

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206829Orig1s000**

**CHEMISTRY REVIEW(S)**



Chemistry Assessment Section

**NDA 206829**

**ZERBAXA<sup>TM</sup> (ceftolozane/tazobactam) for Injection  
1.0 g/0.5 g**

**Cubist Pharmaceuticals, Inc.**

**Shrikant Pagay  
ONDQA  
Division of New Drug Quality Assessment II  
Branch V**

**Quality Review for  
the Division of Anti-infective Products**

**Addendum 2 to Review 1**

**(Overall Manufacturing Inspection Recommendation is Attached)**

Chemistry Assessment Section

The NDA is recommended for approval from a CMC perspective (refer to Addendum 1 dated December 18, 2014).

This Addendum includes only a copy of the Panorama record containing an overall Acceptable recommendation from the Office of Compliance regarding the manufacturing facilities.

**Establishment Inspection:**

All facilities were found acceptable. Overall Manufacturing Inspection Recommendation as recorded in Panorama is attached .



# CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

## . Administrative

### A. Reviewer's Signature

Shrikant Pagay

### B. Endorsement Block

ChemistryTeamLeaderName/ Dorota Matecka

ProjectManagerName/Date

### C. CC Block

## **NDA 206829**

**ZERBAXA™ (ceftolozane/tazobactam) for Injection**  
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**Shrikant Pagay**  
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**Branch V**

**Quality Review for**  
**the Division of Anti-infective Products**

**Addendum 1 to Review 1**

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**NDA 206-829**

**Ceftolozane and Tazobactam Powder for Injection**

# Chemistry Review Data Sheet

1. NDA #: **206829**
2. REVIEW #: Addendum 1 to Review 1
3. REVIEW DATE: December 14, 2014
4. REVIEWER: Shrikant Pagay
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Type A Meeting minutes	2-22-2013
Type A meeting minutes	2/13/2014
Pre-NDA Meeting Minutes	3/12/2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Letter date original (rolling submission)	4/16/2014
Amendment	6/19/2014
Amendment	7/8/2014
Amendment	7/25/2014
Amendment	8/27/2014
Amendment	10/24/2014
Amendment	11/18/2014
Amendment	12/12/2014

7. NAME & ADDRESS OF APPLICANT

Name: Cubist Pharmaceuticals, Inc.  
Address: 65 Hayden Avenue, Lexington, MA 02421

## Chemistry Review Data Sheet

Representative: Charles Miller,

Telephone: 781-860-8060

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zerbaxa™
- b) Non-Proprietary Name (USAN): ceftolozane/tazobactam for injection
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: NME
  - Submission Priority: P

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

## 10. PHARMACOL. CATEGORY: Anti-infective

## 11. DOSAGE FORM: Powder for Injection

## 12. STRENGTH/POTENCY: 1000 mg ceftolozane and 500 mg tazobactam

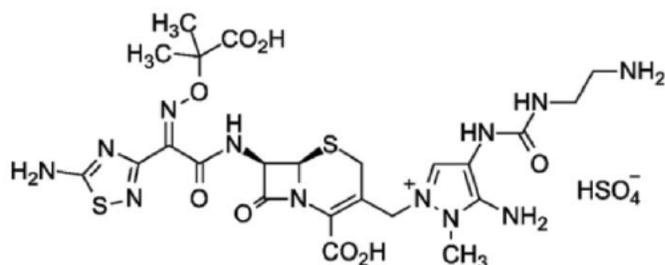
## 13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

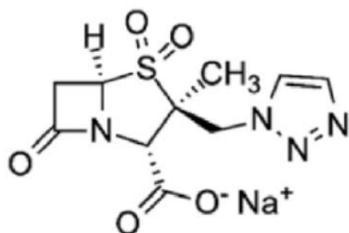
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Chemistry Review Data Sheet

Ceftolozane sulfate  $C_{23}H_{30}N_{12}O_8S_2 \cdot H_2SO_4$  MW= 764.77



Tazobactam sodium  $C_{10}H_{11}N_4NaO_5S$  MW= 322.28



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	1/15/2014	
	II				Amendment to review 5/23/2014	11/16/2014	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

Chemistry Review Data Sheet

- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall Acceptable	12/15/2014	
Pharm/Tox	Complete		
Biopharm			
LNC			
Methods Validation	Pending		
OPDRA			
EA	Categorical exclusion		<i>Based on Review</i>

# The Chemistry Review for NDA 206829

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The NDA provided satisfactory information to assure the identity, strength, purity and quality of the drug substances and the drug product. The Biopharmaceutics Reviewer has recommended approval from the biopharmaceutics perspective. The Product Quality Microbiology Reviewer has also recommended approval from the product quality microbiology perspective. The labels and labeling are finalized by the project team. The Office of Compliance has made an overall acceptable recommendation for the manufacturing and testing facilities. Therefore, the application is recommended for approval from a CMC perspective.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Ceftolozane Sulfate Drug Substance: Ceftolozane sulfate is a member of the cephalosporin class of antibiotics; it is a new chemical entity. It is chemically synthesized with (b) (4) materials (b) (4)

