

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213645Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213645 Assessment # 2

Drug Product Name	DAPZURA RT (daptomycin for injection)
Dosage Form	Powder for injection
Strength	500 mg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Baxter Healthcare Corporation
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
0022	July 30, 2021	Drug Product (<i>Pharm/Tox</i>)
0023	November 11, 2021	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rohit Tiwari	Ali Al Hakim
Drug Product *	George Lunn	David Claffey
Manufacturing	Kshitij Patkar	David Anderson
Microbiology	Koushik Paul	Jesse Wells
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Labeling	George Lunn	Dorota Matecka
Environmental Analysis	<i>Refer to the Drug Product Review</i>	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

**Drug Product Review is the only updated review included in the current OPQ Assessment # 2;
for all other individual discipline reviews, refer to the OPQ Assessment #1 dated April 26, 2021*

QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs*:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	January 8, 2021	<i>Reviewed by Ying Lin</i>
	III				N/A*	
	III				N/A*	
	V					

*Sufficient information was provided in the NDA for the container/closure system

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
pIND	(b) (4)	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	Adequate (qualification of leachables)	<i>Refer to the P/T review in DARRTS</i>	Dr. Ines Pagan
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, daptomycin for injection. All manufacturing and testing facilities are deemed acceptable and an overall “Approve” recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on November 9, 2021. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This 505(b)(2) NDA provides for a new formulation of daptomycin for injection, 500 mg/vial, to be used for the same indications as the listed drug (LD), Cubicin RF (daptomycin for injection), 500 mg/vial, approved under NDA 21572 (originally held by Cubist Pharmaceuticals, Inc. and acquired by Merck Sharp & Dohme Corp.).

The new formulation of daptomycin for injection proposed in the current NDA contains mannitol and sorbitol, as opposed to sucrose present in the formulation of Cubicin RF. Due to the differences in the product formulation, this application was submitted as a 505(b)(2) and not as a 505(j) application. In view of the similarities between the proposed and listed drugs, the Applicant is relying on previous findings of efficacy and safety for Cubicin RF for approval of this product. Therefore, no clinical studies have been conducted by this Applicant, and the majority of information submitted in the current NDA relates to the product quality. In addition, a biowaiver of the requirement to conduct a BE study comparing the proposed drug to the LD is being requested by the Applicant.

The proposed drug product is a lyophilized powder for injection, which needs to be reconstituted and further diluted for intravenous administration.

Proposed Indication(s) including Intended Patient Population	• Complicated skin and skin structure infections (cSSSI) in adult and pediatric patients (1 to 17 years of age); • <i>Staphylococcus aureus</i> bloodstream infections (bacteremia), in adult patients including those with right-sided infective endocarditis; and • <i>Staphylococcus aureus</i> bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age)
Duration of Treatment	Varies (see package insert)
Maximum Daily Dose	Adult patients: 6 mg/kg (every 24 hours) Pediatric patients: 12 mg/kg (every 24 hours)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

This NDA was originally submitted on June 30, 2020 and issued a Complete Response (CR) letter on April 29, 2021. Most of the CMC information, including information submitted for the manufacturing and testing facilities submitted in the original NDA was found acceptable by the OPQ review team, and no specific Product Quality related deficiencies were included in the CR letter. However, the qualification information for leachables, submitted as part of the extractable/leachable assessment for the proposed drug product commercial container closure system, was consulted with the Pharmacology/Toxicology team and found inadequate. Therefore, this NDA was not recommended for approval by the OPQ review team (refer to the OPQ Assessment # 1 dated April 26, 2021, in DARRTS).

The current NDA resubmission (dated July 30, 2021) includes information to address the non-clinical deficiency cited in the CR letter, specifically qualification data for several identified leachables. The NDA resubmission does not provide any changes to the CMC sections. Most of the OPQ disciplines (except for Drug Product) found the CMC information submitted in the original NDA acceptable. Therefore, the only updated review included in the current OPQ Assessment is the Drug Product Review.

Drug Substance: Adequate

No new information was provided in the NDA resubmission for the proposed drug substance (refer to the Drug Substance Review included in the OPQ Assessment # 1 dated April 26, 2021, in DARRTS).

Drug Product: Adequate

Most of the CMC information provided for the proposed drug product in the original NDA was found sufficient and adequate in the first review cycle (*refer to the OPQ Assessment # 1 dated April 26, 2021*). The only unresolved item was the qualification of several identified leachables from the proposed commercial container closure system. At the time of the first review, sufficient analytical information was supplied and the leachables/extractables testing was described at an adequate level of detail. Several leachables were identified, and the nature and amount of each leachable was consulted with the Pharm/Tox team. The Pharm/Tox team did not find these leachables adequately qualified at the observed levels and recommended a CR action for the NDA. Therefore, the leachable/extractable assessment for the proposed container closure system was found inadequate also from the Drug Product perspective.

The toxicology qualification information for leachables submitted in the current NDA resubmission was reviewed and found adequate by the Pharm/Tox review team. Therefore, the CMC information provided in the NDA is now found acceptable from the Drug Product perspective (*for further details, refer to the Drug Product Review, below*).

Labeling: Adequate

The review of the CMC sections of the labeling, including the container/carton labels, has resulted in several recommendations, which were conveyed to the PM (*refer to the Labeling Review in the OPQ Assessment #1 dated April 26, 2021, in DARRTS*). These recommendations were accepted by the Applicant.

Manufacturing: Adequate

The proposed drug product manufacturing process and all manufacturing and testing facilities were found adequate in the first review cycle (*refer to the OPQ Assessment # 1 dated April 26, 2021*).

No changes to the process or facilities have been proposed in the NDA resubmission. The updated overall facility recommendation of "Approve" was entered for this NDA into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on November 9, 2021.

Biopharmaceutics: Adequate

No new information was provided in the NDA resubmission from the Biopharmaceutics perspective (*refer to the OPQ Assessment # 1 dated April 26, 2021, in DARRTS*).

Microbiology (if applicable): Adequate

No new information was provided in the NDA resubmission from the Microbiology perspective (*refer to the OPQ Assessment # 1 dated April 26, 2021, in DARRTS*).

