CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208385Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality (OPQ) Review

NDA 208385

OPQ Review # 2

Review Date:	September 12, 2017
Submission:	NDA 208385 Resubmission (Class 2); SDN#16
Submission date:	March 24, 2017
OND Division:	Division of Anti-Infective Products (DAIP)
Product Name:	Daptomycin for Injection, 350 mg/vial
Applicant:	Sagent Pharmaceuticals, Inc.

Executive Summary:

NDA 208385 originally submitted on August 25, 2015 was recommended for Complete Response (CR) by the OPQ Review Team due to several product quality deficiencies, which included: 1) unacceptable status of the drug substance manufacturing facility; 2) an (b) (4) in the drug product bulk solution during registration batch manufacturing; and 3) (b) (4) not adequately justified acceptance criteria proposed for impurities (b) (4) in the drug product specification (refer to the OPQ Review # 1 dated May 27, 2016 in Panorama and a CR letter dated June 23, 2016 in DARRTS). The current NDA resubmission (Class 2) includes only responses to the CR comments with no additional updates to other CMC sections. Specifically, the originally proposed acceptance criteria for individual impurities/related substances (b) (4) in the drug product specification were revised and the drug product specification, as revised, has been now found acceptable (refer to the review by Dr. Pagay, Attachment 1). Also, a justification provided for (b) (4) the drug product bulk solution was found acceptable by the Process Reviewer (refer to the review by Dr. Anderson, Attachment II). In addition, the status of the manufacturing facilities was assessed by Dr. Cassandra Abellard who found them acceptable in support of this NDA based on the review of the application and inspectional documents of the facilities responsible for manufacturing the drug product and the drug substance (refer to the facilities review, Attachment III). The analytical procedures were verified and found acceptable by the FDA laboratory with comments addressed by the Drug Substance Reviewer (refer to Dr. Sithamalli memorandum, Attachment IV) and the labeling and labels were found acceptable by Dr. Pagay (refer to the labeling review in Attachment V). In addition, the Biopharmaceutics Review conducted for the original NDA submission has been now updated to provide a clarification on the regulation supporting the bridge between the proposed drug product, daptomycin for injection, 350 mg/vial, and the listed drug CUBICIN®, daptomycin for injection, 500 mg/vial (refer to Dr. Chikhale's review, Attachment VI). Based on the above assessments and the overall recommendation of "Approve" entered by the Office of Process and Facilities (OPF) into Panorama on September 12, 2017, this NDA can be now recommended for approval.

Recommendation:

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

Attachments

Attachment I (Drug Product - Dr. Shrikant Pagay)

Attachment II (Process - Dr. David Anderson)

Attachment III (Facilities - Dr. Cassandra Abellard)

Attachment IV (Drug Substance - Dr. Sithamalli Chandramouli)

Attachment V (Labeling - Dr. Shrikant Pagay)

Attachment VI (Biopharmaceutics – Dr. Elsbeth Chikhale)

Attachment VII (Risk Table)

Application Technical Lead (ATL) Signature:

Dorota M. Matecka -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001232911, cn=Dorota M. Matecka -S
Date: 2017.09.12 17:17:11 -04'00'

This NDA is recommended for approval from the Product Quality perspective.
On behalf of the OPQ Review Team
Dorota Matecka, Ph.D., ATL for NDA 208385

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LABELING

NDA 208385 Review 2

Highlighted portions are the revisions from Review 1.

I. Package Insert

DAPTOMYCIN for injection, for intravenous use

1. *Highlights of Prescribing Information*

NO new comments
(See Review 1 for the information in the table)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	
Dosage form, route of administration	
Controlled drug substance symbol (if applicable)	
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	

2. *Section Dosage and Administration*

There are different formulations of daptomycin that have differences concerning storage and reconstitution. Carefully follow the reconstitution and storage procedures in labeling.

2.5 Reconstitution of Daptomycin for Injection Vial

Daptomycin for Injection is supplied in single-dose vials, each containing 350 mg daptomycin as a sterile, lyophilized powder. The contents of a Daptomycin for Injection vial should be reconstituted, using aseptic technique, to 50 mg per mL as follows:

1. To minimize foaming, AVOID vigorous agitation or shaking of the vial during or after reconstitution.
2. Remove the polypropylene flip-off cap from the daptomycin for injection vial to expose the central portion of the rubber stopper.
3. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface.
4. Slowly transfer 7 mL of 0.9% sodium chloride injection through the center of the rubber stopper into the daptomycin for injection vial, pointing the transfer needle toward the wall of the vial. It is

recommended that a beveled sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device is used, pointing the transfer needle toward the wall of the vial.

5. Ensure that all of the daptomycin for injection powder is wetted by gently rotating the vial.
   1. Allow the wetted product to stand undisturbed for 10 minutes.
   2. Gently rotate or swirl the vial contents for a few minutes, as needed, to obtain a completely reconstituted solution.