The drug substance is a (b) (4) (b) (4) The solubility in water is only (b) (4) but in a (b) (4) the (b) (4) solubility is over (b) (4)

Ceftolozane sulfate is hygroscopic. The drug substance is synthesized (b) (4) steps process requiring multiple sub-steps. All the synthetic steps are well controlled with in-process controls at each step of the synthesis. Process optimization studies were performed to set upper and lower ranges of process parameters for each step of the synthesis. The fate of impurities was determined through purging studies at each step to insure that none of the impurities emitted from the starting materials are carried to the drug substance. There are 9 process related impurities; all 9 impurities are qualified at the proposed levels. The applicant has developed sufficient experience in manufacturing large scale batches to assure reproducibility of the process. Based on the nine months available stability data, the assigned retest period is (b) (4) months when stored under (b) (4)

Tazobactam Sodium Drug Substance: Tazobactam sodium is a beta lactamase inhibitor antibiotic. It is a semi-synthetic antibiotic obtained from the (b) (4)

## Executive Summary Section

(b) (4) The material is sterile. It is (b) (4) It is hygroscopic and freely soluble in water. The specifications for the drug substance include only one specified impurity. It was approved previously in combination with piperacillin a beta lactam class of antibiotics. The proposed specifications for the drug substance are adequate. The information on sterile tazobactam sodium is submitted under a DMF.

Ceftolozane/Tazobactam Drug Product: The drug product, ceftolozane /tazobactam for injection, 1000 mg/500 mg is a sterile dry powder filled in a vial for reconstitution for intravenous infusion. Each vial of ceftolozane/tazobactam for injection contains approximately (b) (4) mg sterile ceftolozane DPI powder that contains 1147 mg ceftolozane sulfate, which is equivalent to 1000 mg ceftolozane free base, and approximately 537 mg sterile tazobactam sodium drug substance, equivalent to 500 mg tazobactam free acid. The vial is reconstituted with 10 mL of sterile water for injection or 0.9% normal saline. It is further diluted in an infusion bag with 0.9 % sodium chloride or 5% dextrose. Ceftolozane DPI is a sterile lyophilized powder containing ceftolozane sulfate, sodium chloride, L-arginine and citric acid. All excipients used are of USP/NF quality standard. Tazobactam sodium is also a sterile powder, which contains no other excipients. Ceftolozane DPI is manufactured by (b) (4)

The drug product is manufactured by (b) (4)

The vials are stored under refrigeration (2-8°C). The impurities of ceftolozane drug substance are also degradants in the drug product. Also, the impurity from tazobactam is a degradant in the drug product. The proposed levels of these degradants are qualified. The assigned shelf life based on the available stability data is 12 months. The in-use stability data supports the storage of reconstituted solution of ceftolozane/tazobactam drug product for (b) (4) prior to dilution. In addition, in use stability data for IV infusion solution in a bag supports its use up to 7 days storage in a refrigerator (2-8°C) or 24 hours at room temperature.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is administered from an infusion bag by intravenous administration. The infusion solution is prepared by adding 10 mL of water for injection or 10 mL of 0.9% saline for injection in the unit dose vial containing ceftolozane/tazobactam for injection 1.0g/0.5g. The resulting solution is transferred to an infusion bag to make 100 mL of the final concentration in 0.9% saline or 5% dextrose. The infusion solution is administered over (b) (4)

**C. Basis for Approvability or Not-Approval Recommendation**

This application has generally provided sufficient information on the raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the ceftolozane sulfate drug substance, ceftolozane DPI, and ceftolozane/tazobactam drug product. Sufficient stability information is provided in the NDA on the drug product to assure its identity, strength, purity, and quality during its 12 month shelf life. The DMFs for tazobactam sodium drug substance are adequate. The Biopharmaceutics

Executive Summary Section

Reviewer has recommended this NDA for approval. Also, the Product Quality Microbiology Reviewer has recommended approval. Finalization of the labeling is completed by the team. The Office of Compliance has issued a final acceptable recommendation for manufacturing and control facilities for the application. Therefore, the application is recommended for approved at this time from the CMC perspective.

**Table 1: Risk Management**

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations/ Comments
Appearance	Manufacturing failure	L	Controlled via NDA	Acceptable	Controlled via NDA
Identity	Manufacturing failure	L	Controlled via NDA	Acceptable	Controlled via NDA
Uniformity	Manufacturing failure	L	Controlled via NDA	Acceptable	Controlled via NDA
Impurities	Manufacturing failure	M	Controlled via NDA	Acceptable	Controlled via NDA
Assay	Manufacturing failure	L	Controlled via NDA	Acceptable	Controlled via NDA
Water	Manufacturing failure	M	Controlled via NDA	Acceptable	Controlled via NDA
Sterility	Manufacturing failure	M	Controlled via NDA	Acceptable	Controlled via NDA
Container-closure system	Substandard materials, inadequate sealing, misfilling of vials	M	Controlled by associated DMFs, adequacy of sealing process, and Visual examination	Acceptable	Changes to sealing process Visual examination & other optical device

*Note on the Impurities section in the Risk Analysis Table:*

(b) (4)