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Consideratio ns/ Comments
		H, M, or L	(b) (4)	Acceptable or Not Acceptable	
Assay, stability	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
pH	Formulation Raw materials Process parameters Scale/equipment	Low		Acceptable	
Particulate Matter	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	
Bacterial endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	High		Acceptable	

Sterility	Formulation Raw materials Process parameters Scale/equipment Site	High	(b) (4)	Acceptable	
Extractable /leachable*	Formulation Raw materials	Medium		Acceptable*	
Facilities	Site	High		Acceptable	

*The only update from the risk table included in the OPQ Assessment # 1

D. List of Deficiencies for Complete Response - None

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/s/

DOROTA M MATECKA
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RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 213645 Assessment # 1

Drug Product Name	DAPZURA RT (daptomycin for injection)
Dosage Form	Powder for injection
Strength	500 mg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Baxter Healthcare Corporation
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
0000	June 30, 2020	All
0001	September 8, 2020	Drug Product, Microbiology, Facilities
0004	September 25, 2020	Process
0007	November 3, 2020	Process
0008	December 3, 2020	Drug Product
0009	December 16, 2020	Labeling
0010	January 12, 2021	Drug Substance
0012	February 4, 2021	Drug Product
0013	February 12, 2021	Drug Product
0014	February 22, 2021	Labeling
0015	March 12, 2021	Drug Product
0017	March 22, 2021	Drug Product
0018	March 31, 2021	Drug Product
0019	April 13, 2021	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rohit Tiwari	Ali Al Hakim
Drug Product	George Lunn	Dorota Matecka
Manufacturing	Kshitij Patkar	David Anderson
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Environmental Analysis	<i>Refer to the Drug Product Review</i>	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

QUALITY ASSESSMENT DATA SHEET

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	III				N/A*	
	III				N/A*	
	V					

*Sufficient information was provided in the NDA for the container/closure system

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description
pIND	(b) (4)	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	Inadequate (qualification of leachables)	<i>Refer to the P/T review in DARRTS</i>	Dr. Ines Pagan
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA has provided comprehensive chemistry, manufacturing and controls (CMC) information for the proposed drug substance (daptomycin) and the drug product (daptomycin for injection). The overall CMC information, including information submitted for the manufacturing and testing facilities, was found acceptable by the OPQ review team, and no specific Product Quality related deficiencies were identified.

However, the qualification information submitted as part of the extractable/leachable assessment for the drug product container closure system, was consulted with the Pharmacology/Toxicology team and it was found inadequate. Therefore, this NDA is not recommended for approval by the OPQ review team at this time.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This 505(b)(2) NDA provides for a new formulation of daptomycin for injection, 500 mg/vial, to be used for the same indications as the listed drug (LD), Cubicin RF (daptomycin for injection), 500 mg/vial, approved under NDA 21572 (originally held by Cubist Pharmaceuticals, Inc. and acquired by Merck Sharp & Dohme Corp.).

The new formulation of daptomycin for injection proposed in the current NDA contains mannitol and sorbitol, as opposed to sucrose present in the formulation of Cubicin RF. Due to the differences in the product formulation, this application was submitted as a 505(b)(2) and not as a 505(j) application. In view of the similarities between the proposed and listed drugs, the Applicant is relying on previous findings of efficacy and safety for Cubicin RF for approval of this product. Therefore, no clinical studies have been conducted by this Applicant, and the majority of information submitted in the current NDA relates to the product quality. In addition, a biowaiver of the requirement to conduct a BE study comparing the proposed drug to the LD is being requested by the Applicant.

The proposed drug product is a lyophilized powder for injection, which needs to be reconstituted and further diluted for intravenous administration.

Proposed Indication(s) including Intended Patient Population	• Complicated skin and skin structure infections (cSSSI) in adult and pediatric patients (1 to 17 years of age); • <i>Staphylococcus aureus</i> bloodstream infections (bacteremia), in adult patients including those with right-sided infective endocarditis; and • <i>Staphylococcus aureus</i> bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age)
Duration of Treatment	Varies (see package insert)
Maximum Daily Dose	Adult patients: 6 mg/kg (every 24 hours) Pediatric patients: 12 mg/kg (every 24 hours)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The chemistry, manufacturing and control information for daptomycin drug substance is referenced to DMF (b) (4). This DMF is currently adequate and no amendments were submitted after the recent review dated January 8, 2021, which was conducted to support another application. Some of the information derived from the DMF has been included in the NDA to support the quality of the drug substance batches used in the manufacture of the drug product. In addition, results of the testing on those batches conducted by the Applicant have also been included. These data, including the description and validation of the analytical procedures used for the determination of the drug substance assay and related substances, were found acceptable. Daptomycin drug substance is packaged (b) (4).

(b) (4) The retest period for daptomycin established by the DMF holder is (b) (4) months when stored (b) (4) at (b) (4) °C.

For further details, refer to the Drug Substance Review, below.

Drug Product: Inadequate

Daptomycin for injection is a lyophilized powder that is intended for reconstitution with sterile water for injection or bacteriostatic water for injection, prior to intravenous administration. The drug product is described as a pale yellow to light brown lyophilized powder supplied in a 10 mL clear glass vial fitted with a (b) (4) rubber stopper, an aluminum flip-

off seal, and a purple polypropylene flip-off cap, each containing 500 mg of daptomycin. Sodium hydroxide and hydrochloric acid are used to adjust the pH (b) (4)

(b) (4) The drug product has a reconstitution time of $\leq$ (b) (4) minutes and should be stored at 20-25°C. The inactive ingredients include (b) (4) excipients, mannitol and sorbitol. The inactive ingredients are compendial and are not of human or animal origin.

The drug product specification includes all important tests for the proposed dosage form, such as appearance, assay, impurities, reconstitution time, color, pH, osmolality, particulates, extractable volume, identity, dose uniformity, endotoxins, and sterility. The tests and acceptance criteria have been found adequate. In addition, descriptions of the analytical procedures, including validation data were also found acceptable. All impurities greater than the identification and qualification thresholds have been identified. This product has (b) (4)

(b) (4) as determined by LC-MS.

