

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207131Orig1s000

CHEMISTRY REVIEW(S)

NDA 207-131

**Cefazolin Injection, USP, 2 g/ 100 mL
Celerity Pharmaceuticals, LLC**

Addendum 1 to Review # 1

Chunchun Zhang, Ph.D.

**ONDP
Division of New Drug Product I
Branch III**

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Chemistry Review Data Sheet

1. NDA 207-131
2. REVIEW #: Addendum 1 to Review #1
3. REVIEW DATE: 29-Jul-2015
4. REVIEWER: Chunchun Zhang

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	16-Oct-2014
Amendment	20-Feb-2015
Amendment	20-Apr-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Celerity Pharmaceuticals, LLC
Address:	9450 W. Bryn Mawr Ave., Suite 640, Rosemont, IL 60018
Representative:	Brent Yurschak
Telephone:	847-999-0492

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cefazolin Injection USP
- b) Non-Proprietary Name (USAN): Cefazolin
- c) Code Name/# (ONDP only): N/A
- d) Chem. Type/Submission Priority (ONDP only):
 - Chem. Type: 5
 - Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Anti-Infective

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 2g / 100mL

13. ROUTE OF ADMINISTRATION: Intravenous

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

SPOTS product – Form Completed

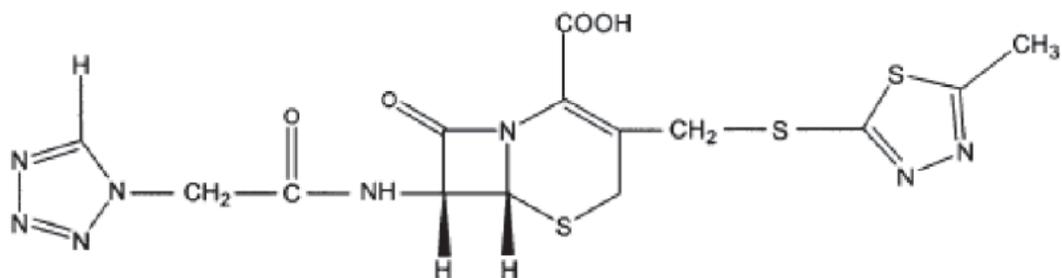
Not a SPOTS product

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

USAN: Cefazolin

Chemical Name: 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[[1*H*-tetrazol-1-yl)acetyl]amino]-(6*R*-*trans*)

Chemistry Review Data Sheet



Molecular Weight: 454.51

Molecular Formula: C₁₄H₁₄N₈O₄S₃

Chemical Abstract: 25953-19-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	31-May-2015	LoA: 11-Jun-2014
	III			1	Adequate	27-Feb-2015	LoA: 11-Jul-2014

¹ 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")

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

B. Other Documents: N/A

18. STATUS:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			N/A
Facilities	Acceptable	29-Jul-2015	Steve Hertz
Pharm/Tox	Acceptable	30-Mar-2015	Amy L Ellis
Biopharm	Acceptable	13-Mar-2015	Kelly Kitchens
LNC			NA
Methods Validation	NA		
OPDRA			NA
EA	Categorical exclusion is requested, and granted (see review)	11-May-2015	Chunchun Zhang
Microbiology	Acceptable	29-Jun-2015	Vinayak Pawar

The Chemistry Review for NDA 207-131

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The biowaiver request has been granted as noted in the biopharmaceutics review Dr. Kelly Kitchens, dated Mar 13, 2015. Product Quality Microbiology has recommended approval. Labeling comments are marked up in this review and will be finalized during team labeling review. The Office of Process and Facilities (OPF) has provided an overall recommendation of “acceptable” for the facilities on Jul 29, 2015. Therefore, from CMC perspective, this NDA is recommended for approval.

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

None.

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance, cefazolin USP, was referenced to (b) (4). The DMF was reviewed and found adequate on 16-Feb-2015. The drug substance is manufactured and the stability testing is performed at (b) (4) site.

Cefazolin USP drug substance is a (b) (4). Cefazolin is soluble in water (> (b) (4) in the pH range of 4 to 7), Cefazolin has two stereocenters with specific rotation -17° at 25°C . Cefazolin melts at about 190°C .

The specification for Cefazolin USP conforms to the acceptance criteria in the current USP monograph: identification, water determination, assay, organic impurity, residual solvent, heavy metals are some of the attributes in the specification. Manufacturing process and control strategy are provided in the DMF and is adequate.

Stability data provided in the DMF supports a drug substance retest period of (b) (4)

Executive Summary Section

Drug Product

Cefazolin injection, USP 2g/100 mL is a frozen, premixed, iso-osmotic, sterile, nonpyrogenic solution in Galaxy plastic container (PL2040). The maximum daily dose is 2 g per day. The formulation, manufacturing process and equipment of the current proposed drug product (b) (4)

Cefazolin injection formulation contains 2g of Cefazolin USP and the following compendial excipients: Dextrose USP (adjust the osmolality), sodium bicarbonate (adjust pH) and water for injection.

The commercial Cefazolin injection manufacturing process has the following steps (b) (4)

The manufacturing control strategy is based on the capability to operate on the critical in-process controls for the (b) (4)

The drug product quality is tested for the following final specification: pH, identification, assay, impurities, osmolality, sterility, bacterial endotoxins particulate matter, and fill volume. The biowaiver request, as noted above, has been granted (please see biopharm Review by Dr. Kelly Kitchens). Quality microbiology concludes that sterility is assured and all microbial processes are adequate. Additionally, all methods have been adequately validated and the specification acceptance criteria justified appropriately.

Overall, the manufacturing process and controls and the drug product specification will ensure the drug product has the overall quality necessary for safe and effective treatment of patients.

Commercial drug product is manufactured and released at Baxter's site at Round Lake, IL.