**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

ChemistryTeamLeaderName/Date: Dorota Matecka

ProjectManagerName/Date

**C. CC Block**

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION CONSULT REQUEST FORM**

**TO: FDA**  
**Division of Pharmaceutical Analysis**  
**Attn: Michael Trehy**  
**Suite 1002**  
**1114 Market Street**  
**St. Louis, MO 63101**

**FROM:** Shrikant Pagay, CMC Reviewer  
Dorota Matecka, CMC Lead  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: shrikant.pagay@fda.hhs.gov  
Phone: (301)-796-1429

**Through:** Rapti Madurawe, Ph.D., Branch Chief, Branch V, ONDQA  
Phone: (301)- 796-1408  
**And** Youbang Liu, Ph.D., ONDQA Methods Validation Project Manager  
Phone: (301)-796-1926  
Fax: (301)796-9877

**SUBJECT:** Methods Validation Request

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Application Number: NDA 206829

Name of Product: Zerbaxa (Ceftolozane/Tazobactam for Injection) 1.0g/0.5g

Applicant: Cubist Pharmaceuticals

Applicant's Contact Person: Charles Miller

Address: 65 Hayden Avenue, Lexington, MA 02421

Telephone: 781-860-8060

---

Date NDA Received by CDER: **4/16/2014**

Submission Classification/Chemical Class: 1/NME

Date of Amendment(s) containing the MVP:

Special Handling Required: yes (Sample store at (b) (4))

DATE of Request: **10/21/2014**

DEA Class: N/A

Requested Completion Date: **12/15/2014**

**Format of Methods Validation Package (MVP)**

PDUFA User Fee Goal Date: **12/19/2014**

Paper  Electronic  Mixed

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We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

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MVP Reference #	<b>METHODS VALIDATION REQUEST</b>			NDA # 206829
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1, 3.2.S.4.2,
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1, 3.2.P.5.2
Supporting Data for Accuracy, Specificity, etc.				3.2.S.4.3,3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.R
Other:				
⇒ ITEM 3: <b>REQUESTED DETERMINATIONS</b> Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
	Assay and Related Substances by HPLC for Cefotolozane sulfate	3.2.S.4.2	0	
	Assay and Related Substances by HPLC for Zerbaxa (Drug Product)	3.2.P.4.2	0	
	(b) (4) in Cefotolozane Sulfate	3.2.S.4.2	0	
	(b) (4)	3.2.S.4.2	0	
	(b) (4)	3.2.S.4.2	0	
<b>Method Title</b>		<b>MVR Cat. Volume Page</b>		

## Methods Validation Request Criteria

MV Request Category	Description
<b>0</b>	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
<b>1</b>	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
<b>2</b>	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
<b>3</b>	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
<b>4</b>	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
<b>5</b>	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
<b>6</b>	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
<b>7</b>	Methods that are subject to a “for cause” reason

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
-----

SHRIKANT N PAGAY  
10/29/2014

RAPTI D MADURawe  
10/30/2014

YOUBANG LIU  
11/03/2014

## **NDA 206829**

**ZERBAXA™ (ceftolozane/tazobactam) for Injection**  
**1.0 g/0.5 g**

**Cubist Pharmaceuticals, Inc.**

**Shrikant Pagay**  
**ONDQA**  
**Division of New Drug Quality Assessment II**  
**Branch V**

**Quality Review for**  
**the Division of Anti-infective Products**

**NDA 206-829**  
**Ceftolozane and Tazobactam Powder for Injection**

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C. CC Block .....	10
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S DRUG SUBSTANCE [Ceftolozane Sulfate].....	13
P DRUG PRODUCT.....	63
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R REGIONAL INFORMATION .....	97
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III. List Of Deficiencies To Be Communicated.....	103

**NDA 206-829**

**Ceftolozane and Tazobactam Powder for Injection**

# Chemistry Review Data Sheet

1. NDA #: **206829**
2. REVIEW #: 1
3. REVIEW DATE: July 4, 2014
4. REVIEWER: Shrikant Pagay
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Type A Meeting minutes	2-22-2013
Type A meeting minutes	2/13/2014
Pre-NDA Meeting Minutes	3/12/2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Letter date original (rolling submission)	4/16/2014
Amendment	6/19/2014
Amendment	7/8/2014
Amendment	7/25/2014
Amendment	8/27/2014

7. NAME & ADDRESS OF APPLICANT:

Name: Cubist Pharmaceuticals, Inc.

