CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209949Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: ***Approval***

NDA 209949
Review # 1

Drug Name/Dosage Form	Daptomycin for Injection
Strength	350 mg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Xellia Pharmaceuticals ApS
US agent, if applicable	Edward Eichmann

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	December 20, 2016	All
Amendment (eCTD 003)	April 10, 2017	Biopharmaceutics
Amendment (eCTD 005)	June 27, 2017	Microbiology
Amendment (eCTD 007)	July 28, 2017	Drug Product, Process
Amendment (eCTD 009)	July 31, 2017	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarker	Benjamin Stevens
Drug Product	Milton Sloan	Balajee Shanmugam
Process	Ying Wang	Upinder Atwal
Microbiology	Yuansha Chen	Neal Sweeney
Facilities	Frank Wackes	Christina Capacci-Daniel
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Environmental Assessment*	Milton Sloan	Balajee Shanmugam
Regulatory Business Process Manager	Luz Rivera	N/A
Application Technical Lead	Dorota Matecka	N/A

*Refer to the Drug Product Chapter

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Completed	Comments
27179	II	Xellia Pharmaceuticals Ltd.	Daptomycin	Adequate	January 11, 2016 (DARRTS) July 18, 2017 (Panorama)	Review by Hongbiao Liao Review by Haripada Sarker
(b) (4)	III		(b) (4)	Current 09/09/2016	N/A	Sufficient information provided in the NDA
	III			Adequate	06/14/2017	Reviewed by D. LopezPrerez
	V			Adequate	04/05/2017	Reviewed by D. Schu

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21572	Listed Drug, Cubicin (daptomycin for injection), 500 mg
ANDA	206005	Daptomycin for Injection, 500 mg (ANDA held by Crane Pharmaceuticals LLC, subsidiary of Xellia Pharmaceuticals ApS, approved on June 15, 2016)

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, daptomycin 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 September 26, 2017. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. Summary of Quality Assessments

A. Product Overview

Daptomycin is a cyclic lipopeptide antibacterial agent which acts by binding to bacterial membranes and causing a rapid depolarization of the membrane potential. This loss of membrane potential causes inhibition of DNA, RNA, and protein synthesis, which results in bacterial cell death. Daptomycin for injection, which was approved under NDA 21572 [Cubicin® (daptomycin for injection), 500 mg/vial] and has been marketed by Cubist Pharmaceuticals, Inc., is indicated for the treatment of complicated skin and skin structure infections and Staphylococcus aureus bloodstream infections (including those with right-sided infective endocarditis).

The drug product proposed via this NDA, Daptomycin for Injection, 350 mg/vial, has the same active ingredient, excipients, dosage form, (b) (4) route of administration, and indications as the listed drug, Cubicin®. The differences between the two products include the strength (i.e., amount of daptomycin in a vial): 350 mg/vial for the current drug product versus 500 mg/vial for the listed drug, as well as the volume (7 mL and 10 mL, respectively) of the reconstitution agent (saline) required for the reconstitution of the drug product powder.

Proposed Indication(s) including Intended Patient Population	Complicated Skin and Skin Structure Infections; Staphylococcus aureus Bloodstream Infections (Bacteremia) Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates/Adult Patients
Duration of Treatment	Varies (see package insert)
Maximum Daily Dose	6 mg/kg (every 24 hours)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Daptomycin is a cyclic lipopeptide antibacterial agent antibiotic [redacted] The chemistry, manufacturing and controls (CMC) information for daptomycin drug substance in support of this NDA is provided via a reference to DMF 27179 (held by the manufacturer, Xellia Pharmaceuticals Ltd., Hungary). This DMF was found to be adequate via a chemistry review dated January 11, 2016 referenced for another application and a follow-up review dated July 18, 2017 of several subsequent DMF amendments. The retest period for daptomycin drug substance established by Xellia Pharmaceuticals Ltd. is [redacted] when stored at [redacted] However, the retest period established by the drug product manufacturer [redacted] for daptomycin drug substance is [redacted].