Three registration stability batches at more than 20% of commercial scale of Cefazolin Injection, USP 2 g/100 mL were manufactured at the commercial site Baxter's Round Lake, IL. Stability results are available through 30 months of long term storage (-20 °C); and 37 days under refrigerated condition (5°C); and at room temperature (25°C) for up to 72 hours after storage under refrigeration (5°C) for 30 days. No significant changes were observed in the drug product quality. Overall, the stability data supports a 24-month expiration dating period at -20 °C with a thawed label statement of "30 days under refrigeration (5°C/41°F) and 48 hours at room temperature (25°C/77°F)" when stored in GALAXY plastic container (PL 2040).

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

Executive Summary Section

Cefazolin Injection, USP 2g/100mL is intended for intravenous use after thawing at room temperature or under refrigeration. Product labeling directs that no additional medication or additives are to be added prior to administration.

Cefazolin Injection, USP 2 g is supplied in a 100-mL GALAXY plastic container (PL 2040). The container label instruction recommends, “store at -20°C with a 24-month shelf life; with a thawed label statement of “30 days under refrigeration (5°C/41°F) and 48 hours at room temperature (25°C/77°F)”.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes, in-process controls, and adequate specification to assure consistent quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, quality, purity, and potency of the drug product through the expiration dating period of 24 months. Biopharm recommends approval of this NDA. Labeling will be finalized during team labeling review. Product Quality Microbiology also recommends approval of the NDA (please see review by Vinayak Pawar dated 6/29/2015). The Office of Process and Facilities has provided an overall recommendation of “acceptable” for the facilities on 7/29/2015. Therefore, from CMC perspective, this NDA is recommended for approval.

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments
Assay	In-coming materials, pH, temp	low	Controlled through in-process controls and drug product specification.	Acceptable	NA
Particulate matter	solubility	low	Drug product is a sterile solution and met USP<788> at release and on stability.	Acceptable	NA
pH	amount of sodium bicarbonate	low	Very tight range of (b) (4) in-process control. Also controlled in the drug product specification.	Acceptable	NA
Impurities	drug substance assay, pH and temp	medium	The proposed impurities control is found acceptable by Pharm/Tox Dr. Amy Ellis's review.	Acceptable	NA
Endotoxin	validated sterilization process	medium	Refer to product Quality Micro Dr. Vinayak Pawar's review.	Acceptable	NA
Sterility	validated sterilization process	high	Refer to product Quality Micro Dr. Vinayak Pawar's review.	Acceptable	NA

Executive Summary Section

III. Administrative**A. Reviewer's Signature**

Chunchun Zhang

On file

Chunchun Zhang -S



Digitally signed by Chunchun Zhang S
DN: c=US, o=U.S. Government, ou=FDA, ou=People, cn=Chunchun Zhang S
0.9.2342.19200300.100.1.1=2001178137
Date: 2015.07.29 21:43:22 -04'00'

B. Endorsement Block

Balajee Shanmugam

On file

Balajee

Shanmugam -S



Digitally signed by Balajee Shanmugam S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300217143, cn=Balajee Shanmugam S
Date: 2015.07.29 22:14:36 -04'00'

C. CC Block*On file*

Chemistry Assessment

**I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body Of Data**

CMC Review #1 dated 17-Jun-2015 contains a complete assessment of the NDA. The Quality Microbiology review recommendation and the overall recommendation from the Office of Compliance are PENDING at that time for the establishment evaluation. This addendum #1 to CMC Review #1 contains an overall recommendation of acceptable for the facilities and an approval from the Quality Microbiology reviewer.

S **DRUG SUBSTANCE [Cefazolin USP, (b) (4)]**

S.2 **Manufacture [Cefazolin USP, (b) (4)]**

Reviewer’s Evaluation: Adequate. Refer to recent review of DMF (b) (4) by this reviewer for drug substance manufacturing details. The drug substance manufacturers are summarized in Table 1.

Table 1. Manufacturing and Testing Facilities for the Drug Substance

Company Name	Facility Name and Address	Responsibility
		(b) (4) Drug Substance Manufacturer: DMF Number (b) (4) Manufacturing Packaging Labeling Drug Substance Testing Drug Substance Release Drug Substance Stability Testing Warehousing Operations
		Drug Product Manufacturer: Drug Substance Testing Drug Substance Release

Chemistry Assessment Section

P DRUG PRODUCT [Cefazolin Injection, USP]**P.3 Manufacture [Cefazolin Injection, USP]****P.3.1 *Manufacturers***

Reviewer Evaluation: Adequate. The drug product manufacturing facilities are shown in the Table 1. The facility was acceptable on 22-Jul-2015.

Table 1. Manufacturing, Packaging, and Testing Facilities for the Drug Product

Company Name	Facility Name and Address	Responsibility
Baxter Healthcare Corporation Facility Establishment Identifier Number: 1416980 DUNS Number: 194684502	25212 W. Illinois Route 120 Round Lake, IL 60073 USA Contact Name: Mr. Jeffrey Fedyk Director, Quality Round Lake, IL Manufacturing Facility 25212 W. Illinois Route 120 Round Lake, IL 60073 USA Phone: 224-270-3228 Fax: 224-270-3699 Email: jeffrey_fedyk@baxter.com	Drug Product Manufacturer: Excipient Testing Manufacture of Dosage Form ^a Finished Product Testing Finished Product Release Stability Testing

(b) (4)

P.3.3 *Description of Manufacturing Process and Process Controls*

Reviewer Evaluation: Adequate.

The manufacturing process is adequately described by the master production record. In addition, three stability executed batch records (54913, 54914 and 54915) are submitted in the Section 3.2.R. Evaluation of (b) (4) sterility assurance is conducted by the microbiology reviewer, Dr. Vinayak Pawar. Refer to his review for the acceptability of the sterile processing of the Cefazolin Injection drug product.