Address: 65 Hayden Avenue, Lexington, MA 02421

Representative: Charles Miller,

Telephone: 781-860-8060

Page 3 of 104

**NDA 206-829**  
**Ceftolozane and Tazobactam Powder for Injection**

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zerbaxa™  
 b) Non-Proprietary Name (USAN): ceftolozane/tazobactam for injection  
 c) Code Name/# (ONDC only):  
 d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: NME
  - Submission Priority: P

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

## 10. PHARMACOL. CATEGORY: Anti-infective

## 11. DOSAGE FORM: Powder for Injection

## 12. STRENGTH/POTENCY: 1000 mg ceftolozane and 500 mg tazobactam

## 13. ROUTE OF ADMINISTRATION: Intravenous

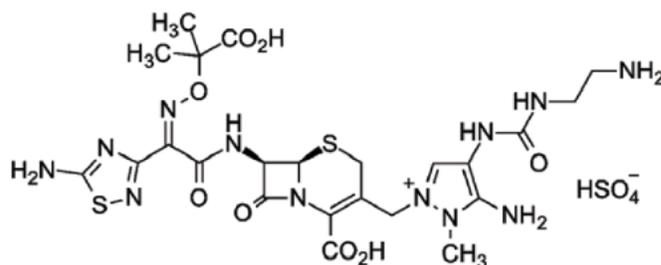
14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ceftolozane sulfate  $C_{23}H_{30}N_{12}O_8S_2 \cdot H_2SO_4$  MW= 764.77

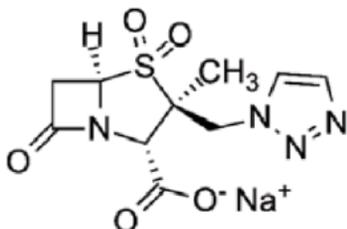


**NDA 206-829**

**Ceftolozane and Tazobactam Powder for Injection**

Chemistry Review Data Sheet

Tazobactam sodium C<sub>10</sub>H<sub>11</sub>N<sub>4</sub>NaO<sub>5</sub>S MW= 322.28



**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II			1	Adequate	1/15/2014	
	II				Amendment to review 5/23/2014	<i>Draft completed – no major issues identified</i>	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Chemistry Review Data Sheet

18. STATUS:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics			
EES	Pending		<i>Submitted on May 23, 2014</i>
Pharm/Tox	Complete		<i>Information on impurities provided in the NDA will need to be discussed with the Pharmacology/Toxicology Reviewer</i>
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA	Categorical exclusion		<i>Based on Review</i>
Microbiology			

# The Chemistry Review for NDA 206829

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The NDA has generally provided satisfactory information to assure the identity, strength, purity and quality of the drug substances and the drug product. However, there are several additional pending comments and issues that need to be addressed (see Section II.c of the Executive Summary). The Biopharmaceutics Reviewer has recommended approval from the biopharmaceutics perspective. The Product Quality Microbiology Reviewer has also recommended approval from the product quality microbiology perspective. However, labels and labeling will need to be finalized during the labeling team review. In addition, the Office of Compliance has not made an overall acceptable recommendation for the manufacturing and testing facilities. Therefore, the application is not recommended for approval at this time.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Ceftolozane Sulfate Drug Substance: Ceftolozane sulfate is a member of the cephalosporin class of antibiotics; it is a new chemical entity. It is chemically synthesized (b) (4) starting materials (b) (4)

The drug substance is a (b) (4) (b) (4) The solubility in water is only (b) (4) but in a (b) (4) the solubility is over (b) (4) Ceftolozane sulfate is hygroscopic. The drug substance is a (b) (4) process requiring multiple sub-steps. All the synthetic steps are well controlled with in-process controls at each step of the synthesis. Process optimization studies were performed to set upper and lower range of process parameters for each step of the synthesis. The fate of impurities was determined through purging studies at each step to insure that none of the impurities emitted from the starting materials are carried to the drug substance. There are 9 process related impurities; all 9 impurities are qualified at the proposed levels. The applicant has developed sufficient experience in manufacturing large scale batches to assure reproducibility of the process. Based on the nine months available stability data, the assigned retest period is (b) (4) months when stored under (b) (4)

## Executive Summary Section

Tazobactam Sodium Drug Substance: Tazobactam sodium is a beta lactamase inhibitor antibiotic. It is a semi-synthetic antibiotic obtained from the (b) (4). The material is sterile. It is (b) (4). It is hygroscopic and freely soluble in water. The specifications for the drug substance include only one specified impurity. It was approved previously in combination with piperacillin a beta lactam class of antibiotics. The proposed specifications for the drug substance are adequate. The information on sterile tazobactam sodium is submitted under a DMF.

Ceftolozane/Tazobactam Drug Product: The drug product, ceftolozane /tazobactam for injection, 1000 mg/500 mg, is a sterile dry powder filled in a vial for reconstitution for intravenous infusion. Each vial of ceftolozane/tazobactam for injection contains approximately (b) (4) sterile ceftolozane DPI powder that contains 1147 mg ceftolozane sulfate, which is equivalent to 1000 mg ceftolozane free base, and approximately 537 mg sterile tazobactam sodium drug substance, equivalent to 500 mg tazobactam free acid. The vial is reconstituted with 10 mL of sterile water for injection or 0.9% normal saline. It is further diluted in an infusion bag with 0.9 % sodium chloride or 5% dextrose. Ceftolozane DPI is a sterile lyophilized powder containing ceftolozane sulfate, sodium chloride, L-arginine and citric acid. All excipients used are of USP/NF quality standard. Tazobactam sodium is also a sterile powder, which contains no other excipients. Ceftolozane DPI is manufactured by (b) (4).

The drug product is manufactured by (b) (4).

