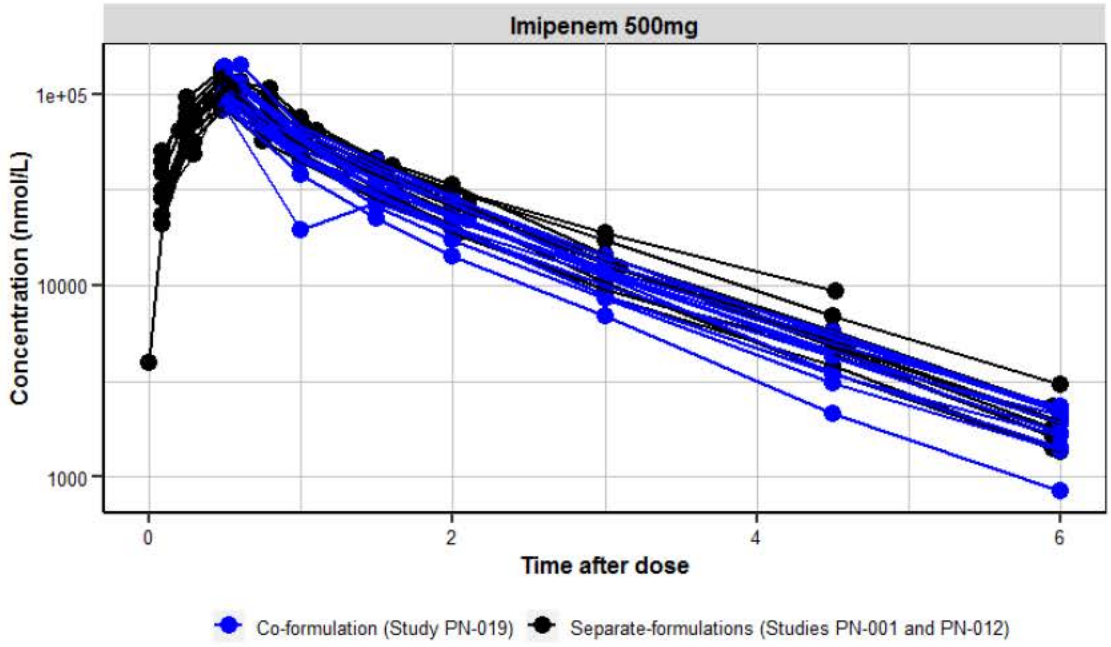

Figure 1: Imipenem concentration-vs-time profiles after single dose administration of imipenem 500mg in phase 1 studies PN-001, PN-012, and PN-019

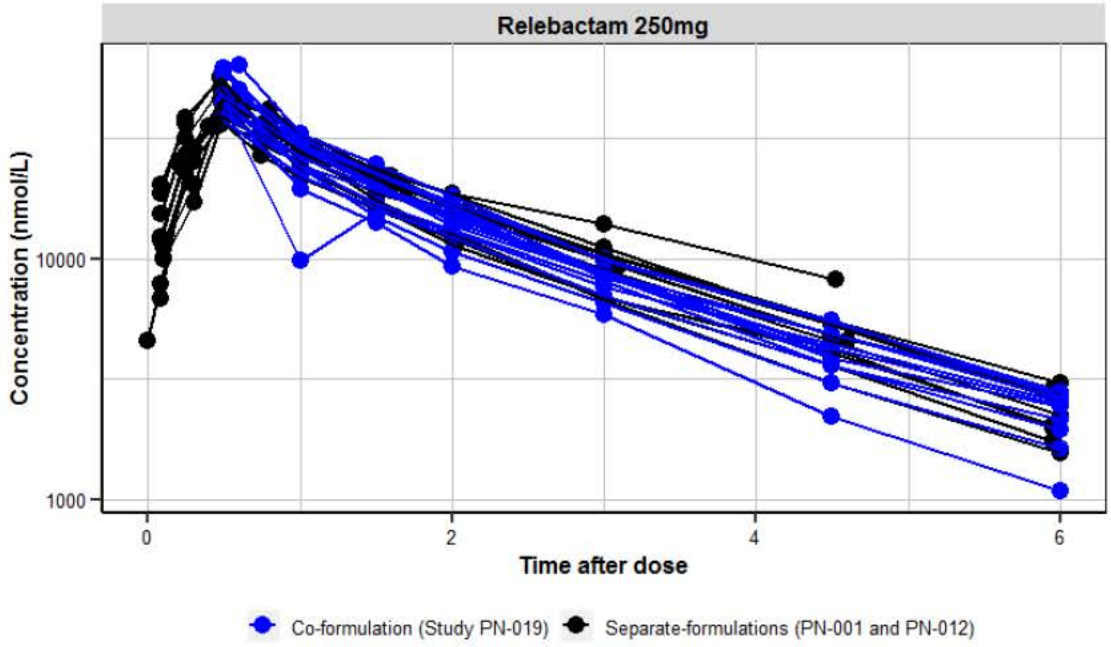

Figure 2: relebactam concentration-vs-time profiles after single dose administration of relebactam 250mg in phase 1 studies PN-001, PN-012, and PN-019