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

(b) (4)



Chemistry Assessment Section

OPF Summary Report: Overall recommendation.

OPF Facility Recommendations for Facilities on NDA 207131 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Re-Evaluation Date	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion
NDA 207131-Orig1-New - Expedited Review - User Fee - Form 3674/NDA - Request - Coversheet(4)				(b) (4)	Approve Facility	(b) (4)	Complete	1/28/2015
NDA 207131-Orig1-New - Expedited Review - User Fee - Form 3674/NDA - Request - Coversheet(4)					Approve Facility		Complete	7/22/2015
NDA 207131-Orig1-New - Expedited Review - User Fee - Form 3674/NDA - Request - Coversheet(4)							Cancelled	2/11/2015

NDA 207-131

Cefazolin Injection, USP, 2 g/ 100 mL
Celerity Pharmaceuticals, LLC

Chunchun Zhang, Ph.D.

ONDP
Division of New Drug Product I
Branch III

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Chemistry Review Data Sheet

1. NDA 207-131

2. REVIEW #: 1

3. REVIEW DATE: 06-17-2015

4. REVIEWER: Chunchun Zhang

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	16-Oct-2014
Amendment	20-Feb-2015
Amendment	20-Apr-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Celerity Pharmaceuticals, LLC
Address:	9450 W. Bryn Mawr Ave., Suite 640, Rosemont, IL 60018
Representative:	Brent Yurschak
Telephone:	847-999-0492

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cefazolin Injection USP
- b) Non-Proprietary Name (USAN): Cefazolin
- c) Code Name/# (ONDP only): N/A
- d) Chem. Type/Submission Priority (ONDP only):
 - Chem. Type: 5
 - Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Anti-Infective

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 2g / 100mL

13. ROUTE OF ADMINISTRATION: Intravenous

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

SPOTS product – Form Completed

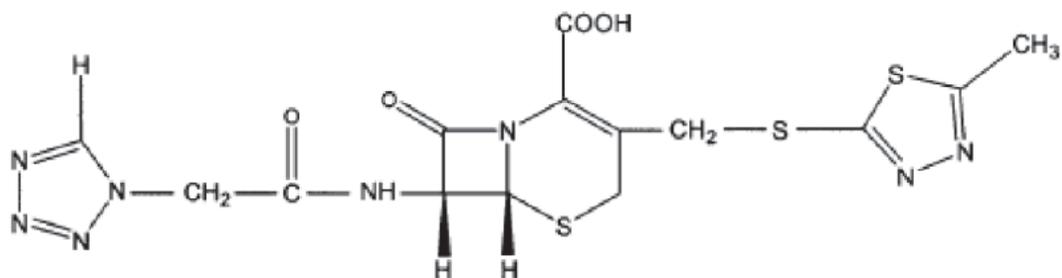
Not a SPOTS product

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

USAN: Cefazolin

Chemical Name: 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[[1*H*-tetrazol-1-yl)acetyl]amino]-(6*R*-*trans*)

Chemistry Review Data Sheet



Molecular Weight: 454.51

Molecular Formula: C₁₄H₁₄N₈O₄S₃

Chemical Abstract: 25953-19-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	31-May-2015	LoA: 11-Jun-2014
	III			1	Adequate	27-Feb-2015	LoA: 11-Jul-2014

¹ 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")

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

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER
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Chemistry Review Data Sheet

REVIEWS			
Biometrics			N/A
EES	Pending	06-17-2015	
Pharm/Tox	Acceptable	30-Mar-2015	Amy L Ellis
Biopharm	Acceptable	13-Mar-2015	Kelly Kitchens
LNC			NA
Methods Validation	NA		
OPDRA			NA
EA	Categorical exclusion is requested, and granted (see review)	11-May-2015	Chunchun Zhang
Microbiology	Pending	06-17-2015	Vinayak Pawar

The Chemistry Review for NDA 207-131

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The biowaiver request has been granted as noted in the biopharmaceutics review Dr. Kelly Kitchens, dated Mar 13, 2015. Labeling comments are marked up in this review and will be finalized during team labeling review. However, final recommendations from Quality Microbiology and the Office of Process and Facilities (OPF) for the facilities are PENDING as of 17-Jun-2015. Therefore, from CMC perspective, this NDA is not recommended for approval until an overall recommendation of acceptable is made for the establishments and a recommendation of approval from the Quality Microbiology reviewer.

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

None.

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance, Cefazolin USP, was referenced to (b) (4) DMF (b) (4). The DMF was reviewed and found adequate on 31-May-2015. Drug substance manufacturing and stability testing is performed at (b) (4) site.

Cefazolin USP drug substance is a (b) (4). Cefazolin is soluble in water (b) (4) in the pH range of 4 to 7). Cefazolin has two stereocenters with specific rotation -17° at 25°C . Cefazolin melts at about 190°C .

The specification for Cefazolin USP conforms to the current USP monograph; identification, water determination, assay, organic impurity, residual solvent, heavy metals are some of the quality attributes in the specification. Manufacturing process and control strategy provided in the DMF is adequate.

Stability data provided in the DMF supports a drug substance retest period of (b) (4)

Executive Summary Section

Drug Product

Cefazolin injection, USP 2g/100 mL is a frozen, premixed, iso-osmotic, sterile, nonpyrogenic solution in Galaxy plastic container (PL2040). The maximum daily dose is 2 g per day. The formulation, manufacturing process and equipment of the current proposed drug product (b) (4)

Cefazolin injection formulation contains 2g of Cefazolin USP and the following compendial excipients: Dextrose USP (to adjust osmolality), sodium bicarbonate (adjust pH) and water for injection.