Daptomycin for Injection, 350 mg/vial, is a pale yellow to light brown lyophilized powder, which does not contain any excipients other than sodium hydroxide used as a pH adjusting agent. The proposed drug product is intended to be a copy of the listed drug, Cubicin® , with the same active ingredient, excipients, [redacted] route of administration, dosage form and indications. The only difference between the two products is the strength (i.e., the amount of daptomycin per vial) with Cubicin® product and the drug product proposed via this NDA containing 500 mg and 350 mg of daptomycin per vial, respectively. However, the concentration of the solution following the reconstitution is the same for the proposed drug product and the listed drug (i.e., 50 mg/mL) due to the lower volume of 0.9% sodium chloride (7 mL instead of 10 mL) required for the reconstitution of the drug product powder. The Applicant requested a waiver of the bioequivalence (BE) requirement for their product, Daptomycin for Injection, 350 mg/vial, in accordance with 21 CFR § 320.22(b)(1) and 320.22(d)(4). Based on the information provided in NDA, including comparable pH and osmolality results for the reconstituted solutions of the currently proposed drug product and the listed drug, the biowaiver request has been granted consistent with 21 CFR § 320.22(b)(1).

The drug product specification contains tests for description, identification, pH of solution (after reconstitution), uniformity of dosage forms, assay, related substances, reconstitution characteristics (completeness of solution, clarity of solution, reconstitution volume, description of solution), color of solution, water content, visible particles, sub-visible particulate matter, endotoxins, sterility, microbiological assay, [redacted]. During the review, several revisions were made to the proposed specification, e.g., the visible particle test, and the drug product specification, as revised, was found adequate. The analytical procedures have been described in reasonable detail and the validation reports have been found adequate. The controls of impurities/degradation products in the drug product specification were found acceptable.

The container-closure system consists of 15 mL (b) (4) clear glass vials with 20 mm (b) (4) rubber stopper (b) (4) and aluminum seal with flip off cap. Glass vials used in the proposed container closure system meet acceptance criteria for (b) (4) glass containers per USP (b) (4), and the rubber stoppers meet the criteria of USP (b) (4) Elastomeric Closures for Injections, (b) (4) stoppers. In addition, the proposed container closure is the same as the container closure system used for another daptomycin product, daptomycin for injection, 500 mg, recently approved under an ANDA held by the same Applicant. Based on the overall information available, the proposed container closure system has been found suitable for the current drug product.

The drug product stability information submitted in the NDA includes long-term (5°C ± 3°C) stability data for three representative drug product batches, which consists of 36-month results for two batches and 9-month results for one batch. In addition, 6-month accelerated (25°C ± 2°C/60% RH ± 5% RH) stability data have been included for the same three batches. No out of specification results and no obvious trends for vials stored in different orientation were observed for these batches. Based on the overall stability information provided in the NDA that includes also photo stability studies, the proposed expiration dating period of 36 months for the proposed drug product stored at (b) (4) was found acceptable. In addition, the results of in-use stability studies (conducted using freshly manufactured and aged drug product samples) were found to be adequate to support the proposed storage statements included in the package insert for the reconstituted and further diluted solutions of the drug product.

The manufacturing process consist of (b) (4)

The overall information regarding the manufacturing process provided in the initial NDA submission and the subsequent amendment was found acceptable.

No deficiencies for the proposed drug product were identified from the product quality microbiology perspective. During the NDA review several comments were forwarded to the Applicant and additional information was provided, (b) (4) the finished drug product. The overall product quality microbiology information provided for the drug product in the NDA and the subsequent amendment was found acceptable.

The NDA includes a Comparability Protocol that provides for an (b) (4) in batch size (from the current batch size of (b) (4) to the proposed (b) (4) size) at the current

manufacturing site, [redacted], using the same manufacturing line and equipment. [redacted] Based on the information provided, the Comparability Protocol was found adequate.

The daptomycin drug substance manufacturer is Xellia Pharmaceuticals Ltd, Hungary and the drug product manufacturer is [redacted]. In addition, two other facilities (Xellia Pharmaceuticals ApS, Denmark and [redacted] are involved in the microbiological testing of the drug substance. Based on the review of the application and inspectional history for all manufacturing and testing sites listed in this NDA, it has been determined that there are no significant outstanding issues with the facilities involved in the manufacturing of the proposed product. Therefore, the overall recommendation of "Approve" was entered into Panorama for this NDA by OPF on September 26, 2017.