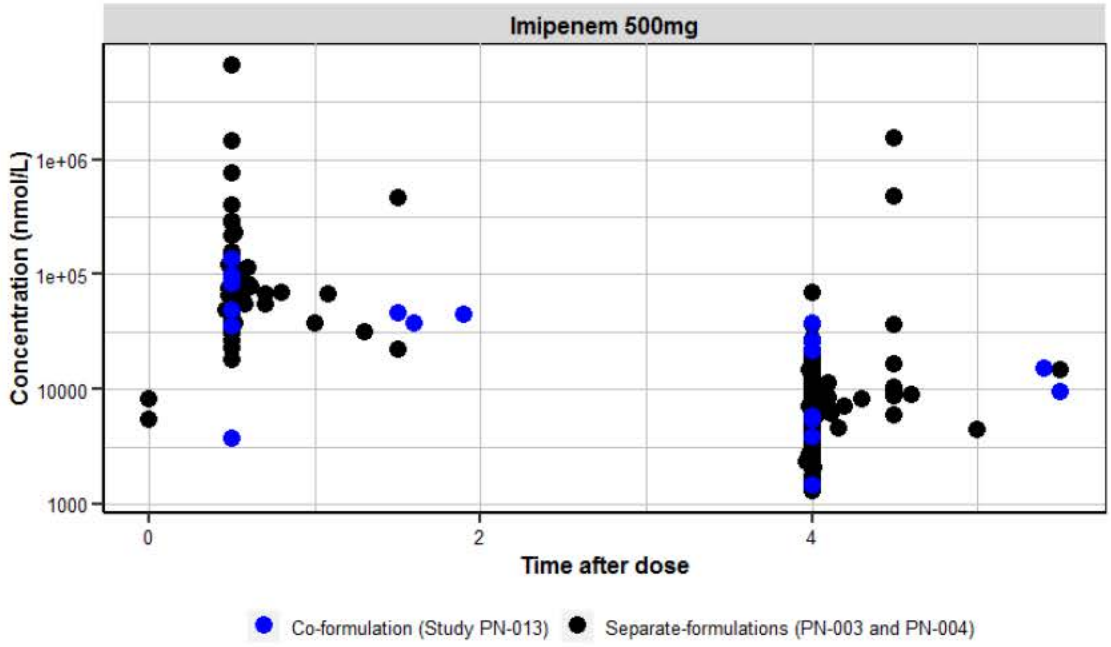

Figure 3: Imipenem concentration-vs-time profiles after first dose of imipenem 500mg in phase 2 studies (PN-003, PN-004), and a phase 3 study (PN-013)

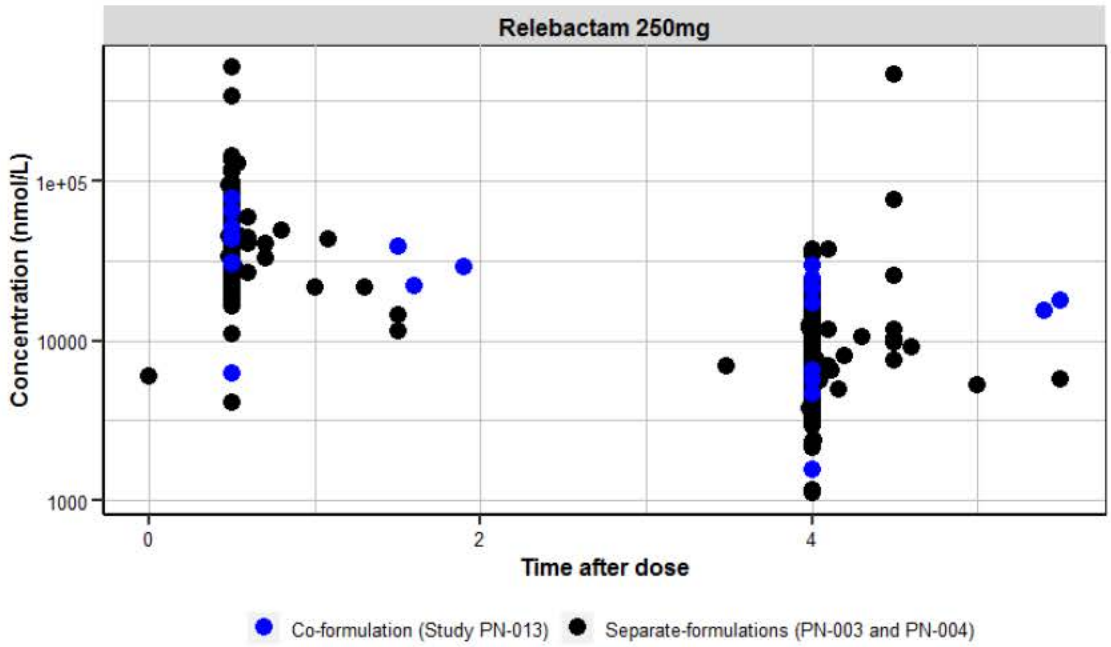

Figure 4: relebactam concentration-vs-time profiles after first dose of relebactam 250mg in phase 2 studies (PN-003, PN-004), and a phase 3 study (PN-013)

Table 1: Imipenem and relebactam Cmax after 30 min intravenous infusion of 500mg imipenem and 250mg relebactam

DRUG	Administration modes	Geometric Mean	LB 95%CI	UB 95%CI
Imipenem	Co-formulation	76800	57000	103500
Imipenem	Separate formulations	80900	72900	89800
Relebactam	Co-formulation	41500	34300	50400
Relebactam	Separate formulations	42800	39400	46600

Table 2: Number of subjects analysed from each study

STUDY	Number of subjects
PN-001	12
PN-003	134
PN-004	178
PN-012	12
PN-013	24
PN-019	26

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Angelica Dorantes

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Review of Common Technical Document-Quality (Ctd-Q) Module 1 Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

----------DOSAGE FORMS AND STRENGTHS----------

TRADEMARK for injection is supplied as sterile powder for constitution in a single-dose vial containing 500 mg imipenem (anhydrate equivalent), 500 mg cilastatin (free acid equivalent), and 250 mg relebactam (anhydrate equivalent).

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	TRADEMARK	Recommend TRADEMARK (imipenem, cilastatin, and relebactam) for injection
Dosage form, route of administration	Sterile powder for constitution; for injection	Adequate
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths and salt equivalency statement	sterile powder for constitution in a single-dose vial containing 500 mg imipenem (anhydrate equivalent), 500 mg cilastatin (free acid equivalent), and 250 mg relebactam (anhydrate equivalent).	Adequate

(b) "Full Prescribing Information" Section

#2: Section 2 Dosage and Administration (21 CFR 201.57(c)(12))

2.1 Recommended Dosage in Adults

The recommended dose of TRADEMARK is (b) (4) (b) (4) administered by (IV) infusion over 30 minutes every 6 hours in patients 18 years of age and older with creatinine clearance (CrCl) (b) (4) 90 mL/min. A dose reduction is recommended for patients with CrCl less than 90 mL/min (b) (4) Table 1 *[see Dosage and Administration (2.2)]*.