Twelve (12) months of stability data obtained at 25°C/60% RH and 30°C/65% RH and six (6) months obtained at 40°C/75% RH have been provided in the NDA for three representative batches. In addition, a photostability study and a thermal cycling study was carried out for one batch each. No out of specification results were observed for any of the tested attributes during drug product stability studies. The obvious trends include (b) (4)

(b) (4) The results of the stability testing support an expiration dating period of 15 months with a storage statement of "Store original packages at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]" as proposed by the Applicant. An in-use study supports the stability and hold times proposed in the labeling for the drug product solutions in the vials, in syringes, or after adding to saline bags.

The Applicant requests a categorical exclusion from the requirement to prepare an Environmental Assessment and the claim is accepted.

The results of the leachables/extractables studies were provided late in the review cycle (Amendment 0017) in response to the FDA recommendation. However, a description of the analytical methods used for leachable testing was not included. This information and other

analytical details were submitted in two subsequent Amendments (0018 and 0019). A number of leachables were identified and this information, including the identity and the observed levels of each leachable, was consulted with the Pharm/Tox review team. The qualification information submitted for leachables was reviewed and found inadequate by the Pharm/Tox review team. Therefore, the overall leachable assessment for the proposed container closure system is found inadequate also from the Drug Product perspective. The deficiencies identified by the Pharm/Tox review team will be included in the Complete Response letter.

Refer to the Drug Product Review and Addendum, below.

Labeling: Choose an item.

The review of the CMC sections of the labeling, including the container/carton labels, has resulted in a number of recommendations, which were conveyed to the PM. These recommendations along with the comments from other disciplines will be forwarded to the Applicant.

Manufacturing: Adequate

The proposed manufacturing process for the drug product, daptomycin for injection, (b) (4) includes the following operations (b) (4)

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

The drug substance is manufactured by (b) (4) and the drug product is manufactured by Baxter Pharmaceutical Solutions LLC (Baxter Bloomington). In addition, several other facilities are involved in the release and other testing of both drug substance and the drug product. All facilities have been found adequate and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on September 10, 2020. Refer to the Manufacturing Review, below.

Biopharmaceutics: Adequate

The biopharmaceutics review of this NDA focused on the review of the data, and information provided in the NDA to support the bridging between the proposed drug product and the LD. Because the proposed

drug product contains different inactive ingredients (i.e., 238 mg sorbitol and 238 mg mannitol versus 713 mg sucrose in the LD), a biowaiver under 21 CFR 320.22(b)(1) does not apply. The Applicant established the bridge between the LD and proposed drug product, based on 21 CFR 320.24(b)(6).

To justify the scientific appropriateness of reliance on the LD, the Applicant provided side-by-side comparisons of product formulations, physiochemical data, and in vitro plasma protein binding data, as well as information available in the labeling and literature, to demonstrate that:

- the proposed drug product and the LD have the same indication, and both are intended for administration either by injection or infusion with the same dose, volume and infusion rate of administration;
- the proposed drug product and the LD have the same active ingredient, the same drug concentration (after reconstitution and further dilution, at the time of administration to patients), and same the dosing regimen;
- the differences in the excipients (i.e., the presence of 238 mg sorbitol and 238 mg mannitol in the proposed formulation versus 713 mg sucrose in the LD formulation) had no significant effect on protein binding as compared to the LD;
- the proposed drug product has physiochemical properties comparable to those of the LD at batch release and on stability. Both, the proposed drug product and the LD are sterile lyophilized white to off-white cake or powder for reconstitution, and upon re-constituted/diluted result in colorless solutions with comparable pH, osmolality, specific gravity, and stability;
- the inclusion of mannitol and sorbitol in the formulation of the proposed drug product, in place of sucrose (b) (4) are not expected to alter the physiological disposition, safety, and efficacy of daptomycin, with respect to those of the LD in humans.

Based on the review of the overall information provided in the NDA, it has been concluded that the regulatory and scientific bridge between the LD and proposed drug product is adequately established under 21 CFR 320.24(b)(6). Refer to the Biopharmaceutics Review, below.

Microbiology (if applicable): Adequate

The manufacturing process for this proposed drug product includes (b) (4)

The product quality microbiology review focused on the assessment of areas related to the proposed drug product sterility assurance, such as manufacturing facilities, procedures and equipment, sterilization and

depyrogenation practices, methods used for environmental monitoring,
 (b) (4) validation, container closure integrity testing, (b) (4)
 (b) (4)
 validation and requalification procedures, etc.

The overall product quality microbiology information provided for the drug product in the NDA and the subsequent amendment was found acceptable. Refer to the Microbiology Review, below

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Consideratio ns/ Comments
		H, M, or L	(b) (4)	Acceptable or Not Acceptable	
Assay, stability	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
pH	Formulation Raw materials Process parameters Scale/equipment	Low		Acceptable	
Particulate Matter	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	
Bacterial endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	High		Acceptable	

Sterility	Formulation Raw materials Process parameters Scale/equipment Site	High	(b) (4)	Acceptable	
Extractable /leachable	Formulation Raw materials	Medium		Not acceptable	
Facilities	Site	High		Acceptable	

D. List of Deficiencies for Complete Response - *None*

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NDA 213645

CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	DAPZURA RT	Adequate
Established name(s)	daptomycin for injection	Adequate
Route(s) of administration	for Intravenous Use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	For Injection: 500 mg lyophilized powder for reconstitution in a single-dose vial	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	single-dose vial	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

Preparation and Administration of DAPZURA RT

There are two formulations of daptomycin that have differences concerning storage and reconstitution. **[No reference to the other formulation?]** Carefully follow the reconstitution and storage procedures in labeling.