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

D. Final Risk Assessment (see Attachment I)

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MICROBIOLOGY

Product Background:

NDA: 209949

Drug Product Name / Strength: Daptomycin for Injection, 350 mg/vial

Route of Administration: IV

Applicant Name: Xellia Pharmaceuticals ApS

Manufacturing Site:

(b) (4)

Method of Sterilization: (b) (4)

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

List Submissions being reviewed (table):

Submitted	Received	Assigned to Reviewer
12/20/2016	12/20/2016	12/29/2016
6/27/2017*	6/27/2017	N/A
*IR response		

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** A pale yellow to light brown lyophilized powder or cake.

- **Drug product composition –**

Ingredient	Quantity (mg/vial)	Function

Daptomycin	350	API
Sodium hydroxide	q.s.	pH adjuster
(b) (4)		

- **Description of container closure system –** (3.2.P.7.)

Components	Description	Manufacturer
Vials	(b) (4)	
Stoppers		
Seals		

Reviewer's Assessment: Adequate

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**
(P.2. Pharmaceutical Development, p89-99)

The container/closure system used for validation was the same as the drug product. The same product code and description were provided for the container/closure system for the CCIT and for the proposed drug product.

Study/Report # and date: VCIR11007-00, dated 9/27/2011

Test method: (b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment: Adequate

- **Antimicrobial Effectiveness Testing -**

  N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Reviewer's Assessment: Adequate

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

The above site is responsible for manufacturing of the drug product, in-process control testing, release and stability testing.

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

(b) (4)

Reviewer's Assessment: Adequate

P.7 Container Closure System - See P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

(P.8.1.)

Proposed Expiry: 36 months stored at (b) (4)

P.8.2 Post-Approval Stability Protocol and Stability Commitment

(P.8.2.)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>	NMT (b) (4) EU/mg
Sterility	USP <71>	Comply

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

Stability storage conditions: (b) (4)

Test	Time (Months)								
	0	3	6	9	12	15	18	24	36
Bacterial Endotoxins	X				X			X	X
Sterility	X				X			X	X

Post Approval Stability Commitment

The applicant stated that since the exhibit batch sizes are the same as the proposed commercial batches, stability data from the three exhibit batches are placed into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Reviewer's Assessment: Adequate

P.8.3 Stability Data

36 months stability data are available for exhibit batches MA101 and MA102. Sterility test and Bacterial Endotoxins test results met the specifications.

Reviewer's Assessment: Adequate

R REGIONAL INFORMATION

R.1 Executed Batch Record

Executed lot #(s): MA101, MA102, MA501

The batch records confirm that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batch.

Reviewer's Assessment: Adequate

R.2 Comparability Protocol – No CP was included in the application.

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

A. PACKAGE INSERT

(P.1.14.)

Storage temperature: (b) (4); Route of administration: IV Container: Single dose

Reconstituted/Further Diluted Drug Product

Daptomycin for Injection should be reconstituted with 0.9% NaCl to 50 mg/mL in the vials. For IV injection over a period of 2 minutes, administer the appropriate volume of the reconstituted Daptomycin for injection. For IV infusion over a period of 30 minutes, the appropriate volume of the reconstituted drug solution should be further diluted into a 50 mL IV infusion bag containing 0.9% sodium chloride injection. The combined storage time (reconstituted solution in vial and diluted solution in infusion bag) should not exceed 12 hours at room temperature or 48 hours under refrigeration.

Daptomycin for injection is compatible with 0.9% sodium chloride injection and lactated Ringer's injection.

Post dilution microbiological study
(P.2. pharmaceutical-development)

(b) (4)

(b) (4)

e.
s
C.

Reviewer's Assessment: Adequate

List of Deficiencies:
None

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D. 7/10/2017

CDER/OPF/DMA

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Neal, J. Sweeney, Ph.D. 7/11/17

CDER/OPF/DMA

Yuansha Chen

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Neal Sweeney

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BIOPHARMACEUTICS

Product Background:

NDA: 209949
Drug Product Name / Strength: Daptomycin for Injection, 350 mg/vial (lyophilized powder [in single-dose vial] for reconstitution to 50 mg/mL solution with 0.9% sodium chloride solution)
Route of Administration: For Intravenous Injection
Applicant Name: Xellia Pharmaceuticals ApS

Review Recommendation:
The Applicant's biowaiver request in relation to NDA 209949 for Daptomycin for Injection 350 mg/vial is granted, based on 21 CFR § 320.22(b)(1). From the Biopharmaceutics perspective, NDA 209949 for Daptomycin for Injection 350 mg/vial is recommended for **APPROVAL**.