The vials are stored under refrigeration (2-8°C). The impurities of ceftolozane drug substance are also degradants in the drug product. Also, the impurity from tazobactam is a degradant in the drug product. The proposed levels of these degradants are qualified. The assigned shelf life based on the available stability data is 12 months. The in-use stability data for ceftolozane/tazobactam administration in IV infusion bag supports its use up to 7 days storage in a refrigerator (2-8C) and (b) (4) in ambient condition.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is administered from an infusion bag by intravenous administration. The infusion solution is prepared by adding 10 mL of water for injection or 10 mL of 0.9% saline for injection in the unit dose vial containing ceftolozane/tazobactam for injection 1.0g/0.5g. The resulting solution is transferred to an infusion bag to make 100 mL of the final concentration in 0.9% saline or 5% dextrose. The infusion solution is administered over (b) (4).

**C. Basis for Approvability or Not-Approval Recommendation**

This application has generally provided sufficient information on the raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the ceftolozane sulfate drug substance, ceftolozane DPI, and ceftolozane/tazobactam drug product. Sufficient stability information is provided in the NDA on the drug product to assure its identity, strength, purity, and quality during its 12 month shelf

Executive Summary Section

life. The DMFs for tazobactam sodium drug substance are adequate. The Biopharmaceutics Reviewer has recommended this NDA for approval. Also, the Product Quality Microbiology Reviewer has recommended approval. However, there are several comments that need to be addressed and reach agreement with the applicant.(listed at the end of this review). Also, there is an ongoing discussion with the Pharm/Tox team on the leachable data provided by the applicant for the drug product container closure system. Finalization of the labeling is pending team review. The Office of Compliance has not issued a final recommendation for manufacturing and control facilities for the application. Therefore, the application is not recommended for approved at this time from the CMC perspective.

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations/ Comments
Appearance	Manufacturing failure	L	Controlled via NDA	Acceptable	Controlled via NDA
Identity	Manufacturing failure	L	Controlled via NDA	Acceptable	Controlled via NDA
Uniformity	Manufacturing failure	L	Controlled via NDA	Acceptable	Controlled via NDA
Impurities	Manufacturing failure	M	Controlled via NDA	Acceptable	Controlled via NDA
Assay	Manufacturing failure	L	Controlled via NDA	Acceptable	Controlled via NDA
Water	Manufacturing failure	M	Controlled via NDA	Acceptable	Controlled via NDA
Sterility	Manufacturing failure	M	Controlled via NDA	Acceptable	Controlled via NDA
Container-closure system	Substandard materials, inadequate sealing, misfilling of vials	M	Controlled by associated DMFs, adequacy of sealing process, and Visual examination	Acceptable	Changes to sealing process Visual examination & other optical device

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Shrikant Pagay,  
ChemistryTeamLeaderName/Date: Dorota Matecka  
ProjectManagerName/Date

**C. CC Block**

94 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHRIKANT N PAGAY  
09/23/2014

DOROTA M MATECKA  
09/23/2014

## IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **206829**

2. DATES AND GOALS:

Letter Date: April 16, 2014	Submission Received Date : April 21, 2014
PDUFA Goal Date: December 21, 2014	

3. PRODUCT PROPERTIES:

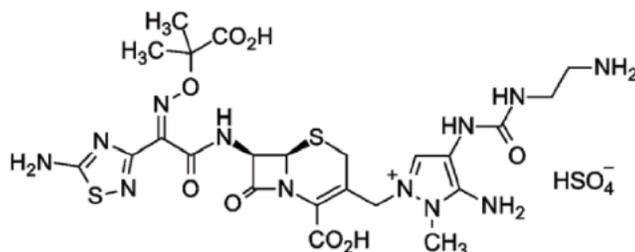
Trade or Proprietary Name:	ZERBAXA ( <i>proposed name</i> )
Established or Non-Proprietary Name (USAN):	ceftolozane and tazobactam
Dosage Form:	Powder for injection
Route of Administration	Intravenous
Strength/Potency	1000 mg (ceftolozane) and 500 mg (tazobactam)
Rx/OTC Dispensed:	Rx

4. INDICATION:

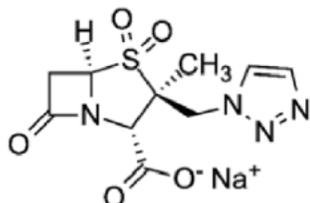
Treatment of complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAIs)

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Ceftolozane sulfate  $C_{23}H_{30}N_{12}O_8S_2 \cdot H_2SO_4$



Tazobactam sodium  $C_{10}H_{11}N_4NaO_5S$



CMC

6. NAME OF APPLICANT (as indicated on Form 356h):

Cubist Pharmaceuticals, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Priority (PDUFA V NDA)
Submission Classification (Chemical Classification Code):	1
Application Type:	505(b)(2)
Breakthrough Therapy	Yes
Responsible Organization (Clinical Division):	DAIP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		<i>Submitted on May 23, 2014</i>
Pharmacology/Toxicology	X		<i>Information on impurities provided in the NDA will need to be discussed with the Pharmacology/Toxicology Reviewer</i>
Methods Validation	X		
Environmental Assessment	X		<i>Categorical exclusion</i>
CDRH		X	
Other			N/A