Reconstitution of DAPZURA RT Vial

DAPZURA RT must be reconstituted within the vial only with either Sterile Water for Injection or Bacteriostatic Water for Injection. **[Supported by data in NDA P.1]**

Do **NOT** use saline based diluents for the reconstitution in the vial because this will result in a hyperosmotic solution that may result in infusion site reactions if the reconstituted product is administered as an intravenous injection over a period of 2 minutes. **[Osmolality for solutions reconstituted as recommended is experimentally determined as 349-355 mOsm/kg, P.5.4. Reconstitution with saline would increase those numbers.]**

DAPZURA RT is supplied in single-dose vials, each containing 500 mg daptomycin as a sterile, lyophilized powder. The contents of a DAPZURA RT vial should be reconstituted, using aseptic technique, to 50 mg/mL as follows:

1. Remove the polypropylene flip-off cap from the DAPZURA RT vial to expose the central portion of the rubber stopper.
2. 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.
3. Transfer 10 mL of Sterile Water for Injection or Bacteriostatic Water for Injection through the center of the rubber stopper into the DAPZURA RT vial. Use a beveled sterile transfer needle that is 21 gauge or smaller in diameter, pointing the transfer needle toward the wall of the vial.
4. Rotate or swirl the vial contents for a few minutes, as needed, to obtain a completely reconstituted solution. **[Preparation instructions supported by data in NDA P.1]**

Administration Instructions

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

Slowly remove reconstituted liquid (50 mg daptomycin/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:

No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of final IV solution. Table 4 below provides in-use storage conditions for reconstituted DAPZURA RT in acceptable intravenous diluents in the syringe, vial and intravenous bag (for reconstitution and dilution). Do not exceed the listed shelf-life of reconstituted and diluted solutions of DAPZURA RT. Discard unused portions of DAPZURA RT.

Table 1. In-Use Storage Conditions for DAPZURA RT Once Reconstituted in Acceptable Intravenous Diluents

Container	Diluent	In-Use Shelf-Life	
		Room Temperature (20°C–25°C, 68°F–77°F)	Refrigerated (2°C–8°C, 36°F–46°F)
Vial	Sterile Water for Injection	18 Hours	3 Days
	Bacteriostatic Water for Injection	2 Days	5 Days
Syringe*	Sterile Water for Injection	18 Hours	3 Days
	Bacteriostatic Water for Injection	2 Days	5 Days
Intravenous Bag	Reconstitution: Sterile Water for Injection for immediate dilution with 0.9% sodium chloride injection	1 Day	3 Days
	Reconstitution: Bacteriostatic Water for Injection for immediate dilution with 0.9% sodium chloride injection	2 Days	5 Days

*Polypropylene syringe with elastomeric plunger stopper.

[Microbiological data to support the table above are found in the NDA at P.2.5. CMC data are found in P.8]

(b) (4) **Compatible Intravenous Solutions**

Reconstituted DAPZURA RT is compatible with Sterile Water for Injection, Bacteriostatic Water for Injection, and 0.9% sodium chloride injection. [See Dosage and Administration (2.7).]

[See remarks above.]

(b) (4) Incompatibilities

(b) (4) is not compatible with dextrose-containing diluents.

DAPZURA RT 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 (b) (4) with other IV substances, additives and other medications should not be added to DAPZURA RT single-dose vials or infusion bags, or infused simultaneously with DAPZURA RT 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 DAPZURA RT.

[No CMC information contradicts the above statement.]

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	A number of CMC-related statements are made, see above.	Adequate. Each of these statements is supported by CMC data in the NDA. See comments in red above.

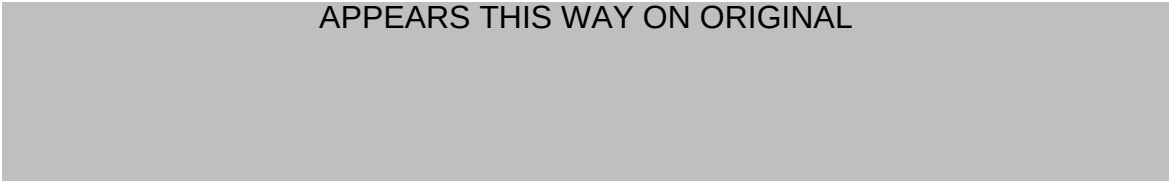
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

For Injection: 500 mg daptomycin as a sterile, pale yellow to light brown lyophilized powder for reconstitution in a single-dose vial.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Single-dose vial	Adequate
Strength(s) in metric system	500 mg/vial	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	sterile, pale yellow to light brown lyophilized powder for reconstitution in a single-dose vial	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	Adequate
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	single-dose vial.	Adequate

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL



Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	DAPZURA RT (daptomycin for injection)	Adequate
Dosage form(s) and route(s) of administration	for injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	238 mg sorbitol and 238 mg of mannitol and sodium hydroxide and/or hydrochloric acid used to adjust the pH	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	238 mg sorbitol and 238 mg of mannitol and sodium hydroxide and/or hydrochloric acid used to adjust the pH	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Statement of being sterile (if applicable)	Present	Adequate
Pharmacological/therapeutic class	cyclic lipopeptide antibacterial agent derived from the fermentation of <i>Streptomyces roseosporus</i>	Adequate
Chemical name, structural formula, molecular weight	All are present	Generally adequate. In chemical name "Dseryl" should be "D-seryl" Structural formula should show stereochemistry
If radioactive, statement of important nuclear characteristics.	NA	

Other important chemical or physical properties (such as pKa or pH)	The pH of the solution upon reconstitution is 6.8. Freshly reconstituted solutions of DAPZURA RT range in color from pale yellow to light brown.	Adequate
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Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	None observed	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

DAPZURA RT (daptomycin for injection) is supplied as a sterile pale yellow to light brown lyophilized powder in a single-dose 10 mL vial containing 500 mg of daptomycin: Package of 1 (NDC 60977-145-01).

Store original packages at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] [see *Dosage and Administration* (2.7)].