(b) (4) **Preparation of TRADEMARK Solution for IV Administration**

TRADEMARK is supplied as a dry powder in a single-dose vial that must be constituted and further diluted using aseptic technique prior to IV infusion (b) (4)

- To prepare the infusion solution, contents of the vial must be constituted with the appropriate diluent (b) (4)
  - 0.9% Sodium Chloride Injection, USP
  - 5% Dextrose Injection, USP
  - 5% Dextrose Injection, USP + 0.9% Sodium Chloride Injection, USP
  - 5% Dextrose Injection, USP + 0.45% Sodium Chloride Injection, USP
  - 5% Dextrose Injection, USP + 0.225% Sodium Chloride Injection, USP [Data supplied in P.2.6. Data provided for first 3 diluents but not the last 2. Testing is in progress for the last

(b) (4)

- After constitution, shake vial well and transfer resulting suspension into the remaining 80 mL of the infusion bag.
- Add the (b) (4) 10 mL of infusion diluent to the vial and shake well to ensure complete transfer of vial contents; repeat transfer of the resulting suspension to the infusion solution before administering. Agitate the resulting mixture until clear.
- Constituted solutions of TRADEMARK range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

(b) (4)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if discoloration or visible particles are observed.

Table 2: Preparation (b) (4)

Creatinine Clearance (mL/min)	**Dosage of TRADEMARK (imipenem/cilastatin/relebactam (b) (4)**	(b) (4)
(b) (4)		

(b) (4)

2.5 Storage of Constituted Solution

TRADEMARK, as supplied in single-dose glass vials upon constitution with the appropriate diluent and following further dilution in the infusion bag, maintains satisfactory potency for at least (b) (4) hours at room temperature (up to 30°C) or for at least 24 hours under refrigeration at 2 to 8°C (36 to 46°F). Do not freeze solutions of TRADEMARK. (b) (4)

2.6 (b) (4)

(b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Special instructions for product preparation (e.g., reconstitution, (b) (4))	Information provided in (b) (4) as annotated in red above	Adequate for storage of constituted solutions and equipment used. Testing is in progress to provide data for the two constitution solutions mentioned above. Note that compatibility testing was standard physical compatibility (turbidity, appearance, particulate) testing only and did not include chemical analysis. Defer to clinical team as to the listing of drugs that are compatible. Mention that propofol is not compatible should be retained. Reduced dosing in cases if renal insufficiency is supported by data in the NDA.

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

TRADEMARK (imipenem, cilastatin, and relebactam) for injection is supplied as a white to light yellow sterile powder for constitution in a single-dose glass vial containing (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	sterile powder for constitution	Adequate
Strengths: in metric system and salt equivalency statement	(b) (4)	Recommend: imipenem 500 mg (equivalent to 530 mg imipenem monohydrate), cilastatin 500 mg (equivalent to 531 mg cilastatin sodium), and relebactam 250 mg (equivalent to 263 mg relebactam monohydrate)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. Include "functional score", if present.	single-dose glass vial	Adequate

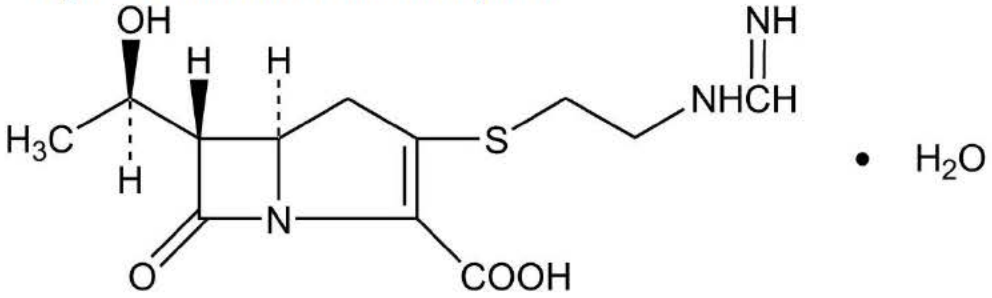
#11: Description (21CFR 201.57(c)(12))

TRADEMARK (imipenem, cilastatin, and relebactam) for injection is an antibacterial combination product consisting of imipenem, a carbapenem antibacterial drug, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a beta-lactamase inhibitor, for intravenous administration.

Imipenem

Imipenem is a beta-lactam antibacterial drug. Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. The chemical name is (5*R*,6*S*)-3-[[2-(formimidoylamino)ethyl]thio]-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound, (b) (4) sparingly soluble in water. The empirical formula is $C_{12}H_{17}N_3O_4S \cdot H_2O$ and the molecular weight is 317.37.

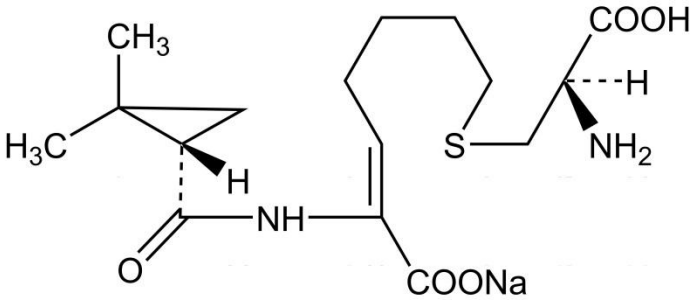
Figure 1: Chemical structure of imipenem



Cilastatin

Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. The chemical name is sodium (*Z*)-7-[[(*R*)-2-amino-2-carboxyethyl]thio]-2-[(*S*)-2,2-dimethylcyclopropanecarboxamido]-2-heptenoate. It is an off-white to white, hygroscopic, amorphous compound, (b) (4) very soluble in water. The empirical formula is $C_{16}H_{25}N_2NaO_5S$ and the molecular weight is 380.44.