Administration Instructions

Parenteral drug products should be inspected visually for particulate matter prior to administration.

Slowly remove reconstituted liquid (50 mg daptomycin per mL) from the vial using a beveled sterile needle that is 21 gauge or smaller in diameter. Administer as an intravenous injection or infusion as described below:

Adults

Intravenous Injection over a period of 2 minutes

- For intravenous (IV) injection over a period of 2 minutes in adult patients **only**: Administer the appropriate volume of the reconstituted daptomycin for injection (concentration of 50 mg per mL).

Intravenous Infusion over a period of 30 minutes

- For intravenous (IV) infusion over a period of 30 minutes in adult patients: The appropriate volume of the reconstituted daptomycin for injection (concentration of 50 mg per mL) should be further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride injection.

No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of final IV solution. Do not exceed the In-Use storage conditions of the reconstituted and diluted solutions of Daptomycin for Injection described below. Discard unused portions of daptomycin for injection.

In-Use Storage Conditions for Daptomycin for Injection Once Reconstituted in Acceptable Intravenous Diluents

Stability studies have shown that the reconstituted solution is stable in the vial for 12 hours at room temperature and up to 48 hours if stored under refrigeration between 2° and 8°C (36° and 46°F).

The diluted solution is stable in the infusion bag for 12 hours at room temperature and 48 hours if stored under refrigeration. 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.

2.6 Compatible Intravenous Solutions

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

2.7 Incompatibilities

Daptomycin for Injection is not compatible with dextrose-containing diluents.

Daptomycin for Injection should not be used in conjunction with ReadyMED® elastomeric infusion pumps. Stability studies of daptomycin for injection solutions stored in ReadyMED® elastomeric infusion pumps identified an impurity (2-mercaptobenzothiazole) leaching from this pump system into the daptomycin for injection solution.

Because only limited data are available on the compatibility of daptomycin for injection with other IV substances, additives and other medications should not be added to Daptomycin for Injection single-dose

vials or infusion bags, or infused simultaneously with Daptomycin for Injection through the same IV line. If the same IV line is used for sequential infusion of different drugs, the line should be flushed with a compatible intravenous solution before and after infusion with Daptomycin for Injection.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Yes; Section 2.5

3. *Section 3 Dosage Forms and Strengths*

No new comments

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

(See Review 1for the information in the table)

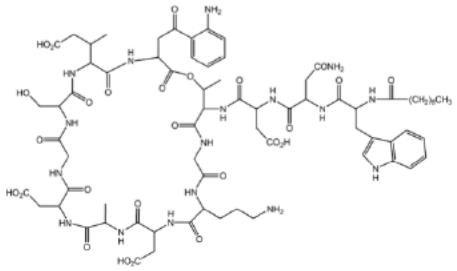
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	
Strengths: in metric system	
Active moiety expression of strength with equivalence statement (if applicable)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	

Section 11 Description

Revised the pH is 4.0 to 5.0 as per Review 1

No new comments

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 ε_1-lactone. The chemical structure is:

4. 

5.

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 from 4.0 to 5.0. Freshly reconstituted solutions of Daptomycin for Injection range in color from pale yellow to light brown.

(See Review 1for the information in the table)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	
Dosage form and route of administration	
Active moiety expression of strength with equivalence statement (if applicable)	
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	
Statement of being sterile (if applicable)	
Pharmacological/ therapeutic class	
Chemical name, structural formula, molecular weight	
If radioactive, statement of important nuclear characteristics.	
Other important chemical or physical properties (such as pKa or pH)	

Section 16 How Supplied/Storage and Handling

How Supplied
Daptomycin for Injection is supplied as a sterile, nonpyrogenic, preservative-free, pale yellow to light brown lyophilized cake in single-does vials as follows:

NDC	Daptomycin for Injection	Package Factor
25021-179-15	350 mg Single-Dose Vial	1 vial per carton
25021-179-16	350 mg Single-Dose Vial	10 vials per carton

The container closure is not made with natural rubber latex.

Storage Conditions
Store refrigerated between 2°C and 8°C (36°F and 46°F); avoid excessive heat. Discard unused portion.

(See Review 1for the information in the table)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	
Available units (e.g., bottles of 100 tablets)	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	
Special handling (e.g., protect from light)	
Storage conditions	
Manufacturer/distributor name (21 CFR 201.1(h)(5))	

Reviewer's Assessment of Package Insert: Adequate

II. Labels:

1. Container and Carton Labels

For Container:
Added "must be refrigerated "
Added "must be reconstituted"
Added "Discard unused portion"

For Carton:
Added per Review 1 "inactive ingredients on the side panel"

(b) (4)

(b) (4)

[redacted]

(See Review 1for the information in the table)

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		
Dosage strength		
Net contents		
"Rx only" displayed prominently on the main panel		
NDC number (21 CFR 207.35(b)(3)(i))		
Lot number and expiration date (21 CFR 201.17)		
Storage conditions		
Bar code (21CFR 201.25)		
Name of manufacturer/distributor		
And others, if space is available		

Reviewer's Assessment of Labels: Adequate
Note: Since the drug product is sterile and non-pyrogenic, it is included in the label with concurrence from OPQ Microbiology.