Review Summary:
This 505(b)(2) NDA submission for Daptomycin for Injection (350 mg/vial) relies for approval on FDA's findings of safety and effectiveness established for the Listed Drug approved under NDA 21572, Cubicin® 500 mg/vial (b) (4)). The Applicant requested a waiver of the requirement to conduct a bioequivalence (BE) study, per 21 CFR § 320.22(b). The proposed drug product is the same as the Listed Drug in terms of (b) (4) presentation/dosage form (lyophilized powder/cake in single dose vial, for Injection), drug concentration (i.e., upon reconstitution of the powder [50 mg/mL], and further dilution with the appropriate volume of 0.9% NaCl solution per labeling instructions), indications, and mode/route of administration (for intravenous bolus injection over 2 min or for intravenous infusion over 30 min). Note that to ensure equivalence of drug concentrations of the injectable solutions at the point of patient contact, the proposed drug product (350 mg/vial) is initially reconstituted with a lower volume (7 mL) of normal saline solution, i.e., instead of 10 mL as indicated in the approved labeling of the Listed Drug (500 mg/vial). Of note, in addition to 500 mg/vial, the 350 mg/vial presentation of Cubicin® Powder for Injection (for reconstitution to 50 mg/mL using 7 mL of 0.9% sodium chloride solution) is commercially available in European countries.

Note that the *in vitro* data provided for both the reconstituted and diluted solutions of the proposed drug product indicate similarity of physicochemical properties (i.e., osmolality, pH, clarity) as compared to the solutions prepared from the Listed Drug. (b) (4) the proposed drug product is preservative-free, and the lyophilized powder is recommended to be stored under refrigeration. Furthermore, both OPQ-recommended edits to Section 2.5 of the proposed labeling, as well as the OPQ-recommended Finished Product QC Specifications would ensure comparability of the proposed drug product to the Listed Drug with respect to quality attributes including Assay, Appearance of powder and reconstituted solution

(i.e., clarity of solution), Sterility, pH of reconstituted solution, and the limits for Bacterial Endotoxins, and Particulates. Refer to the Drug Product Review for the overall evaluation of the Finished Drug Product QC specifications.

List Submissions reviewed:
SDN-1, 12/201/2016 (Original NDA Submission)
SDN-4, 4/10/2017 (Response to Quality Information Request: comparative osmolality)

Highlight of Key Outstanding Issues from Last Cycle:
Not Applicable (Original NDA)

Concise Description of Outstanding Issues:
None

List of Deficiencies:
None.

Primary Biopharmaceutics Reviewer Name and Date: *Gerlie Gieser, PhD (8/1/2017)*

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
I concur with Dr. Gieser's assessment and recommendation
Elsbeth Chikhale, PhD (8/13/2017)