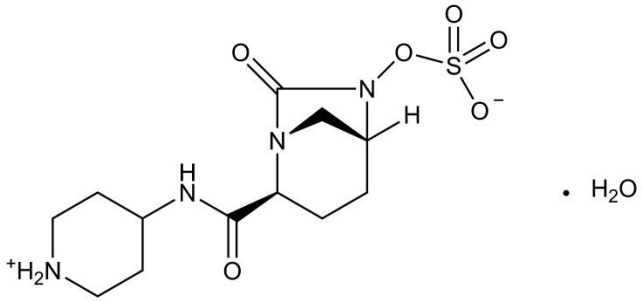
Figure 2: Chemical structure of cilastatin sodium



Relebactam

Relebactam is a (b) (4) beta-lactamase inhibitor. The chemical name is (1*R*,2*S*,5*R*)-7-Oxo-2-(piperidin-1-ium-4-ylcarbamoyl)-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate hydrate. It is a white to off-white powder, (b) (4) soluble in water. The empirical formula is $C_{12}H_{20}N_4O_6S.H_2O$ and the molecular weight is 366.39.

Figure 3: Chemical structure of relebactam



TRADEMARK is supplied as a white to light yellow sterile powder for constitution in a single-dose vial containing (b) (4)

Each vial of TRADEMARK is buffered with 20 mg sodium bicarbonate to provide solutions in the pH range of 6.5 to 7.6. The total sodium content of the mixture (b) (4) 37.5 mg (b) (4) (1.6 mEq) (b) (4) Solutions of TRADEMARK range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	TRADEMARK (imipenem, cilastatin, and relebactam) for injection	Adequate
Dosage form and route of administration	for injection	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	(b) (4) [redacted] .	Recommend: 500 mg imipenem (equivalent to 530 mg imipenem monohydrate), 500 mg cilastatin (equivalent to 531 mg cilastatin sodium), and 250 mg relebactam (equivalent to 263 mg relebactam monohydrate).
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Each vial of TRADEMARK is buffered with 20 mg sodium bicarbonate to provide solutions in the pH range of 6.5 to 7.6.	Adequate
Statement of being sterile (if applicable)	Present	Adequate
Pharmacological/ therapeutic class	imipenem, a carbapenem antibacterial drug, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a beta-lactamase inhibitor, for intravenous administration	Adequate. In opening paragraph recommend imipenem, a penem antibacterial drug, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a diazabicyclooctane (DABCO) beta-lactamase inhibitor. Recommend deleting "Imipenem is a beta-lactam antibacterial drug" in second paragraph.
Chemical name, structural formula, molecular weight	Present	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Each vial of TRADEMARK is buffered with 20 mg sodium bicarbonate to provide solutions in the pH range of 6.5 to 7.6. The total sodium content of the mixture (b) (4) 37.5 mg (b) (4) (1.6 mEq) (b) (4). Solutions of TRADEMARK range from colorless to yellow. Variations of color within this range do not affect the potency of the	Recommend: The total sodium content of the mixture (b) (4) in a vial is 37.5 mg (b) (4) (1.6 mEq (b) (4)).

	product.	

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

TRADEMARK (imipenem, cilastatin, and relebactam) for injection is supplied as a white to light yellow sterile powder for constitution in a single-dose glass vial containing (b) (4)

The vials are supplied as a single-dose glass vial (NDC 0006-3856-01) and in cartons containing 25 vials (NDC 0006-3856-02).

Store TRADEMARK vials at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (between 59°F to 86°F) [See USP Controlled Room Temperature]. Keep vials in the (b) (4) carton.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	(b) (4)	Recommend: imipenem 500 mg (equivalent to 530 mg imipenem monohydrate), cilastatin 500 mg (equivalent to 531 mg cilastatin sodium), and relebactam 250 mg (equivalent to 263 mg relebactam monohydrate).
Available units (e.g., bottles of 100 tablets). Include child-resistant closure, induction seal, coil, and desiccant as appropriate.	single-dose glass vial (NDC 0006-3856-01) and in cartons containing 25 vials (NDC 0006-3856-02).	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Include "functional score", if present.	single-dose glass vial	Adequate
Special handling (e.g., protect from light, do not freeze)	Keep vials in the (b) (4) carton.	Adequate, supported by photostability testing. (b) (4) Recommend deleting the word " (b) (4)
Storage conditions	Store TRADEMARK vials at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (between 59°F to 86°F) [See USP Controlled Room Temperature].	Adequate, supported by stability data

Manufacturer/distributor name listed at the end of PI, following Section #17

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-mk7655A-iv-XXXXrXXX

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**, Whitehouse Station, NJ 08889, USA	Adequate

2. Container and Carton Labeling

See separate review

Outstanding Issues: Testing is in progress to provide data for two constitution solutions as mentioned above. Defer to clinical team as to the listing of drugs that are compatible.

The issues described above have been discussed with the complete review team and incorporated in the label, as appropriate.

George Lunn

Digitally signed by George Lunn
Date: 5/29/2019 01:34:36PM
GUID: 508da72000029f40833369b0a181e8b3
Comments: Revised version

Erika Englund

Digitally signed by Erika Englund
Date: 5/29/2019 01:48:38PM
GUID: 51389ea30003450414230afb8c3e8114

Recommendation: Approval

NDA 212819
Review # 1

Drug Name/Dosage Form	imipenem/cilastatin/relebactam/ Powder for Injection
Strength	500 mg imipenem, 500 mg cilastatin, 250 mg relebactam
Route of Administration	Intravenous/IV
Rx/OTC Dispensed	Rx
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
eCTD 0028	*4/12/2019*	*Quality*
eCTD 0026	*4/11/2019*	*Quality*
eCTD 0022	*03/28/2019*	*Toxicology (Note: although listed as a quality amendment, this amendment was reviewed by toxicology and not CMC)*
eCTD 0021	*03/28/2019*	*Quality*
eCTD 0016	*03/22/2019*	*Quality*
eCTD 0014	*03/21/2019*	*Quality*
eCTD 0012	*03/20/2019*	*Quality*
eCTD 0011	*03/15/2019*	*Quality*
eCTD 0010	*03/15/2019*	*Quality*
eCTD 0009	*03/13/2019*	*Quality*
eCTD 0007	*03/11/2019*	*Quality*
eCTD 0006	*03/05/2019*	*Quality*
eCTD 0002	*01/29/2019*	*Quality*
Original NDA	*11/16/2019*	*All disciplines*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Mohd Kabir Shahjahan	Suong Tran
Drug Product	George Lunn	Balajee Shanmugam
Process	David Acevedo Santana	Steven Frisbee
Microbiology	Samata Tiwari	Neal Sweeny
Facility	David Acevedo Santana	Steven Frisbee
Biopharmaceutics	N/A	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika E. Englund	
Laboratory (OTR)	N/A	
ORA Lead	Caryn McNab	
Environmental	Refer to DP review	