## CMC

**Overall Filing Conclusions and Recommendations****Overall Product Quality Filing Recommendation:****Is the Product Quality Section of the application fileable from an Overall Product Quality Perspective?****Yes**

Overall Product Quality Issues:

*See details below for individual Quality disciplines.***CMC:****Is the Product Quality Section of the application fileable from a CMC perspective?****Yes**

CMC Filing Issues:

*None***Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?****No**

CMC Comments for 74-Day Letter:

*None***Biopharmaceutics:****Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?****Yes**

Biopharmaceutics Filing Issues:

*N/A***Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?****No**

Biopharmaceutics Comments for 74-Day Letter:

*N/A (No biopharmaceutics review will be needed for this NDA. A memorandum by the biopharmaceutics reviewer initially assigned to this NDA will be entered into DARRTS.)***Microbiology:****Is the Product Quality Section of the application fileable from a Microbiology perspective?****Yes**

Microbiology Filing Issues:

*See Microbiology Filing Review for details and for any potential Microbiology review issues.*

CMC

## Summary of Initial Quality Assessment-CMC

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes	No
Suggested expertise for team:		
<i>The Product Quality Review Team:                      CMC Reviewer: Shrikant Pagay, Ph.D.                      Product Quality Microbiology Reviewer: Erica Pfeiler, Ph.D.                      Biopharmaceutics Reviewer: Minerva Hughes, Ph.D.</i>		

**Summary of Critical Issues and Complexities:**

*This NDA provides for ceftolozane sulfate and tazobactam sodium, a drug combination of a novel cephalosporin and  $\beta$ -lactamase inhibitor (BLI). CMC information for ceftolozane sulfate is provided in the NDA. However, the CMC information for tazobactam drug substance is provided via a reference to two Type II DMFs (b) (4) and (b) (4) (DMF (b) (4) has not been reviewed previously and will need to be reviewed for the purpose of this NDA).*

*The proposed drug product ceftolozane and tazobactam for injection, 1000 mg/500 mg, is presented as a combination of two sterile active powders (ceftolozane drug product intermediate (DPI) and tazobactam sodium) sequentially into a single vial intended for reconstitution and intravenous infusion. The ceftolozane component of the proposed drug product is prepared by (b) (4)*

*The tazobactam component of the proposed drug product combination is presented as a sterile powder, tazobactam sodium drug substance without any excipients.*

*The most critical issue for this NDA will be the inspection of the drug product facility (Steri-Pharma, Syracuse, NY). As discussed and agreed at the pre-NDA meeting, this facility will be ready for inspection no later than August 25, 2014. The Office of Compliance was involved in these discussions and is aware of this date.*

## Initial Quality Assessment- CMC

This NDA provides for ceftolozane sulfate and tazobactam sodium, a drug combination of a novel cephalosporin anti-infective with  $\beta$ -lactamase inhibitor (BLI), indicated as a single agent for the treatment of complicated urinary tract infections (cUTIs) and, in combination with metronidazole, for the treatment of complicated intra-abdominal infections (cIAIs).

This NDA was granted a Qualified Infectious Disease Product (QIDP) and Fast Track designations for both cIAI and cUTI. In addition, the NDA was granted a rolling review designation with the first Reviewable Unit 1 dated February 13, 2014 and the final unit submitted on April 21, 2014. The majority of the CMC information was provided in the final unit and the EA information is submitted in Unit 1. With the submission of the final unit, the applicant is requesting a Priority Review.

The product was developed via an IND 104490 and several important meetings were held over the course of development between the sponsor and the FDA. The correspondences relevant to CMC activities during the development of this product (documented in DARRTS) include:

1. Type A meeting minutes (dated February 22, 2013)
2. Type A meeting minutes (dated February 13, 2014)
3. Pre-NDA meeting minutes (dated March 12, 2014)

It should be noted that the pre-NDA meeting minutes include the following CMC and facility agreements:

1. *Additional stability information will be submitted as a minor component amendment to the NDA within 60 days of the NDA submission date.*
2. *An amendment containing the remaining sterility assurance validation package and notification of readiness for the pre-approval inspection of Steri-Pharma will be submitted no later than August 25, 2014.*

### **Drug Substance – Sterile Tazobactam Sodium**

Reference is made to two Type II DMFs; DMF (b) (4) for (b) (4) has been reviewed previously and found adequate. DMF (b) (4) was found incomplete by the Office of Generic Drugs. However, the DMF holder provided the missing information in the subsequent amendment dated May 12, 2014. *Comment: This DMF will need to be reviewed for the purpose of the current NDA. Some general information and a specification for sterile tazobactam sodium have been provided in Module 2 of the NDA.*

### **Drug Substance – Ceftolozane Sulfate**

CMC information for ceftolozane sulfate is provided in the NDA.