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Single-dose vial	Adequate
Strength(s) in metric system	500 mg/vial	Adequate
Available units (e.g., bottles of 100 tablets)	Package of 1	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	sterile pale yellow to light brown lyophilized powder in a single-dose 10 mL vial	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose vial	Adequate

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	None	Adequate, the product is photostable, see P.7
If the product contains a desiccant, ensure the size and shape differ from the dosage	NA	

form and desiccant has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store original packages at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] [see <i>Dosage and Administration</i> (2.7)].	Generally adequate. Section 2.7 provides the reconstitution directions. Perhaps we could say: [see <i>Dosage and Administration</i> (2.7) <i>for reconstitution directions</i>].
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	No mention of latex.	The product is indeed free of latex, see P.7. Should state: “Not made with natural rubber latex.”
Include information about child-resistant packaging	NA	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Baxter Healthcare Corporation Deerfield, IL 60015 USA	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Patient Counseling Information is provided but contains no CMC-related information.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label (as of 2/22/21)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Dapzura RT (daptomycin for injection)	Adequate
Dosage strength	500 mg per vial	Adequate
Route of administration	For intravenous use	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	
Net contents (e.g. tablet count)	None	Acceptable
"Rx only" displayed on the principal display	Present	Adequate
NDC number	NDC 60977-145-01	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F. See package insert for Usual Dosage and storage of reconstituted and further diluted product.	Not all of the standard USP language is used but this is acceptable for reasons of space
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Baxter Healthcare Corporation	Adequate
Medication Guide (if applicable)	NA	
No text on Ferrule and Cap overseal	No text	Adequate
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	
And others, if space is available	No reference to reconstitution directions, inactive ingredients, lack of preservatives, and latex-free stoppers.	Acceptable for reasons of space. These items (except for latex) are on the carton.

3.2 Carton Labeling (as of 2/22/21)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Dapzura RT (daptomycin for injection)	Adequate
Dosage strength	500 mg per vial	Adequate
Route of administration	For intravenous use	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	
Net contents (e.g. tablet count)	This package contains one single-dose vial	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	NDC 60977-145-01	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature.] See package insert for storage of reconstituted and further diluted product.	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Baxter Healthcare Corporation Deerfield, IL 60015	Adequate
Medication Guide (if applicable)	NA	
No text on Ferrule and Cap overseal	No text	Adequate
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	
And others, if space is available	Reconstitute with 10 mL Sterile Water for Injection or Bacteriostatic Water for Injection to obtain a final concentration of 50 mg/mL. Not made with natural rubber latex. Each vial also contains 238 mg sorbitol and 238 mg of mannitol. Sodium hydroxide and/or hydrochloric acid are used to adjust the pH. Contains no preservatives. Note: Parenteral drug products should be inspected visually for particulate matter prior to administration.	Generally, adequate, supported by data in NDA P.1.

Assessment of Carton and Container Labeling: *Adequate*

As modified in the Amendment of 2/22/21 the carton and container label are adequate.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: George Lunn, Ph.D., 4/23/21

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Dorota Matecka, Ph.D., 4/23/21*



George
Lunn

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Comments: All recommendations have been conveyed to OND.



Dorota
Matecka

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	213645; 505(b)(2) Type 5-New Formulation
Assessment Cycle Number	1
Drug Product / Strength	DAPZURA RT (daptomycin for injection), 500 mg/vial
Route of Administration	Intravenous (IV)
Applicant Name	Baxter Healthcare Corporation
Therapeutic Classification/ OND Division	Anti-Infectives OND/OID/DAI
Associated INDs	IND 140912
Listed Drug	NDA 021572; CUBICIN® RF (daptomycin for injection), 500 mg/vial; Cubist Pharms LLC.
Proposed Indication	DAPZURA RT is a lipopeptide antibacterial indicated for the treatment of: • Complicated skin and skin structure infections (cSSSI) in adult and pediatric patients (1 to 17 years of age) and, • <i>Staphylococcus aureus</i> bloodstream infections (bacteremia), in adult patients including those with right-sided infective endocarditis, • <i>Staphylococcus aureus</i> bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age).
Primary Assessor	Qi Zhang, Ph.D.
Secondary Assessor	Elsbeth Chikhale, Ph.D.
Assessment Recommendation	<i>Adequate</i>

ASSESSMENT SUMMARY

This 505(b)(2) application for DAPZURA RT (daptomycin for injection), 500 mg/vial, relies for approval on FDA's findings of safety and effectiveness of the Listed Drug (LD) approved under NDA 021572, CUBICIN RF (500 mg/vial). Because the proposed drug product (DP) contains different inactive ingredients (i.e., 238 mg sorbitol and 238 mg mannitol vs. 713 mg sucrose (b) (4)), a biowaiver under 21 CFR 320.22(b)(1) does not apply. The Applicant established the bridge between the LD and proposed drug product, based on 21 CFR 320.24(b)(6). The Biopharmaceutics review is focused on the data and information supporting the bridging between the proposed DP and the LD.

To justify the scientific appropriateness of reliance on the LD, the Applicant provided side-by-side comparisons of product formulations, physiochemical data, and in vitro plasma protein binding data, as well as information available in the labeling and literature, to demonstrate that:

- the proposed drug product and the LD have the same indication, and both are intended for administration either by injection or infusion with the same dose, volume and infusion rate of administration;
- the proposed drug product and the LD have the same active ingredient, the same drug concentration (after reconstitution and further dilution, at the time of administration to patients), and same the dosing regimen;
- the differences in the excipients (i.e., the presence of 238 mg sorbitol and 238 mg mannitol in the proposed formulation vs. 713 mg sucrose in the LD formulation) had no significant effect on protein binding as compared to the LD;
- the proposed drug product has physiochemical properties comparable to those of the LD at batch release and on stability. Both, the proposed drug product and the LD are sterile lyophilized white to off-white cake or powder for reconstitution, and upon reconstituted/diluted result in colorless solutions with comparable pH, osmolality, specific gravity, and stability;
- the inclusion of mannitol and sorbitol in the formulation of the proposed drug product, in place of sucrose (b) (4) are not expected to alter the physiological disposition, safety, and efficacy of daptomycin, with respect to those of the LD in humans.

Overall, based on the provided collective information, the regulatory and scientific bridge between the LD and proposed drug product is adequately established under 21 CFR 320.24(b)(6). Refer to the FDA's labeling review for the recommended labeling to ensure safe and effective use of the proposed DAPZURA RT (daptomycin for injection), 500 mg/vial.

List of Submissions Being Assessed:

Document(s) Assessed	Sequence	Date Received
Original Submission	0000	06/30/2020

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

Recommendation:

From a Biopharmaceutics perspective, NDA 213645 for DAPZURA RT (daptomycin for injection), 500 mg/vial is recommended for **APPROVAL**.