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
Various	Type III	See DP Review				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	108754	MK-7655
NDA	50587	Primaxin

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	See DS and DP reviews			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. 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 April 15, 2019. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

Note: there are two pending information requests regarding the compatibility of the drug product with co-administered drugs and two of the proposed diluents in the PI (5% Dextrose Injection+ 0.45% Sodium Chloride Injection and 5% Dextrose Injection+ 0.225% Sodium Chloride Injection). The responses to these information requests will impact the labeling, but are not considered approvability issues.

II. Summary of Quality Assessments

A. Product Overview

This NDA provides for a single strength of a fixed dose combination of cilastatin, imipenem, and relebactam (500/500/250 mg) as a sterile powder for injection presented in a single-dose vial. The only excipient in this product is sodium bicarbonate, which

functions as a buffer. This product is indicated for (b) (4) This 505(b)(2) NDA references Primaxin (NDA 50587). Primaxin is a fixed dose combination of cilastatin and imipenem (500 mg/500 mg) indicated for the treatment of serious infections caused by designated susceptible bacteria. NDA 212819 references NDA 50587 for the supporting CMC information of both cilastatin and imipenem.

Imipenem is a carbapenem antibacterial, and cilastatin, is a renal dehydropeptidase-I inhibitor. The new API in NDA 212819, in comparison to Primaxin, is relebactam. Relebactam is a non-β-lactam β-lactamase inhibitor with activity against AmpC, a common Class C β-lactamase encountered in many bacteria and responsible for resistance in a majority of imipenem-resistant Pseudomonas aeruginosa. Relebactam is also active against the Class A β- lactamases, including the Klebsiella pneumoniae carbapenemase (KPC) present in some Enterobacteriaceae, including Klebsiella strains.

The product will be constituted with 0.9% NaCl, 5% dextrose injections, or 5% dextrose injection with either 0.9, 0.45 or 0.225% NaCl. In-use stability data was provided to support the labeled storage conditions of the constituted product. **Note: the compatibility of this product in 5% dextrose with 0.45% NaCl and 5% dextrose with 0.225% NaCl is pending the response to the information request. An addendum to this IQA will be written following evaluation of the requested data.**

NDA 212819 was developed under IND 108754 and received Fast Track Designation on 09/13/2013. The NDA was submitted with a request for priority review, which was granted on 1/14/2019. The applicant met with the Agency throughout development under IND 108754. Two meetings to highlight from a CMC perspective include a Written Response Only on 10/17/2016 (type-C CMC meeting) and a teleconference meeting held on 06/11/2018 to discuss the proposed established conditions. This NDA included both Established Conditions for drug product process parameters and a comparability protocol for changes to the drug substance manufacturing process. Following discussion with OLDP, the updated filing categories of the established conditions and comparability protocol were found acceptable.

1	⇦	**Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	(b) (4)

	(b) (4) (b) (4)
Duration of Treatment	500/500/250 mg imipenem/cilastatin/relebactam by IV infusion over 30 minutes every 6 hours.
Maximum Daily Dose	2000/2000/1000 mg imipenem/cilastatin/relebactam
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The drug product contains 3 drug substances: imipenem, cilastatin and relebactam. There are USP monographs for imipenem and relebactam, and the manufacture and control of both of these drug substances were cross-referenced to NDA 50587. Relebactam is an NME, and the supporting CMC information was submitted to this NDA. No DMFs were referenced for these three drug substances.

Relebactam is a white to off-white powder with three chiral centers. (b) (4) The limits of the impurities in the drug substance specification either complied with ICH Q3A, or were qualified by the non-clinical studies. The residual solvents in the drug substance were controlled per ICH Q3C, and the elemental impurities were evaluated per ICH Q3D. (b) (4) No change in the physical and chemical condition of the drug substance and no degradation impurities are noted during the stability study at both conditions stated above. The NDA is recommended for approval from a drug substance perspective.

For additional details, refer to the drug substance review by Kabir Shahjahan.

Comparability Protocol:

The NDA included a comparability protocol (b) (4) The comparability protocol and proposed reporting categories were discussed the post-marketing group, including Dr. Ramesh Gopalaswamy of OLDP. After group discussion, the recommendations from OLDP are captured in this IQA.

Based on the evaluation of these changes by both ONDP and OLDP, the following comments were sent to the applicant on March 11, 2019:

We agree that the approaches proposed in the CP are reasonable. However, as to the submission category of CBE-0, we suggest the following:

(b) (4)

The applicant responded on March 15, 2019. They acknowledge the FDA comment that the reporting category would change to a CBE-30 if a cGMP inspection was required at the time the supplement is submitted. They also updated the reporting category (b) (4)

(b) (4)

(b) (4) The updated comparability protocol is acceptable.

Drug Product:

The drug product consists of a sterile powder in a glass vial fitted with a (b) (4) stopper and (b) (4) flip-off seal. The glass, vials, and stoppers comply with USP requirements. Each vial contains the equivalent of 500 mg imipenem, 500 mg cilastatin, and 250 mg relebactam as well as 20 mg of sodium bicarbonate as a buffer.

The specification contains tests for appearance, identity, assay, degradants, content uniformity, container-closure integrity, appearance of solution, visible particles, particulates, pH, endotoxins, and sterility. The impurity limits are based on those for the approved Primaxin (imipenem and cilastatin) NDA with which the applicant has 30 years' experience. The proposed product is (b) (4)

Satisfactory stability data are provided for 5 representative batches stored at 30 °C/75% RH for 18 months and at 40 °C/75% RH for 6 months. Vials are stored upright and inverted. There are no out of specification results and no obvious trends (b) (4)

(b) (4)

The package label will recommend storage of the vial in the outer carton. The proposed expiration dating period of 30 months when stored at 20-25 °C is acceptable. This NDA is recommended for approval from a drug product perspective. An addendum will be submitted to this IQA with updated labeling recommendations following receipt of the IR responses.