The synthesis of ceftolozane sulfate consists of (b) (4) manufacturing stages (b) (4)

## CMC

(b) (4) (see Attachment 1, below). Details of those stages, including process controls and controls of materials are provided in Section 3.2.S.2. This includes information on the proposed (b) (4) starting materials (b) (4).  
*Comments: It should be noted that the discussions at the pre-NDA meeting included agreements on starting materials in the synthesis of ceftolozane sulfate drug substance.*

(b) (4)  
The overall information for the proposed starting materials including the proposed specifications will need to be reviewed in detail. In addition, Section 3.2.S.2.6 Manufacturing Process Development provides information on process optimization and includes discussion of CQAs, CPPs, PARs, etc.

The characterization of the ceftolozane sulfate drug substance provided in Section 3.2.S.3 includes information on potential impurities. Further detailed information on purging studies and evaluation of mutagenic potential of some of the impurities has been provided in Section 3.2.S.2.6 Manufacturing Process Development. *Comment: This information will need to be reviewed in detail and consulted with the Pharm/Tox Reviewer of this NDA.*

Stability studies are on-going for three primary batches of ceftolozane sulfate drug substance and two supportive batches manufactured at (b) (4). The batches have been studied for up to 18 months at (b) (4) and for 6 months at (b) (4). The retest period of (b) (4) month has been proposed for the ceftolozane sulfate when stored at (b) (4). *Comment: The proposed retest date will need to be evaluated based on the overall information provided.*

### **Drug Product- Ceftolozane/Tazobactam for Injection**

The proposed drug product, Ceftolozane/Tazobactam for Injection, 1000 mg/500 mg is an antibacterial drug combination consisting of ceftolozane, a novel cephalosporin, with tazobactam, a well-established  $\beta$ -lactamase inhibitor.

Ceftolozane/Tazobactam for Injection, 1000 mg/500 mg, is presented as a combination of two sterile active powders. The ceftolozane component of the proposed drug product is prepared by (b) (4).  
The tazobactam component of the proposed drug product combination is presented as a sterile powder, tazobactam sodium drug substance without any excipients (see Attachment 2, below). The finished drug product is prepared by (b) (4) filling the two powders sequentially into a single vial intended for reconstitution and intravenous infusion.

Each vial of ceftolozane/tazobactam for injection contains approximately (b) (4) ceftolozane sterile DPI powder that contains 1147 mg ceftolozane sulfate, which is equivalent to 1000 mg ceftolozane free base, as well as approximately 537 mg tazobactam sodium sterile drug substance, equivalent to 500 mg tazobactam free acid. At the time of administration, the vial is reconstituted with 10 mL vehicle, sterile Water for Injection or 0.9% Sodium Chloride Injection USP, then the vial contents further diluted in an infusion bag of 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP, for administration. A study was performed to assess the

## CMC

stability of ceftolozane/tazobactam for injection (Lot 13 SPP2) in the intravenous (IV) bag. The drug product vials were reconstituted with Water for Injection, USP (WFI) or 0.9% Sodium Chloride (Saline) Injection, USP then transferred to 100 mL IV bags of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP (D5W). Results of these studies are described in Section 3.2.P.2.6. *Comment: The results of compatibility studies presented in this section will need to be evaluated in collaboration with the Product Quality Microbiology Reviewer.*

The primary container-closure system is a Type I 20 mL molded glass vial with 20 mm neck finish. The vial is sealed by a 20 mm rubber stopper and 20 mm plastic flip-cap seal with (b) (4). The container-closure components are described in Section 3.2.P.7. *Comment: In addition, information on safety, compatibility and suitability of the proposed container closure including evaluation of extractables and leachables is provided in Section 3.2.P.2.4. This information may also need to be discussed with the Pharm/Tox Reviewer of this NDA.*

The drug product manufacturing process includes (b) (4). (b) (4)  
(b) (4)  
(b) (4) (which will be performed at the Steri-Pharma facility), the finished drug product is prepared by (b) (4)

Three different drug product vial configurations were produced to support the clinical studies. Batch analysis for all batches of drug product manufactured for clinical and commercialization has been provided in the NDA. Six lots of ceftolozane/tazobactam drug product were manufactured at Steri-Pharma using the (b) (4) proposed commercial process. Detailed information on batch size, corresponding drug product intermediates lots, batch use and analytical results are provided in Section 3.2.P.5.4 (the drug product proposed specification is reproduced below, Attachment 3).

Stability studies are on-going for three primary batches of ceftolozane/tazobactam for injection drug product and three future clinical batches manufactured at Steri-Pharma. The primary stability batches have been studied for up to 6 months at 5±3°C, 25°C/60% RH and 40°C/75% RH. The applicant states that the studies support a (b) (4) shelf-life for the ceftolozane/tazobactam for injection at 5±3°C. *Comment: The proposed shelf life will be granted based on the assessment of overall stability information provided in the NDA (including supportive data). As stated above, per pre-NDA meeting agreements, additional (b) (4) data for these batches should be submitted within 60 days of the NDA submission date.*

Several manufacturing facilities (seven in total - mostly foreign) are involved in the manufacture of the proposed drug substances and the drug product. The facilities were entered into EES for evaluation. *Comment: As stated above, the finished drug product facility will be ready for inspection after August 25, 2014. This agreement was reached between the sponsor and the FDA at the pre-NDA meeting.*