The commercial Cefazolin injection manufacturing process involves the following steps: (b) (4)

The manufacturing control strategy is based on the capability to operate on the critical in-process controls for the (b) (4)

The drug product quality is tested for the following final specification: pH, identification, assay, impurities, osmolality, sterility, bacterial endotoxins particulate matter, and fill volume. The biowaiver request, as noted above, has been granted (please see Biopharm Review by Dr. Kelly Kitchens). Additionally, all analytical methods have been adequately validated and the specification acceptance criteria justified adequately.

Overall, the manufacturing process and controls and the drug product specification will ensure the drug product provides overall quality necessary for the safe and effective treatment of patients.

Commercial drug product is manufactured and released at Baxter's site at Round Lake, IL.

Three registration stability batches at more than 20% of commercial scale of Cefazolin Injection, USP 2 g/100 mL were manufactured at the commercial site Baxter's Round Lake, IL. Stability results are available through 30 months of long term storage (-20 °C); and 37 days under refrigerated condition (5°C); and at room temperature (25°C) for up to 72 hours after storage under refrigeration (5°C) for 30 days. No significant changes were observed in the drug product quality. Overall, the stability data supports a 24-month expiration dating period at -20°C with a thawed label statement of "30 days under refrigeration (5°C/41°F) and 48 hours at room temperature (25°C/77°F)" when stored in GALAXY plastic container (PL 2040).

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

Executive Summary Section

Cefazolin Injection, USP 2g/100mL is intended for intravenous use after thawing at room temperature or under refrigeration. Product labeling directs that no additional medication or additives are to be added prior to administration.

Cefazolin Injection, USP 2 g is supplied in a 100-mL GALAXY plastic container (PL 2040). The container label instruction recommends, “Store at -20°C with a 24-month shelf life; with a thawed label statement of “30 days under refrigeration (5°C/41°F) and 48 hours at room temperature (25°C/77°F)”.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes, in-process controls, and adequate specification to assure consistent quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, quality, purity, and potency of the drug product through the expiration dating period of 24 months. Biopharm recommends approval of this NDA. Labeling will be finalized during team labeling review. However, final recommendations from Quality Microbiology and the Office of Process and Facilities (OPF) for the facilities are PENDING as of 17-Jun-2015. Therefore, from CMC perspective, this NDA is not recommended for approval until an overall recommendation of acceptable is made for the establishments and a recommendation of approval from the Quality Microbiology reviewer.

Executive Summary Section

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments
Assay	In-coming materials, pH, temp	low	Controlled through in-process controls and drug product specification.	Acceptable	NA
Particulate matter	solubility	low	Drug product is a sterile solution and met USP<788> at release and on stability.	Acceptable	NA
pH	amount of sodium bicarbonate	low	Very tight range of (b) (4) in-process control. Also controlled in the drug product specification.	Acceptable	NA
Impurities	drug substance assay, pH and temp	medium	The proposed impurities control is found acceptable by Pharm/Tox Dr. Amy Ellis's review.	Acceptable	NA
Endotoxin	validated sterilization process	medium	Refer to product Quality Micro Dr. Vinayak Pawar's review.	Acceptable	NA
Sterility	validated sterilization process	high	Refer to product Quality Micro Dr. Vinayak Pawar's review.	Acceptable	NA

III. Administrative

A. Reviewer's Signature

Chunchun Zhang

On file
Chunchun
Zhang -S

Digitally signed by Chunchun Zhang -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Chunchun
Zhang -S,
0.9.2342.19200300.100.1.1=2001178137
Date: 2015.06.17 08:04:32 -0400

B. Endorsement Block

Balajee Shanmugam

On file

Balajee
Shanmugam -S

Digitally signed by Balajee
Shanmugam -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130021
7143, cn=Balajee Shanmugam -S
Date: 2015.06.17 08:15:10 -0400

C. CC Block

On file

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

Chemistry Assessment Section

Executed batch records are provided and are acceptable.

Table 1. Executed Batch Records



II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Labeling is reviewed during the team label meeting for the NDA. The container and carton labels are listed below. The Package Insert, including an information section for patients, is provided in the conventional form. We had the discussions with the DMEPA reviewer Dr. Sevan Kolejian and the following statements for inclusion on the container labels were conveyed to the applicant:

- *Revise the statement “Each 100 ml contains...” to include the excipient “water for injection, USP”.*
- *Revise the statement “Single Dose Container” to read “single use only – discard unused portions”.*
- *Revise the caution statement to read “No further dilution is necessary. Do not add supplementary medication or additives. Must not be used in series connections. Check for minute leaks and solution clarity. Contains no preservative”.*

In the Amendment dated on Jun 11, 2015, the applicant agreed to include “water for injection, USP” statement on the container label. The applicant did not agree to include

Chemistry Assessment Section

the other proposed statements by the agency. DMEPA reviewer Dr. Sevan Kolejian has found the revised container labels and carton labeling are acceptable from a medication error perspective, refer to Dr. Kolejian's review in DARRTS on Jun 11, 2015. The revised container labels will be submitted to the agency shortly.

1) Container labels:**3) Patient Package Insert:**

These are the CMC relevant sections of the package insert. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

CEFAZOLIN INJECTION, USP in GALAXY CONTAINER (PL 2040 Plastic), for intravenous use. Initial U.S. Approval: 1973

-----INDICATIONS AND USAGE-----

Chemistry Assessment Section

Cefazolin Injection, USP is a cephalosporin antibacterial indicated for (b) (4)

-----DOSAGE AND ADMINISTRATION-----

- For intravenous use only over approximately 30 minutes.
- (b) (4) in patients who require the entire 2 gram dose and not any fraction (b) (4).
- -----DOSAGE FORMS AND STRENGTHS-----
- Cefazolin Injection, 2 g in 100 mL

3 DOSAGE FORMS AND STRENGTHS

Single-use GALAXY container:

- 2 g per 100 mL Cefazolin (b) (4) is a frozen, premixed, iso-osmotic, sterile, nonpyrogenic solution.