For additional details, refer to the drug product review by George Lunn.

Microbiology:

(b) (4)

The microbiology review referenced the previously submitted information and reviews for imipenem and cilastatin. NDA 212819 provided information for relebactam, (b) (4) sodium bicarbonate and finished drug product. The microbiology review also evaluated the in-use stability of the product. The test results indicate that the reconstituted drug solution did not support adventitious microbial growth under the storage conditions (24 hours at 2-8 °C) specified in the product labeling.

The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling. The submission is recommended for approval from a microbiology perspective.

For further details, refer to the microbiology review by Samata Tiwari

Process and Facilities:

Facilities

Drug substance: 7 sites

(b) (4)

Drug product: 1 site Merck Sharp & Dohme Corp. (FEI: 1112271 profile SPW)

This NDA included a total of 8 sites, and there were no scheduled PAIs for this NDA. The overall recommendation was Approve for these sites.

Process:

The manufacturing process involves (b) (4) (b) (4) (b) (4) This NDA is recommended for approval from a process and facilities perspective.

Established Conditions:

Established Conditions (ECs) were proposed (b) (4) by the applicant. The ECs were specific to the process parameters included in the drug product manufacturing process A teleconference meeting was previously held on 06/11/2018 to discuss the proposed established conditions prior to submission of this NDA. An internal meeting was held with members from ONDP, OPF, OPPQ, and OLDP to discuss the Established Conditions submitted to the NDA. Dr. Ramesh Gopalaswamy of OLDP reviewed the ECs. An information request was sent on 02/26/2019 (following the internal meeting), and the ECs were updated in the NDA on 03/21/2019 and on 04/12/2019.

A table was submitted in the 3.2.R.5 describing the process step, process parameter or in-process control, limits, reporting category and PACMP or Post-approval CMC. The applicant included a statement that all changes to other aspects of module 3 which are outside the scope of the ECs proposed will be reported in accordance with the applicant regulatory guidance, including any change to an EC that consequently impacts other parameters or product attributes. The ECs and proposed reporting categories were found acceptable by OPF and OLDP.

For further details, refer to the process and facilities review by David Acevedo Santana.

Biopharmaceutics:
The proposed commercial drug product has the same formulation as that evaluated in the pivotal clinical trial (PN013) and in other Phase 3 trials. A biowaiver is not requested nor required, and there is no need for additional bridging between different

formulations. This NDA is recommended for approval from a Biopharmaceutics perspective.

For further details, refer to the review by Elsbeth Chikhale.

Environmental Assessment:

The applicant requests a categorical exclusion from the requirement to perform an Environmental Assessment under 21 CFR 25.31(b) because the Estimated Introduction Concentration will be below 1 ppb. A statement of no extraordinary circumstances was also submitted. The requested categorical exclusion was accepted.

For further details, refer to the drug product review by George Lunn.

Labeling:

There are 2 outstanding Information requests regarding the compatibility of the drug product with co-administered drugs and in 2 of the 5 diluents. The responses to these information requests are not approvability issues, but will impact the labeling of the product. An addendum to this IQA will be written when the responses are received.

C. Special Product Quality Labeling Recommendations (NDA only)

The labeling recommendations will be provided to the OND Project Manager for consideration. An addendum to this IQA will be completed with labeling recommendations when the responses to the outstanding IRs are received.

D. Final Risk Assessment (see Attachment)

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QUALITY ASSESSMENT

MICROBIOLOGY

NDA: 212819

Drug Product Name / Strength: Imipenem/Cilastatin/Relebactam Powder for Injection, 500 mg, 500 mg, 250 mg

Route of Administration: Sterile powder for injection, intravenous, single dose

Applicant Name: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Manufacturing Site:
Drug product: Merck Sharp & Dohme Corp. (b) (4)

Method of Sterilization: (b) (4)

Review Summary: The submission is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed: November 16, 2018, January 29, 2019, March 13, 2019 and March 15, 2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

Supporting/Related Documents:
NDA 50-587/ SCM-063 and NDA 50-630/SCM-025 and associated Microbiology Review N050587SCM063bundleR1.doc dated 14/12/2005 (adequate) for sterilization process validation for Imipenem and Cilastatin.

Remarks Section: Microbiology Information Requests were issued to the applicant on January 15, 2019, and the applicant forwarded responses on January 29, 2019. (b) (4) (b) (4) (b) (4) An addition Microbiology Information Requests were issued to the applicant on March 05, 2019, and the applicant forwarded responses on March 13, 2019 and March 15, 2019.

S Drug Substance

The sterile drug product Cilastatin/Imipenem/Relebactam Powder for Injection is made up of the following:

- Imipenem (API)

- Cilastatin (API)
- Relebactam (API)
- Sodium bicarbonate excipient

Each of these will be reviewed separately in this section.

Cilastatin (API), Imipenem (API)

- **Description of drug substance-**

The applicant refers to approved NDA 050587 PRIMAXIN® (imipenem and cilastatin) for CMC information related to the components imipenem and cilastatin. (b) (4)

(b) (4)

Note to Reviewer: The manufacturing process and (b) (4) process validations for Imipenem-Cilastatin was submitted in NDA 50-587/SCM-063 and NDA 50-630/SCM-025, lead NDA prior approval supplements for comparability protocol (b) (4) (b) (4) (reviewed in microbiology review N050587SCM063bundleR1.doc, dated 12/14/05) and NDA 50-587/SCS-067 containing the data for the comparability protocol described in supplement NDA 50-587/SCM-063 (see memo review by B. Riley, dated 11/29/07) and found adequate. Please refer the above-mentioned reviews for more information.