B.1 BCS DESIGNATION

Assessment: Not Applicable for parenteral drug products

Solubility:

Daptomycin is freely soluble in water and buffer solutions at pH from 1.2 to 7.5. Per the proposed labeling, the daptomycin lyophilized powder contains sodium hydroxide and hydrochloride acid as pH adjusters, and the pH of the daptomycin solution is approximately 6.8 upon reconstitution with water to produce daptomycin injection.

Permeability:

Not provided in the submission, and it is not needed.

Dissolution:

Not applicable for parenteral drug products.

B.12 BIOWAIVER REQUEST

Assessment: Not Applicable

The proposed drug product will rely on CUBICIN® RF [NDA 021572; Cubist Pharmaceuticals, LLC (Merck, Sharp & Dohme Corp.)] as the Listed Drug (LD).

The LD, CUBICIN RF (daptomycin for injection) is a lyophilized 500 mg daptomycin powder in a single dose 10 mL vial approved for intravenous use. The current labeling for CUBICIN RF¹ states that “Each (10 mL) vial contains 713 mg sucrose, and sodium hydroxide is used to adjust the pH. The pH of the solution upon reconstitution is 6.8.”

Noted the LD is also available in a different formulation, CUBICIN® 500 mg/vial containing sodium hydroxide, the only inactive ingredient, which is used for pH adjustment. The two different formulations of daptomycin have different reconstitution and storage procedures. Cubicin RF requires sterile or bacteriostatic water (SWFL or BWFL) as a diluent for reconstitution whereas Cubicin uses 0.9% sodium chloride. Cubicin RF may be stored at room temperature whereas Cubicin is stored at refrigerated temperatures (refer to the labeling for the detailed information).

Unlike the LD, for the proposed DP formulation, each 10 mL vial contains “238 mg sorbitol and 238 mg of mannitol, and sodium hydroxide and/or hydrochloric acid to adjust the pH to approximately 6.8” in addition to the 500 mg daptamycin powder. However, there are no changes proposed for the dosage form, strength, and mode of administration, indication and dosing regimen, and reconstitution/dilution procedures and storage conditions (refer to the proposed labeling revised by the FDA).

Since the proposed formulation contains different excipients compared to the relied upon LD (238 mg mannitol and 238 sorbitol vs. 713 mg sucrose), a biowaiver under 21 CFR 320.22(b)(1) does not apply. However, bridging under 21 CFR 320.24(b)(6) is feasible, which is discussed under the Section B.13.

B.13 BRIDGING

Assessment: Adequate

The Applicant had previously discussed with FDA regarding the biowaiver approach for the proposed daptomycin injection [refer to PIND 140912 meeting written response in DARRTS dated 11/30/2018]. FDA provided feedback that a biowaiver is not applicable for the proposed drug product under 21 CFR 320.22(b)(1), however, a bridge could be established between the proposed drug product and the LD under 21 CFR 320.24(b)(6), as

¹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021572s060lblcubicinRF.pdf

outlined in the meeting written response, i.e., the Applicant must characterize the differences in formulation and physicochemical properties, and provide information demonstrating that the differences do not affect the in vivo physiological disposition, safety and efficacy of the proposed DP relative to the LD. In the current NDA submission, the Applicant provided the requested information including a side-by-side comparison of product formulation (Appendix-Tables 1 and 2) and physicochemical data (such as pH, osmolality, and gravity; Appendix-Table 3) between the proposed DP and the LD after reconstitution/dilution.

Presence of Mannitol and Sorbitol (b) (4)

Collectively, the following information support that the inclusion of mannitol and sorbitol used in place of sucrose as lyoprotants in the LD formulation, are not expected to affect the distribution/disposition kinetics, as well as the efficacy and safety of daptomycin:

- 1) The provided comparative physicochemical data demonstrate that the proposed formulation resulted in a solution with similar pH, osmolality, and stability, as compared to the LD after appropriate reconstitution and dilution prior to administration (refer to “Comparative Physicochemical Properties” below).
- 2) Results of an in vitro plasma protein binding assay show that the presence of mannitol and sorbitol in the proposed formulation had no significant effect on the protein binding compared to the LD. The in vitro plasma protein binding assay was performed with 3 registration lots of the proposed formulation and 2 lots of the LD. The mean plasma protein binding of daptomycin at 10 µg/mL ranged between 94.7 and 96.4%, and at 100 µg/mL ranged between 93.3 and 94.7% for the proposed formulation and the LD respectively (refer to Appendix-Table 4).
- 3) Mannitol and sorbitol are unlikely to induce interference with daptomycin in the solution. No data were found in the scientific literature assessing the chemical or physical interaction of mannitol and/or sorbitol with daptomycin or similar molecules. No clinical literature was found that demonstrates that mannitol and sorbitol would have an impact on daptomycin disposition in human subjects.
- 4) A search of the FDA’s Inactive Ingredients Database (IID) indicates there are other FDA approved drugs with levels of mannitol and sorbitol similar to or higher than those in the proposed daptomycin drug product. The Applicant provided additional literature information on the clinical safety of mannitol and sorbitol at the proposed levels, to support the maximum duration of dosing (up to 6 weeks for bacteremia/endocarditis) for the proposed daptomycin drug product. Refer to the Clinical Review for the supporting information.
- 5) The proposed indication, dosage and route of administration (IV), and dosing regimen are the same as those approved for the LD, based on the proposed labelling in comparison with the LD. The proposed DP and the LD will have the same concentration of the active ingredient after reconstitution (50 mg/mL for IV injection over a period of 2 minutes) and dilution (1 mg/mL for IV infusion over a period of 30 minutes) at the time administration to the patients.

Comparative Physicochemical Properties

The comparative physicochemical properties of the proposed DP (3 registration stability lots, #935055, 935056 and 935057); 11 months old at 25 °C lyophilized storage conditions)

and the LD (#S007458), after reconstitution with 10 mL of diluent (BWFI) and further dilution in 0.9% sodium chloride injection, are provided in Study Report BXU551373SR in Section 1.12.15.