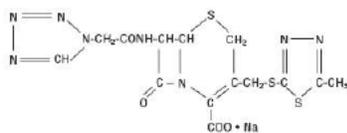
11 DESCRIPTION

Cefazolin Injection, (b) (4) is a frozen, premixed, iso-osmotic, sterile, nonpyrogenic, single use 100 mL solution containing cefazolin sodium equivalent to 2 g of Cefazolin, USP in the GALAXY container (PL 2040 Plastic). Dextrose, USP has been added to adjust osmolality (4 g as dextrose hydrous).

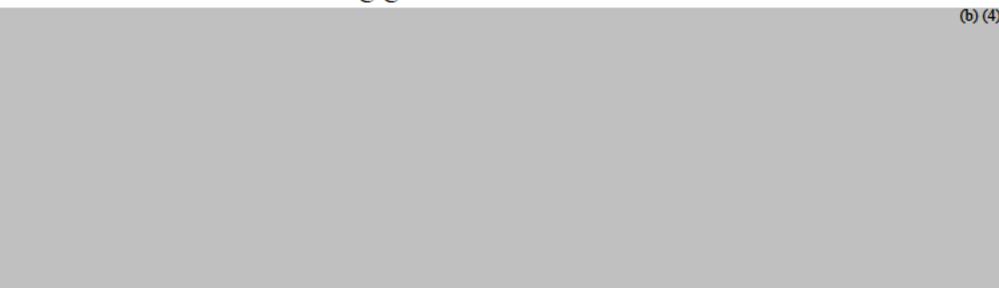
The approximate osmolality for Cefazolin Injection, (b) (4) is 290 mOsmol/kg.

Cefazolin Injection, (b) (4) is a semi-synthetic cephalosporin for parenteral administration and has the following IUPAC nomenclature: Sodium (6*R*,7*R*)-3-[[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[2-(1*H*-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. Its molecular formula is C₁₄H₁₄N₈O₄S₃·Na and its molecular weight is 454.51 (free base).

Cefazolin Sodium, USP has the following structural formula:



The sodium content is 48 mg/g of cefazolin sodium.



(b) (4) The pH of Cefazolin Injection, (b) (4) has been adjusted with sodium bicarbonate. Water for Injection, USP is added as (b) (4)

Chemistry Assessment Section

drug vehicle. The solution is intended for intravenous use after thawing to room temperature.

This GALAXY container (PL 2040 Plastic) is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. However, the suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cefazolin Injection, (b) (4) is supplied as a premixed frozen iso-osmotic solution in 100 mL single dose GALAXY plastic containers as follows:

2G3508	NDC 67798-3508-1	2 g cefazolin in 100 mL	Supplied 12/case
--------	------------------	-------------------------	------------------

Store (b) (4) -20°C/-4°F. [see (b) (4)]

Handle frozen product containers with care. Product containers may be fragile in the frozen state.

B. Environmental Assessment Or Claim Of Categorical Exclusion

A claim of categorical exclusion was made by Celerity Pharmaceuticals Cefazolin Injection USP referring to 21 CFR §25.31(b). No extraordinary circumstances exist in regards to these actions. The categorical exclusion from the preparation of an environment assessment (EA) is acceptable based on the applicant's proposed concentration of an EIC of below 1 ppb (part per billion).

III. List Of Deficiencies To Be Communicated**IR# 1, Feb 8, 2015**

1. Section 3.2.S.4.2 indicates that the drug substance solution (b) (4) and we are trying to evaluate how this affects the (b) (4) of the drug product. We were not able to locate this information in the NDA. Please indicate where in the NDA it is presented or submit this information.
2. Provide details of the forced degradation study on the drug product with relevant chromatograms.

IR# 2, Mar 19, 2015

Chemistry Assessment Section

1. The "in-process controls" listed in Section 3.2.P.3.4-1 have the potential to impact critical quality attributes. Please identify the critical process parameters for the proposed manufacturing process based on preselection of operating ranges or magnitude of product quality response. Please note that changes from the preselected targets/ranges (i.e. changes outside of the Proven Acceptable Ranges) could have a minor, moderate or substantial potential to adversely affect product quality. The Agency's expectation is that the potential impact of changes to process parameters and in-process controls, including those designated as non-critical process parameters, as well as the parameters in Master Batch Record, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70. Based on the information submitted, we recommend designating the identified [REDACTED] (b) (4)
[REDACTED]
2. With reference to Table 1 in section 3.2.P.8.2 which provides details on the post-approval stability commitment we do not agree with [REDACTED] (b) (4)
[REDACTED] We recommend that you follow ICH Q1A(R2) in that the frequency of testing at long term storage condition should normally be every 3 months over the first year. Please submit the revised table updating the testing frequency.

Chemistry Assessment Section

EES Summary Report: Pending.

ONDQA Initial Quality Assessment (IQA) and Filing Review
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IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **207131**

2. DATES AND GOALS:

Letter Date: October 16, 2014	Submission Received Date: October 16, 2014
PDUFA Goal Date: August 16, 2015	

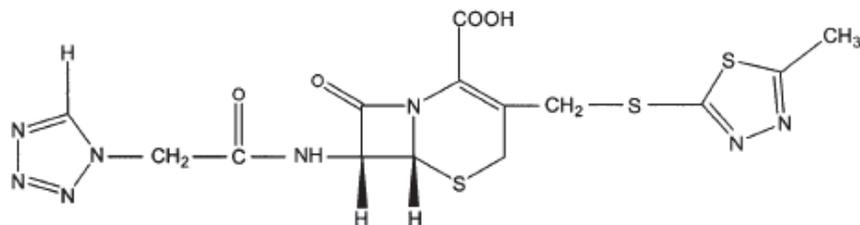
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	<i>None</i>
Established or Non-Proprietary Name (USAN):	Cefazolin Injection, USP (in Galaxy Container)
Dosage Form:	Injection
Route of Administration	Intravenous
Strength/Potency	2 g/100 mL
Rx/OTC Dispensed:	Rx