S.2 Manufacture

S.2.1 Manufacturers

(b) (4)

(b) (4)

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The provided sterility test validation data demonstrate that the drug product did not inhibit recovery of challenge microorganisms using the USP <71> Sterility Test, and that the method is suitable for routine testing during commercial production. Additionally, the dilution for the endotoxin test did not exhibit inhibition/enhancement, and administration of the maximum drug product dose (having the established (b) (4) EU/mg endotoxin limit) will not result in an endotoxin exposure exceeding th (b) (4) EU/kg/hr tolerance threshold level.

Acceptable

P.7 Container Closure

Please see section P.1 for a description of container closure system used to package the drug product

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1 Stability Summary.pdf)

Drug product Formal Stability Studies (FSS) batch were subjected to stability evaluation at accelerated (40°C/75% RH) and long term (30°C/75% RH) conditions.
Proposed expiry: 30 months

Reviewer's Assessment:

Acceptable

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Sterility	USP <71>	No growth observed
Bacterial Endotoxins	USP <85>	NMT (b) (4) EU/mg

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: (b) (4) % RH

Test	Time (Months) (b) (4)
Sterility	
Endotoxin	
CCIT	

Post Approval Stability Commitment

The applicant commits to the first three production lots of the drug product at the long-term stability conditions ((b) (4) % RH). Yearly thereafter, one production batch will be added to the stability program.

Reviewer's Assessment
Acceptable

P.8.3 Stability Data

Long-term and accelerated stability studies were performed for Formal Stability Studies (FSS) (lots 0000598397, 0000610980 and 0000610982) and the provided results were acceptable for 12 months' time points.

Reviewer's Assessment
The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

Acceptable

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable.

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable.

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable.

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable.

R Regional Information

Executed Batch Records

Executed batch records were provided for Formal Stability Studies (FSS) (lots 0000598397, 0000610980 and 0000610982). The batch records confirm that validated

sterilization/depyrogenation (b) (4) manufacturing processes were used for the manufacture of the exhibit batches.

Reviewer's Assessment:
Acceptable

Comparability **Protocols**

The applicant provided a comparability protocols (b) (4)

(b) (4)

Reviewer's Assessment:

Acceptable

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

The subject drug product is a sterile, preservative-free sterile solution for injection. It is supplied in 20 mL (b) (4) single use vials. The subject drug product is stored at room temperature 20-25°C (68-77°F).

The drug product must be diluted in appropriate diluent following further dilution in the infusion bag before administration and maintains satisfactory potency when stored not longer than 24 hours at 2-8°C or for at least (b) (4) hours at room temperature (up to 30°C)

Microbial Proliferation of drug product admixtures with 0.9% saline and 5% dextrose were studied in sample solutions containing imipenem at 5 mg/mL, cilastatin at 5 mg/mL and relebactam at 2.5 mg/mL, and sample solutions containing imipenem at 2 mg/mL, cilastatin at 2 mg/mL, and relebactam at 1 mg/mL.

For each admixture and positive control, one bag was inoculated with an aliquot containing 50 CFU/mL of challenge organism (listed below) and stored at one of the two storage temperatures (20-25°C or 2-8°C) for 48 hours (20-25°C) and 8 days (2-8°C). After storage, the challenge organism was enumerated from each bag at each testing interval. Positive control results were not provided. The negative controls were not inoculated with the challenge organisms. Total viable count of test solution and positive samples were performed at the following intervals at the two storage temperatures.

Challenge microorganisms:
Escherichia coli
Pseudomonas aeruginosa
Staphylococcus aureus
Candida albicans
Aspergillus brasiliensis
Bacillus subtilis

Table 1 Testing Schedule for Microbial Proliferation Studies

Time Point (hours)	Tested Microorganisms	
	Room Temperature (20-25°C)	2 – 8°C
0	SA, PA, EC, CA, and AB	SA, PA, EC, CA, and AB
8	PA, EC, and CA	NT
10	PA, EC, and CA	NT
12	All six (SA, PA, EC, BS, CA, AB)	All six (SA, PA, EC, BS, CA, AB)
24	All six (SA, PA, EC, BS, CA, AB)	All six (SA, PA, EC, BS, CA, AB)
48	All six (SA, PA, EC, BS, CA, AB)	NT
8 days	NT	All six (SA, PA, EC, BS, CA, AB)
NT = Not Tested		

Results:

Table 2 Imipenem 5 mg/mL, Cilastatin 5 mg/mL, Relebactam 2.5 mg/mL in 0.9% saline solution

Organism	Inoculated Saline Control, Log CFU/mL	Theoretical Inoculum, CFU/mL	Log CFU/mL (CFU/mL)									
			Room Temperature (RT)						2-8°C			
			0 h	8 h	10h	12 h	24 h	48 h	0 h‡	12 h	24 h	8D
S. aureus	1.9	80	0.0	NT	NT	0.0	0.0	0.0	0.0	0.0	0.0	0.0
P. aeruginosa	1.8	60	1.4	1.4	1.3	1.2	0.5	0.0	1.4	1.5	1.5	0.3
E. coli	1.7	56	1.3	0.3	0.3	0.0	0.0	0.0	1.3	0.0	0.0	0.0
B. subtilis	1.7	55	NT	NT	NT	0.8	1.0	0.0	NT	0.8	0.8	0.0
C. albicans	2.0	95	1.9	2.0	2.0	1.9	1.9	2.0	1.9	1.9	1.9	1.9
A. brasiliensis	1.6	39	1.5	NT	NT	1.4	1.0	1.2	1.5	1.4	1.4	1.3
Uninoculated Control†	N/A	N/A	0.0	NT	NT	0.0	0.0	NT	0.0	0.0	0.0	NT

CFU: Colony Forming Unit.
NT: Not Tested. Testing was not performed due to inherent inhibitory nature of product, slow growth properties of organism, or tested by a direct method which was deemed invalid.
N/A: Not Applicable.
† All uninoculated controls reported in this study were tested undiluted, and all time points resulted in 0 CFU/mL. As a result, 0.0 log was reported.
‡ At 0-h time point one set of inoculated samples was tested and the same data set was listed for both 2–8°C and room temperature conditions.