The pH data confirmed that there is no difference in pH; the reconstituted pH for both, the proposed drug product and the LD, is approximately 6.8. After further dilution, the pH of both products is consistently similar (approximately 6.2) at final drug concentration levels of 1 mg/mL (refer to Appendix-Table 3). The osmolality data showed that the proposed DP and the LD have comparable osmolality in the reconstituted solution and the same osmolality for reconstituted and dilution solution. When reconstituted with 10 mL of BWFI, the osmolality for the proposed DP is approximately 425 vs. 395 mOsm/Kg for the LD, but such 30 mOsm/kg difference is not a concern when considering the safety of the proposed DP. The osmolality of the proposed DP and LD is approximately 305-310 mOsm/kg with further dilution in a 50 mL of 0.9 % sodium chloride. The gravity data showed that the proposed drug product and LD have the same gravity in reconstituted solution and reconstituted diluted solutions.

In addition, the proposed DP was found to be stable and comparable to LD, since all the critical parameters such as color of reconstituted solution (pale yellow to light brown), reconstitution time (NMT (b)(4) minutes), pH ((b)(4)), osmolality ((b)(4) mOsm/kg when reconstituted with 10 mL of SWFI), assay, and impurities, are found to be complying with proposed specifications at release and on stability. Refer to the Drug Substance and Drug Product Reviews for additional CMC information.

Overall, the bridging between the proposed drug product and the LD is adequately established, based on the side-by-side comparison of the formulation, physicochemical properties between the proposed DP and the LD, as well as information available in the labeling and literature; therefore, an in-vivo bioavailability study, comparing the LD to the proposed DP, is not needed. Refer to the FDA's labeling review for the recommended labeling to ensure safe and effective use of the proposed Daptomycin for Injection.

BIOPHARMACEUTICS LIST OF DEFICIENCIES CONVEYED TO THE APPLICANT DURING THE REVIEW

None.

APPENDIX

Table 1. Comparison of Drug Product Formulation Between Baxter's Daptomycin for Injection and CUBICIN RF

Component	Baxter Proposed Product: Daptomycin for Injection			Reference Product: CUBICIN RF (Daptomycin) for Injection		
	Amount in Container ^a	Concentration upon Reconstitution for Administration	Concentration upon Reconstitution & Dilution ^b	Amount in Container ^a	Concentration upon Reconstitution for Administration	Concentration upon Reconstitution & Dilution ^b
Daptomycin	500 mg	50 mg/mL	7.1 mg/mL	500 mg	50 mg/mL	7.1 mg/mL
Sorbitol	238 mg	23.8 mg/mL	3.4 mg/mL	N/A	N/A	N/A
Mannitol	238 mg	23.8 mg/mL	3.4 mg/mL	N/A	N/A	N/A
Sucrose	N/A	N/A	N/A	713 mg	71.3 mg/mL	10.2 mg/mL
Sodium Hydroxide	As needed	N/A	N/A	As needed	N/A	N/A
Hydrochloric Acid	As needed	N/A	N/A	N/A	N/A	N/A

N/A = Not Applicable

^a Amount stated in prescribing information.

^b Per the prescribing information, the appropriate volume of the reconstituted daptomycin product (concentration of 50 mg/mL) should be further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride injection. The concentration listed assumes 10 mL (500 mg) of reconstituted solution are added to a 50 mL IV infusion bag of 0.9% sodium chloride injection. A 50 mL IV bag contains approximately 60 mL of 0.9% sodium chloride injection; therefore, the total volume in the admixed bag would be approximately 70 mL.

Table 2. Comparison on Dosage Form, Administration, and Storage Between Baxter's Daptomycin for Injection and CUBICIN RF

Attribute	Daptomycin for Injection	CUBICIN RF
Dosage Form	Single-dose vial Injection, powder, lyophilized	Single-dose vial Injection, powder, lyophilized
Route of Administration	Intravenous injection or infusion	Intravenous injection or infusion
Dosage Strength	500 mg of Daptomycin per vial (b) (4) mg per vial with overfill)	500 mg of Daptomycin per vial (b) (4) mg per vial with overfill)
Lyophilized Vial Storage Temperature	20 – 25 °C	20 – 25 °C
Container Closure System	10 mL vial with 20 mm stopper	10 mL vial with 20 mm stopper
Description	Pale yellow to light brown, lyophilized powder	Pale yellow to light brown, lyophilized powder
Administered Volume	Reconstituted concentration is 50 mg/mL. Administration volume will be equivalent to the reference listed drug based on calculated dose.	Reconstituted concentration is 50 mg/mL. Administration volume is based on the calculated dose as described in the prescribing information.
Diluent for Reconstitution & Volume	SWFI and BWFI, 10 mL	SWFI and BWFI, 10 mL
Reconstituted Solution Shelf-life	<u>In Vial:</u> After Reconstitution with SWFI is 18 hours at 20°C–25°C and 3 days at 2°C–8°C. ^a After Reconstitution with BWFI is 2 days at 20°C–25°C and 5 days at 2°C–8°C. ^a <u>In Syringe:</u> After Reconstitution with SWFI is 18 hours at 20°C–25°C and 3 days at 2°C–8°C. ^a After Reconstitution with BWFI is 2 days at 20°C–25°C and 5 days at 2°C–8°C. ^a	<u>In Vial:</u> After Reconstitution with SWFI is 1 day at 20°C–25°C and 3 days at 2°C–8°C. After Reconstitution with BWFI is 2 days at 20°C–25°C and 3 days at 2°C–8°C. <u>In Syringe:</u> After Reconstitution with SWFI is 1 day at 20°C–25°C and 3 days at 2°C–8°C. After Reconstitution with BWFI is 2 days at 20°C–25°C and 5 days at 2°C–8°C.
Diluent for Dilution & Volume	0.9 % NaCl Injection, 50 mL	0.9 % NaCl Injection, 50 mL
Diluted Solution Shelf-life	After Reconstitution with SWFI for immediate dilution with 0.9% sodium chloride injection is 1 day at 20°C–25°C and 3 days at 2°C–8°C. ^a . After Reconstitution with BWFI for immediate dilution with 0.9% sodium chloride injection is 2 days at 20°C–25°C and 5 days at 2°C–8°C. ^a .	After Reconstitution with SWFI for immediate dilution with 0.9% sodium chloride injection is 19 hours at 20°C–25°C and 3 days at 2°C–8°C. After Reconstitution with BWFI for immediate dilution with 0.9% sodium chloride injection is 2 days at 20°C–25°C and 5 days at 2°C–8°C.