4. INDICATION:

(b) (4)

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



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

Celerity Pharmaceuticals, LLC

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7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 5
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAIP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology			TBD
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology			TBD
Methods Validation		X	
Environmental Assessment	X		
CDRH		X	
Other			N/A

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
CMC Filing Issues: <i>None</i>

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No
CMC Comments for 74-Day Letter: <i>None</i>

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Biopharmaceutics Filing Issues: <i>None</i>

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? No
Biopharmaceutics Comments for 74-Day Letter: <i>None</i>

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes
Microbiology Filing Issues: <i>None as indicated by Dr. Stephen Langille at the ONDQA kick-off meeting (refer to Product Quality Microbiology Filing Review for details).</i>

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Summary of Initial Quality Assessment

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

Is a team review recommended?	Yes	No
Product Quality Team:		
CMC Reviewer: Chunchun Zhang, Ph.D.		
Quality Microbiology Reviewer: Vinayak Pawar, Ph.D. (<i>assigned per email dated 12/1/2014</i>)		
Biopharmaceutics Reviewer: Kelly Kitchens, Ph.D.		

Summary of Critical Issues and Complexities
<i>Refer to IQA (below)</i>

Risk Assessment

Product attribute/ CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMEC A RPN Number	Comment, if any
Assay	4	2	1	8	Evaluate the in-coming material specification and COA provided; evaluate the assay method
Sterility	4	5	4	80	Satisfactory validation of the sterilization process will mitigate this issue. Consult Product Quality Microbiology Reviewer.
pH	2	2	1	4	Evaluate release and stability data
Particulate Matter	2	4	2	16	Evaluate if USP<788> is met on stability
Impurities/degradation products including extractables and leachables	2	4	4	32	Evaluate control strategy for impurities; also review CoAs for excipients. Consult Pharm/Tox Reviewer as needed
Appearance	3	3	1	9	Evaluate release and stability data
Endotoxin	2	4	4	32	Consult Product Quality Microbiology Reviewer

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Initial Quality Assessment

This 505(b)(2) NDA provides for Cefazolin Injection, USP in Galaxy Container, 2 g/100 mL. The listed drug is Cefazolin for Injection USP and Dextrose Injection USP in Duplex® Container (2 g/50 mL) manufactured by B. Braun Medical, Inc. (B. Braun) under NDA 50779. The comparison of the proposed drug product and listed drug is provided in the NDA (also attached below, Attachment 1). The drug product proposed via this NDA is manufactured by Baxter Healthcare Corporation (Baxter). Currently, Baxter holds an ANDA 63002, for a pre-mixed-frozen cefazolin product in 1 g/50 mL (0.02 g/mL) strength packaged in the 50 mL GALAXY plastic container (PL 2040). The formulation, process and equipment of the currently proposed drug product (b) (4)

Drug Substance

The CMC information is referenced to DMF Type II (b) (4). In addition, some general information, including the physico-chemical characteristics and specifications is provided in the NDA (Attachment 2, below). *Comment: Information in DARRTS indicates that this DMF has been previously reviewed; however, there are several recent amendments and/or annual updates that may need to be reviewed for the purpose of this NDA.*

Drug Product

The proposed drug product, Cefazolin Injection, USP, is described as a frozen, premixed, iso-osmotic, sterile, nonpyrogenic solution. The drug substance used in the proposed manufacturing process of the drug product is cefazolin, USP. (b) (4)

Comment: The manufacturing process and product characteristics will need to be evaluated in detail during the NDA review. Dextrose, USP has been added to adjust the osmolality. The pH range of the proposed dosage form has been adjusted with sodium bicarbonate (b) (4) to the range of 4.5 – 7.0. The composition of the proposed drug product is provided as the Attachment 3, below.

The Cefazolin Injection, USP drug product is supplied as a ready-to-use, premixed solution in a plastic container. Product labeling directs that no additional medication or additives are to be added prior to administration; therefore, there are no reconstitution diluents or dosage devices applicable to this product. The solution is intended for intravenous use after thawing at room temperature or under refrigeration.

The manufacturing process of the proposed drug product includes (b) (4)

(b) (4) Baxter product, the currently proposed Cefazolin Injection, USP finished drug product is packaged in Baxter's 100 mL single-port PL 2040 Plastic (GALAXY) Container Closure System. PL 2040 (b) (4) intended for medical

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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solution containers of premixed drug products stored at frozen temperatures (at or below -20 deg C) across their shelf life.

The drug product specification includes identification, assay, impurities, pH, osmolality, particulate matter, fill volume, residual solvents, sterility and bacterial endotoxins. *Comment: The proposed drug product specification does not seem to include a test for appearance.*

Three registration stability batches of Cefazolin Injection, USP (2 g/100 mL) in 100 mL GALAXY plastic container (PL 2040) were manufactured between December 8, 2010 and December 10, 2010 at Baxter's Round Lake, IL manufacturing facility (batches 54913, 54914, and 54915). As mentioned above, (b)(4) Baxter's currently approved Cefazolin Injection, USP (1 g/50 mL) in 50 mL GALAXY plastic container (PL 2040) drug product. Each batch is representative of the proposed commercial product and was manufactured with a batch size of at least (b)(4)% of the maximum requested commercial production size (b)(4). Stability results are available through 30 months of long-term frozen (-20 deg C) storage. Results for short-term thawed storage are available after 0, 12, and 24 months of frozen storage.