Table 3 Imipenem 5 mg/mL, Cilastatin 5 mg/mL, Relebactam 2.5 mg/mL in 5% dextrose solution

Organism	Inoculated Saline Control, Log CFU/mL	Theoretical Inoculum, CFU/mL	Log CFU/mL (CFU/mL)									
			Room Temperature (RT)						2-8°C			
			0 h	8 h	10h	12 h	24 h	48 h	0 h‡	12 h	24 h	8D
S. aureus	1.9	80	0.0§	NT	NT	0.0§	0.0§	0.0§	0.0§	0.0§	0.0§	0.0§
P. aeruginosa	1.8	60	1.5	1.6	1.5	1.4	0.7	0.3	1.5	1.5	1.5	0.0
E. coli	1.7	56	1.5	0.0	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0
B. subtilis	1.7	55	NT	NT	NT	1.0	1.0	1.0	NT	1.0	1.0	0.0
C. albicans	2.0	95	1.9	1.7	1.6	1.6	1.2	0.9	1.9	1.7	1.7	1.6
A. brasiliensis	1.6	39	1.5	NT	NT	1.5	1.4	1.4	1.5	1.4	1.4	1.5
Uninoculated Control†	N/A	N/A	0.0	NT	NT	0.0	0.0	NT	0.0	0.0	0.0	NT

CFU: Colony Forming Unit.

NT: Not Tested. Testing was not performed due to inherent inhibitory nature of product, slow growth properties of organism, or tested by a direct method which was deemed invalid.

N/A: Not Applicable.

† All uninoculated controls reported in this study were tested undiluted, and all time points resulted in 0 CFU/mL. As a result, 0.0 log was reported.

‡ At 0-h time point one set of inoculated samples was tested and the same data set was listed for both 2–8°C and room temperature conditions.

§ Antimicrobial properties noted at time zero and, therefore, no organisms recovered. Testing was altered at later time point to allow recovery of potential viable organisms. No increases were noted.

The test results indicate that the reconstituted drug solution did not support adventitious microbial growth under the storage conditions (24 hours at 2-8°C) specified in the product labeling. That is the population increases of the test group were less than 0.5 $\log_{10}$. All negative controls were negative.

Reviewer's Assessment:
The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

Acceptable

Post-Approval Commitments: Not applicable.
Lifecycle Management Considerations: Not applicable.

List of Deficiencies:
None Identified

Primary Microbiology Reviewer Name and Date:
Samata Tiwari, Ph.D. (03/19/2019)
Microbiologist
CDER/OPQ/OPF/DMA/BII

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Neal Sweeney, Ph.D. (03/21/2019)
Senior Microbiologist
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Samata Tiwari

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BIOPHARMACEUTICS

Product Background:

NDA: 212819 (505(b)(2))

Drug Product Name / Strength: Imipenem, cilastatin, relebactam powder for injection/ 500 mg, 500 mg, 250 mg.

Route of Administration: Intravenous infusion

Applicant Name: Merck Sharp and Dohme Corp.

Review Summary:

The proposed fixed-dose combination (FDC) drug product received Qualified Infectious Disease Product (QIDP) and Fast Track designations.

The clinical pharmacology/pharmacokinetic parameters were established using the proposed drug product in healthy subjects. Two dose-ranging Phase 2 comparator-controlled clinical trials were conducted in patients to support the safety and efficacy of the proposed drug product. A pivotal, double-blind Phase 3 trial was conducted to support the efficacy and safety of the proposed drug product. In addition, the Applicant relies, in part, on the Agency's prior findings of safety and effectiveness of the listed drug Primaxin® (imipenem and cilastatin) for Injection (approved under NDA 050587). The Applicant claims that the data contained within this NDA combined with the Agency's previous findings of safety and efficacy with Primaxin® support the clinical use of the proposed drug product for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in patients 18 years and older with limited or no alternative therapies available caused by gram-negative bacteria.

The dosage form of the proposed drug product is a powder for injection, to be administered by intravenous infusion over 30 minutes every 6 hours. The drug product is a clear solution when diluted in normal saline or 5% dextrose solutions. Therefore, there is no need for drug release or dissolution testing.

The proposed commercial drug product has the same formulation as the drug product used in the pivotal clinical trial (PN013) (b) (4)

(b) (4)

Formulations Used in Clinical Trials and Proposed Commercial Formulation

Ingredient	Amount (mg)/Vial				
	Commercial Formulation of IMI (Phase 1 and 2)	Formulation B (Phase 1)	Formulation C (Phase 1 and 2)	Formulation D (Phase 3 and PN019)	Proposed Commercial Formulation
Imipenem[a]	(b) (4)			500	500
Cilastatin[b]				500	500
Sodium bicarbonate				20	20
Relebactam[c]				250	250

(b) (4)

There is no need for additional bridging between different formulations. A biowaiver is not requested, nor required.

Recommendation:

NDA 212819 for Imipenem, cilastatin, relebactam powder for injection/
500 mg, 500 mg, 250 mg is recommended for **APPROVAL** from a Biopharmaceutics perspective.

Biopharmaceutics Team Lead Name and Date: Elsbeth Chikhale, Ph.D., 4/9/2019

Biopharmaceutics Branch Chief Name and Date: Angelica Dorantes, Ph.D., 4/9/2019

Elsbeth Chikhale

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ATTACHMENT I: Final Risk Assessments

IQA Review Guide Reference

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	Formulation, raw materials, process parameters, scale/equipment site	H	The microbiology review found this information adequate	Acceptable	
Endotoxin/ pyrogen	Formulation, raw materials, process parameters, scale/equipment site	M	The microbiology review found this information adequate	Acceptable	
Assay, stability	Formulation, raw materials, process parameter, scale/equipment site	L		Acceptable	
Uniformity of Dose	Formulation, process parameters	L		Acceptable	
Extractables and leachables	Formulation, container	M	Extractable and leachable data was found acceptable	Acceptable	
Particulate matter	Formulation, raw materials, process parameter	M		Acceptable	
Re-dispersibility/ reconstitution time	Formulation, raw materials, process parameter	M		Acceptable	

Erika Englund

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