^a Microbial challenge, chemical and physical stability has been demonstrated for this timeframe.

Table 3. Comparative pH, Osmolality, and Specific Gravity Data Between Baxter's Daptomycin for Injection¹ and CUBICIN RF²

Product	Lot #	pH After Reconstitution + 2 Days Storage at 25 °C	pH After Reconstitution and Dilution + 2 Days Storage at 25 °C
Daptomycin for Injection ^a	934871/935055	6.8	6.2
		6.8	6.2
		6.8	6.2
	934872/935056	6.7	6.2
		6.7	6.1
		6.7	6.2
	934873/935057	6.8	6.2
		6.8	6.3
		6.8	6.2
CUBICIN RF ^a	S007458	6.8	6.2
		6.8	6.2
		6.8	6.2
Product	Lot #	Osmolality After Reconstitution + 2 Days Storage at 25 °C (mOsm/kg)	Osmolality After Reconstitution and Dilution + 2 Days Storage at 25 °C (mOsm/kg)
Daptomycin for Injection ^a	934871/935055	433	311
	934872/935056	422	311
	934873/935057	421	310
CUBICIN RF ^a	S007458	393	305
		400	303
		396	305
Product	Lot #	Specific Gravity After Reconstitution + 2 Days Storage at 25 °C	Specific Gravity After Reconstitution and Dilution + 2 Days Storage at 25 °C
Daptomycin for Injection ^a	934871/935055	1.033	1.011
	934872/935056	1.034	1.012
	934873/935057	1.034	1.012
CUBICIN RF ^a	S007458	1.045	1.013

¹ The Daptomycin for Injection were tested after 11 months of 25 °C lyophilized storage.

² The LD was tested at 6 months before the expiration date (Lot S007458)

^a Reconstituted with 10 mL of BWFI and stored 2 days at 25 °C in the vial or reconstituted with 10 mL of BWFI, diluted in 50 mL bag of 0.9 % Sodium Chloride Injection and stored 2 days at 25 °C.

Table 4. Comparison of In Vitro Plasma Protein Binding of Between Baxter's Daptomycin for Injection and CUBICIN RF

Sample	Lot Number	% Bound (Mean $\pm$ SD)	
		10 $\mu\text{g/mL}$	100 $\mu\text{g/mL}$
Daptomycin for Injection	935055	94.7 $\pm$ 0.5	93.3 $\pm$ 0.3
Daptomycin for Injection	935056	96.4 $\pm$ 0.2	94.3 $\pm$ 0.2
Daptomycin for Injection	935057	96.0 $\pm$ 0.7	94.7 $\pm$ 0.3
CUBICIN RF	R034874	95.6 $\pm$ 0.7	94.4 $\pm$ 0.3
CUBICIN RF	S005478	95.0 $\pm$ 1.1	94.4 $\pm$ 0.3

APPEARS THIS WAY ON ORIGINAL



Elsbeth
Chikhale

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Qi
Zhang

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MICROBIOLOGY

Product Background: Complicated Skin and Skin Structure Infections.

NDA: 213645

Drug Product Name / Strength: Daptomycin for Injection, 500mg/vial (single dose vial).

Route of Administration: Intravenous injection (sterile lyophilized powder).

Applicant Name: Baxter Healthcare Corporation.

Manufacturing Site: Baxter Pharmaceutical Solutions, LLC, 927 South Curry Pike,
Bloomington, IN 47403, USA FEI: 1000115571.

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Theme (ANDA only): N/A

Justification (ANDA only): N/A

Review Summary: (b) (4)

List Submissions Being Reviewed: 06/30/2020 and 09/08/2020.

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The submission is **recommended** for approval on the basis of sterility assurance.

Concise Description Outstanding Issues Remaining: None.

NON-RESPONSIVE

List Number of Comparability Protocols (ANDA only): None.

S Drug Substance- Not Applicable**P.1 Description of the Composition of the Drug Product**

- **Description of the Composition of the Drug Product**
(3.2. P.1. Description and Composition of the Drug Product.pdf)

Daptomycin for Injection, 500mg/vial is supplied as a sterile, preservative-free, pale yellow to light brown, lyophilized powder in a single-dose vial intended for intravenous use following reconstitution with either Sterile Water for Injection or Bacteriostatic Water for Injection, and also after further dilution with 0.9% Sodium Chloride injection (where indicated). The compositions are provided below:

Table 2. Composition of the Dosage Form as Labeled

Component	Quality Standard	Function	Component Concentration in Product Bulk Solution	Component Concentration in Product Bulk Solution	Component Quantity in Finished Product
Daptomycin	In-house	Active Pharmaceutical Ingredient	(b) (4)		500 mg/vial ^a
Mannitol	USP, Ph. Eur., JP	(b) (4)			238 mg/vial
Sorbitol	USP/NF, Ph. Eur., JP				238 mg/vial
Sodium Hydroxide ^c	NF, Ph. Eur., JP				As required for pH adjustment
Hydrochloric Acid ^d	NF, Ph. Eur., JP	pH adjuster			As required for pH adjustment
(b) (4)					

- **Description of container closure system –**
(3.2. P.7. container-closure-system-213645-us.pdf)

The following container-closure systems are used during manufacturing of the drug product:

Table 1. Supplier Information for the Drug Product Container Closure System

Packaging Type	Component	Description	Supplier (Manufacturer)	Manufacturing Facility Address
Primary Container (solution contact)	Vial: 10 mL	(b) (4)		
Primary Container (solution contact)	Stopper: 20 mm			
Primary Container (non-solution contact)	Seal: 20 mm, flip-off cap			

Reviewer's Assessment: Based on the above information the reviewer has concluded that the applicant has provided adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

P.2 Pharmaceutical Development

(b) (4)



Jesse
Wells

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Koushik
Paul

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DOROTA M MATECKA
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