CMC

## FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential filing issue</i> or a <i>potential review issue</i> .				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>	X		

**CMC**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

CMC

	Parameter	Yes	No	Comment
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		<i>Per agreement at the pre-NDA meeting the drug product facility will be ready for inspection on August 25<sup>th</sup>, 2014.</i>

**C. ENVIRONMENTAL ASSESMENT**

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		<i>Provided in Unit 1 dated February 14, 2014.</i>

CMC

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		<i>Tazobactam sodium (sterile) – reference to DMF Type II (b) (4) and DMF Type II (b) (4) Cefprozil sulfate – information submitted in NDA</i>
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			<i>Some discussion on CQAs, CPPs, PARs included in the Manufacturing Process Development section</i>
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			<i>Not immediately obvious</i>

**CMC**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?			<i>Not immediately obvious (but not required either)</i>
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			<i>Not immediately obvious (but not required either)</i>

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
28.	Is there a methods validation package?	X		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>

CMC

29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		
-----	---	---	--	--

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	February 10, 2014	Review in DARRTS 01/15/2014 Adequate
	II		February 10, 2014	GDUFA Incomplete? 04/02/2014 Amendment 5/23/2014	

*In addition, several Type III and Type V DMFs (with LOAs provided in Section 1.4.1)*

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

**Attachment 1** (Synthesis of ceftolozane sulfate)



(b) (4)

**Attachment 2**

3.2.P.1 Description and Composition of the Drug Product [ceftolozane/tazobactam for Injection, 1000mg/500mg]

**Table 1: Unit Composition of Ceftolozane/Tazobactam for Injection, 1000 mg/500 mg**

Component		Quality Standard <sup>a</sup>	Function	Nominal Composition mg per Vial
Ceftolozane DPI <sup>b</sup>	Ceftolozane Sulfate	In-House Section 3.2.S.4.1	Active	1147
	Citric Acid, Anhydrous	USP	(b) (4)	21
	Sodium Chloride	USP	Stabilizing Agent	487
	L-Arginine	USP	(b) (4)	600 <sup>c</sup> (b) (4)
Tazobactam Sodium <sup>d</sup>		In-House Section 3.2.S.4.1	Active	537
				(b) (4)
Total Weight				(b) (4)

<sup>a</sup>Quality standard abbreviations: USP = United States Pharmacopeia; NF = National Formulary. Refer to Section 3.2.P.4.1 for additional information on excipient quality.

<sup>b</sup>Actual amount of ceftolozane DPI will vary based on the measured potency.

<sup>c</sup>L-arginine is added (b) (4) 600 mg per vial is considered a representative total amount.

<sup>d</sup>Actual weight of tazobactam sodium will vary based on the measured potency.

(b) (4)

**Table 2: Container Closure for Ceftolozane/Tazobactam for Injection, 1000 mg/500 mg**

Component	Description
Vial	Type I molded glass, 20 mL, 20 mm neck, USP compliant
Stopper	20 mm gray (b) (4) rubber, USP compliant
Seal	20 mm (b) (4) seal with plastic flip-cap seal, USP compliant

**Attachment 3**

**1. SPECIFICATION [CEFTOLOZANE/TAZOBACTAM FOR INJECTION, 1000MG/500MG]**

Batches of drug product will comply with specifications presented in Table 1.

**Table 1: Ceftolozane Tazobactam Drug Product Specification**

Test	Release	Stability	Analytical Procedure
Appearance	White to yellowish powder, contained in a clear glass vial, metal seal and a grey stopper with a purple flip cap top	White to yellowish powder, contained in a clear glass vial, metal seal and a grey stopper with a purple flip cap top	Visual (TM-231)
Identification, UV Spectrum by HPLC	(b) (4)	(b) (4)	UV (TM-226)
Identification, HPLC by Retention Time			HPLC (TM-226)
Color of Solution			Tintometer (TM-266)
Constituted Solution in water			USP <1> (TM-266)
Constituted Solution in 0.9% Saline			
Reconstitution Time in water			TM-266
Reconstitution Time in 0.9% Saline			pH meter (TM-228)
pH of Reconstituted Solution			

Test	Release	Stability	Analytical Procedure	
Particulate Matter (sub-visible)	(b) (4)	(b) (4)	USP <788>, Method I	
(b) (4)			(b) (4)	
Potency Ceftolozane Tazobactam			HPLC (TM-226)	
Content Uniformity Ceftolozane Tazobactam			HPLC, USP <905>, (TM-226)	
Purity (% Area)			HPLC (TM-227)	
Related Substances (Area %) Specified, Identified Degradants				(b) (4)
(b) (4)				
Each Unspecified Impurity/ Degradant Total Impurities			USP <85> Turbidimetric	
Bacterial Endotoxin			USP <71>	
Sterility			Steri-Pharma Test Method LAB6025	
Container Closure Integrity				

Abbreviations: EP = European Pharmacopoeia; EU = Endotoxin Unit; HPLC = High-performance liquid chromatography; RT = Retention Time; USP = United States Pharmacopoeia; UV = Ultraviolet.

## CMC

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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06/19/2014

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