A request for inspection for all manufacturing facilities listed in the application for the drug substance and the drug product has been submitted to the Office of Compliance. *Comment: The facilities involved in the manufacture of the proposed drug product include the drug substance manufacturer, (b)(4) and the drug product manufacturer, (b)(4)*

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Biopharmaceutics Assessment

The proposed drug product, Cefazolin Injection, USP is a frozen, premixed, iso-osmotic, sterile, non-pyrogenic solution packaged in Baxter Healthcare Corporation's GALAXY container system (2 g as cefazolin/100 mL). Dextrose, USP is added to adjust the osmolality. The pH is adjusted with sodium bicarbonate [REDACTED] (b) (4) with a resultant pH range of 4.5 – 7.0.

Cefazolin Injection, USP is a cephalosporin antibacterial indicated for [REDACTED] (b) (4). The reference drug product for Cefazolin Injection, USP is the 2 g presentation of Cefazolin Sodium USP and Dextrose USP (NDA 50779, approved July 27, 2000), [REDACTED] (b) (4).

The Applicant requests a biowaiver for Cefazolin Injection, USP (2 g/100 mL) per 21 CFR § 320.22 (b)(1), based on the following:

- The proposed drug product is an iso-osmotic, sterile solution intended solely for intravenous administration that has the same active ingredient in the same strength as the reference product.
- The dosage form, route of administration and dosing regimen for the proposed drug are the same as the reference product.

During the May 20, 2014 Type B pre-NDA meeting, the following Applicant question and Agency response were discussed regarding the biowaiver request:

Applicant Question:

In accordance with 21 CFR § 320.22(a), Celerity intends to request a waiver of the requirement to submit in vivo bioavailability/bioequivalence data for the proposed 2 g/100 mL Cefazolin Injection, USP drug product. This request is based on 21 CFR § 320.22(b), which states that for certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident provided:

(1) The drug product:

- (i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and*
- (ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.*

The proposed drug product's self-evident in vivo bioavailability/bioequivalence is based on the fact that the product is an iso-osmotic, sterile solution intended solely for intravenous administration that has the same active ingredient in the same strength as the reference listed drug that is the subject of an approved NDA. Further, the dosage form, route of administration and dosing regimen for the proposed drug are the same as the RLD. The difference in product concentration (2 g/100 mL vs. 2 g/50 mL in RLD) and excipients (dextrose concentration of 4% vs. 3% in RLD and presence of sodium bicarbonate in the proposed product) are not expected to lead to clinical differences. Does the Agency concur with this position?

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Agency Response:

Provided that there is agreement on the active ingredient discussed in question 1,¹ your approach appears reasonable. In your NDA, submit a Biowaiver request along with a justification and all supportive information, such as a side-by-side comparison table between your proposed product and the listed drug, including components and composition, indication, stability, instructions for dilution, etc. Also provide pH and osmolality comparisons between the proposed drug product and the diluted listed drug. Justify any difference (e.g. delivered volume, infusion rate, amount of dextrose, etc.) between the listed drug and the proposed drug with respect to clinical safety and efficacy. The approvability of the Biowaiver request is a review issue under the NDA.

Applicant Clarification Request:

For the osmolality comparison between the Celerity and RLD products, we propose to provide RLD data after initial dissolution and one day of storage at 25°C. Does the Agency agree this is an acceptable approach?

Meeting Discussion:

The Division confirmed that this approach was acceptable and asked Celerity to submit the data to the application.

The Applicant provided the following comparative table for the proposed and reference drug products:

¹

(b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Table 1. Side-by-Side Comparison of Proposed and Reference Listed Drug Products

Parameter	Reference Listed Drug	Proposed Drug Product
Name	Cefazolin for Injection USP and Dextrose Injection USP	Cefazolin Injection, USP
Conditions of Use (Indications)	Cefazolin for Injection USP and Dextrose Injection USP is indicated for the treatment of the following infections when caused by susceptible bacteria. Respiratory Tract Infections Urinary Tract Infections Skin and Skin Structure Infections Biliary Tract Infections Bone and Joint Infections Genital Infections Septicemia Endocarditis Perioperative Prophylaxis	Cefazolin Injection, USP is indicated (b) (4)
Active Ingredient	Cefazolin sodium	Cefazolin sodium
Total Drug Content	2 g (as cefazolin)	2 g (as cefazolin)
Tonicity Adjuster	3% w/v Hydrous Dextrose, USP (1.5 g/50 mL)	4% w/v Hydrous Dextrose, USP ^a (4 g/100 mL)
pH Adjuster	none listed	Sodium Bicarbonate, USP ^b (b) (4) and as required
Vehicle	Water for Injection, USP	Water for Injection, USP
Volume	50 mL in DUPLEX [®] plastic container	100 mL in GALAXY plastic container
Strength	2 g (2 g base in powder form)	2 g (2 g base/100 mL)
Concentration	40 mg/mL (2 g/50 mL)	20 mg/mL (2 g/100 mL)
Osmolality ^c	Iso-osmotic (approx. 290 mOsmol/kg)	Iso-osmotic
pH ^d	4.99 – 6.09	5.5 – 6.4 (proposed limits: 4.5 – 7.0)
Dosage Form	Injectable; sterile lyophilized dry powder packaged with dextrose solution (ready to mix)	Injectable; frozen, iso-osmotic, sterile solution (premixed)
Container Closure System	Dual-chamber (DUPLEX [®]), single-use plastic container for sterile reconstitution of dry powder and diluent for injection	Single-use plastic container (GALAXY) for frozen, premixed, iso-osmotic, sterile solution

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Table 1. Side-by-Side Comparison of Proposed and Reference Listed Drug Products

Parameter	Reference Listed Drug	Proposed Drug Product
Instructions for Use	Do not use directly after storage by refrigeration, allow the product to equilibrate to room temperature before patient use. Unfold the DUPLEX® container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber. Agitate the liquid-powder mixture until the drug powder is completely dissolved.	Thaw frozen container at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). (DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.)
Short-Term Stability	After admixing: 7 days under refrigeration or 24 hours stored at room temperature	After thaw: 30 days under refrigeration and 48 hours at room temperature (proposed)
Route of Administration	Injection: Intravenous infusion	Injection: Intravenous infusion
Dosing Regimen	2 g dose infusion over approximately 30 minutes	2 g dose infusion over approximately 30 minutes
Dosing Volume	50 mL	100 mL
Infusion Rate	100 mL/hour	200 mL/hour
(b) (4)		
(b) (4)		

^c See Section 1.3.