List of Deficiencies: None

Overall Assessment and Recommendation: Adequate

Shrikant N. Pagay, Ph.D. 8/22/2017
Primary Labeling Reviewer Name and Date:

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

Shrikant Pagay

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Date: 8/22/2017 10:22:08PM
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Comments: shanmugam, balajee

Balajee Shanmugam

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BIOPHARMACEUTICS REVIEW Division of Biopharmaceutics - Office of Pharmaceutical Quality			
Application No.:	NDA 208385-Class 2 Resubmission	**Biopharmaceutics Team Lead:** Elsbeth Chikhale, Ph.D.	
Submission Date:	March 24, 2017		
Division:	Division of Anti Infective Products	**Biopharmaceutics Branch Chief (acting):** Angelica Dorantes, Ph.D.	
Applicant:	Sagent Pharmaceuticals, Inc.	**Acting Division Director:** Paul Seo, Ph.D.	
Trade Name:		**Date Assigned:**	April 4, 2017
Generic Name:	Daptomycin for Injection (350 mg/vial)	**Date of Review:**	September 6, 2017
Indication:	Treatment of complicated skin and skin structure infections	**Type of Submission:** 505(b)(2) Resubmission of New Drug Application	
Dosage form/ Strengths:	Powder for injection (after reconstitution)/350 mg		
Route of Administration:	Intravenous (IV) Injection		

BACKGROUND

Resubmission:
The current Class 2 resubmission of 505(b)(2) NDA 208385 for Daptomycin for Injection, 350 mg/vial drug product provides the Applicant's responses to the deficiency Facility and Quality issues listed in the FDA's complete response (CR) letter dated June 23, 2016. It is noted that the CR letter did not include any Biopharmaceutics deficiencies and therefore the current resubmission does not include any new Biopharmaceutics information for review.

Update to the previous Biopharmaceutics Review:
The Original Biopharmaceutics Review for NDA 208385 *(embedded in the Integrated Quality Assessment for NDA 208385 dated May 27, 2016*) states that the Applicant requested a biowaiver and according to 21 CFR 320.22 (b), the biowaiver Daptomycin for Injection was granted. The current Biopharmaceutics Review provides clarification on the CFR regulation supporting the bridging between the proposed drug product, Daptomycin for Injection and the listed drug product CUBICIN® (daptomycin for injection) under NDA 021572.

Under 21 CFR 320.22(b)(1), a drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following criteria:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

Although both, the listed and proposed drug products are formulated as lyophilized powder to be reconstituted to a solution for injection, the proposed drug product is qualitatively the same as the listed drug product, and the concentration of the active ingredient upon reconstitution is the same for the proposed drug product and the listed drug product; the proposed Daptomycin for Injection product does not fully satisfy the above criteria for a biowaiver under 21 CFR 320.22(b)(1) because the quantity of the active ingredient in each vial is different for the proposed drug product compared to the listed drug (350 mg versus 500 mg).

However, it is noted that based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate by the FDA to establish the bridge (BA/BE) between the listed and proposed drug products. Specifically for NDA 208385, the difference in the quantity of the active ingredient is not expected to impact the bioavailability of daptomycin following intravenous administration, because the final concentration in the reconstituted solutions is the same for the listed and proposed drug products (50 mg/mL). Therefore, in accordance with 21 CFR 320.24(b)(6), the overall provided information is deemed adequate to support the bridge between the proposed Daptomycin for Injection product and the listed drug product, CUBICIN® (daptomycin) for Injection.

RECOMMENDATION:

From the Biopharmaceutics perspective, the Class 2 resubmission of NDA 208385 for Daptomycin for Injection, 350 mg/vial is recommended for **APPROVAL**.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics/OPQ
Office of New Drug Products/OPQ

Elsbeth Chikhale

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Angelica Dorantes

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Risk Table

A. Lifecycle Knowledge Management

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**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability. Impurities Overage	Formulation, Process parameters Raw materials Container closure	L	Adequate acceptance criteria for impurities	Acceptable	*Registration batches show a* (b) (4) *in the bulk solution. Future process validation and commercial manufacturing data should be reviewed to see if this trend persists.*
Reconstitution time	Formulation, Process parameters Raw materials	M	The (b) (4) reconstitution is long but acceptable since stability tests results upon storage are (b) (4) minutes(no OOS)	Acceptable	
Leachable (Rubber stopper)	Container closure	L	Powder for injection; extractable study data in the DMF [not for FOI]	Acceptable	
Sterility	Formulation, Process parameters Raw materials Container closure	H		Acceptable	