Gerlie Gieser

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Elsbeth Chikhale

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LABELING

{For NDA only}

R Regional Information

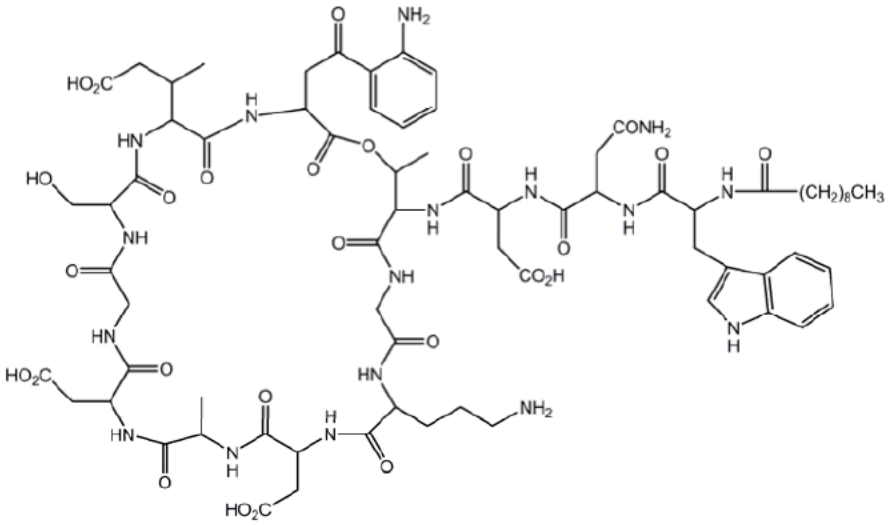
1.14 Labeling

3 DOSAGE FORMS AND STRENGTHS

For Injection: 350 mg daptomycin as a sterile, pale yellow to light brown lyophilized powder for reconstitution in a single-dose vial.

11 DESCRIPTION

Daptomycin for Injection contains daptomycin, a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*. The chemical name is *N*-decanoyl-L-tryptophyl-D-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D- seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine ε1-lactone. The chemical structure is:



The empirical formula is $C_{72}H_{101}N_{17}O_{26}$; the molecular weight is 1620.67. Daptomycin for Injection is supplied in a single-dose vial as a sterile, preservative-free, pale yellow to light brown, lyophilized cake containing approximately 350 mg of daptomycin for intravenous (IV) use following reconstitution with 0.9% sodium chloride injection *[see Dosage and Administration (2.5)]*. The only inactive ingredient is sodium hydroxide, which is used for pH adjustment. Freshly reconstituted solutions of Daptomycin for Injection range in color from pale yellow to light brown.

16 HOW SUPPLIED/STORAGE AND HANDLING

Daptomycin for Injection is supplied as a sterile pale yellow to light brown lyophilized cake in a single-dose 15 mL vial containing 350 mg of daptomycin: Package of 1 (NDC XXXXX-XXX-XX). Store original packages at refrigerated temperatures, 2 to 8°C (36 to 46°F); avoid excessive heat *[see Dosage and Administration (2.5)]*

Reviewer's Assessment: **Adequate**

The above sections in the Package Insert are acceptable. Minor changes may be made on the Word document itself at the designated labeling meetings of the review team.

Immediate Container Label

(b) (4)

[redacted]

Reviewer's Assessment: **Adequate**

Recommended revision:

Please revise (b) (4) [redacted] to 2 to 8°C (36 to 46°F)

The use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. The single-dose container contains more drug than is required for a single dose due to the required overfill in vials. The excess amount constituting more than one dose in the container should be discarded. Hence the statement "Discard Unused portion" is added. Please refer to recent FDA's guidance for industry on *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products*. Furthermore, when dosed over an extended time period, the infusion containers (small volume) is considered single-dose containers because they are designed for use with a single patient as a single infusion. This is consistent with the Reviewer tool document for labeling.

Carton Labeling

(b) (4)

Reviewer's Assessment: **Adequate**

The carton label complies with all regulatory requirements from a CMC perspective. The same editorial comment on the storage temperature applies (below).

List of Deficiencies:

Please revise (b) (4) to 2 to 8°C (36 to 46°F)

Primary Labeling Reviewer Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
8/15/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Balajee Shanmugam, PhD
(Acting) Branch Chief
OPQ/ONDP/Div1/Branch III
8/15/2017

Milton Sloan

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Balajee Shanmugam

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Attachment I: Risk Table

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**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability. Impurities	Formulation, Process parameters Raw materials Container closure	L	Adequate acceptance criteria for impurities	Acceptable	
Uniformity of Dose	Formulation, Process parameters Raw materials Container closure	L	Adequate in-process controls; Acceptable overfill in a vial	Acceptable	
Reconstitution time	Formulation, Process parameters Raw materials	M	(b) (4)	Acceptable	
Leachable (Rubber stopper)	Container closure	L	Powder for injection; same container closure system approved under an (b) (4) for another daptomycin for injection	Acceptable	
Sterility	Formulation, Process parameters Raw materials Container closure	H		Acceptable	
Particulate matter	Formulation, Process parameters Raw materials	M	Data consistent across batches and test included in the specification	Acceptable	

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

Dorota M. Matecka -S

Dorota Matecka, ATL for NDA 209949 *On behalf of OPQ Team*