^d See Section 1.4.

The Applicant provided justification for the differences in dextrose concentration, sodium bicarbonate, osmolality, pH, dosing volume, and infusion rate with respect to clinical safety and efficacy. The justification for the differences between the proposed and reference products will be evaluated during the NDA review process.

Table 2. Composition of the Dosage Form

Component	Quality Standard	Function	Component Quantity
			Per 100 mL ^a
Cefazolin Free Acid	USP	Active ingredient	2 grams ^b
Dextrose, Hydrated ^c	USP	Osmolality adjuster	4 grams
(b) (4)			
Sodium Bicarbonate	USP	pH adjuster	pH adjustment ^d

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Component	Quality Standard	Function	Component Quantity
			Per 100 mL ^a
Water for Injection	USP	Drug vehicle	QS

USP = United States Pharmacopeia; QS = Quantity Sufficient



(b) (4)

A comparison of the osmolality for the proposed and referenced products is provided in the following table:

Table 29. Mean Osmolality for B. Braun Product (RLD)^a and Proposed Celerity Product^b

Parameter	Units	Fresh Admix	Fresh Thaw	5°C 7 Days	5°C 30 Days	25°C 24 Hrs.	30 Days/5°C + 48 Hrs/25°C	Baxter 1 g/50 mL Product Limits
		B. Braun	Celerity	B. Braun	Celerity	B. Braun	Celerity	
Osmolality	mOsmol/kg	291	292	NT	294	296	296	255 - 345 mOsmol/kg
		295		NT		298		

NT = not tested

^a B. Braun results are the mean values for each of two lots (H4D515, H4E705). Each lot was tested in triplicate.

^b Celerity results are the mean values from developmental Study 48287 (Section 1.2). Triplicate testing was performed.

Potential review issues to be forwarded to the Applicant for the 74-day letter:

There are no potential review issues.

RECOMMENDATION:

From the ONDQA Biopharmaceutics perspective, NDA 207131 is fileable. The information supporting the biowaiver request for Cefazolin Injection, USP will be evaluated during the NDA review.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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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</i> filing issue or a <i>potential</i> review issue.				
	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? This question is not applicable for synthesized API.			

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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	Parameter	Yes	No	Comment
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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

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	Parameter	Yes	No	Comment
9.	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: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		Categorical exclusion

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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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		Reference to DMF Type II (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Reference to DMF Type II (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Reference to DMF Type II (b) (4)
15.	Does the section contain controls for the DS?	X		Reference to DMF Type II (b) (4) (also submitted in the NDA)
16.	Has stability data and analysis been provided for the drug substance?	X		Reference to DMF Type II (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			<i>Not immediately obvious but not required either</i>
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			<i>Not immediately obvious but not required either</i>

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
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?			N/A
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>

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

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		
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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)	(b) (4)	June 13, 2014?	Last review dated July 18, 2014; several amendments
(b) (4)	III	(b) (4)		July 11, 2014	Adequate

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		

J. Biopharmaceutics				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?		X	
34.	Is the dissolution test part of the DP specifications?		X	
35.	Does the application contain data to support the proposed dissolution acceptance criteria		X	
36.	Does the application contain the dissolution method development report?		X	

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37.	Does the application contain data on the discriminating ability of the dissolution method		X	
38.	Is there a validation package for the analytical method and dissolution methodology?		X	
39.	Does the application include a biowaiver request?	X		The Applicant requests a biowaiver per 21 CFR § 320.22(b)(1)
40.	Does the application include an IVIVC model?		X	
41.	Is information such as BCS classification mentioned, and supportive data provided?		X	
42.	Is information on mixing the product with foods or liquids included?		X	
43.	Is there any <i>in vivo</i> BA or BE information in the submission?		X	
44.	Does the application include <i>in vitro</i> alcohol interaction studies?		X	

FILING CONCLUSION				
	Parameter	Yes	No	Comment
45.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
46.	If the NDA is not fileable from the product quality and biopharmaceutics perspectives, state the reasons and provide filing comments to be sent to the Applicant.			N/A (fileable)
47.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

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Attachment 1

Table 1. Side-by-Side Comparison of Proposed and Reference Listed Drug Products

Parameter	Reference Listed Drug	Proposed Drug Product
Name	Cefazolin for Injection USP and Dextrose Injection USP	Cefazolin Injection, USP
Conditions of Use (Indications)	Cefazolin for Injection USP and Dextrose Injection USP is indicated for the treatment of the following infections when caused by susceptible bacteria. Respiratory Tract Infections Urinary Tract Infections Skin and Skin Structure Infections Biliary Tract Infections Bone and Joint Infections Genital Infections Septicemia Endocarditis Perioperative Prophylaxis	Cefazolin Injection, USP is indicated (b) (4)
Active Ingredient	Cefazolin sodium	Cefazolin sodium
Total Drug Content	2 g (as cefazolin)	2 g (as cefazolin)
Tonicity Adjuster	3% w/v Hydrous Dextrose, USP (1.5 g/50 mL)	4% w/v Hydrous Dextrose, USP ^b (4 g/100 mL)
pH Adjuster	none listed	Sodium Bicarbonate, USP ^c (b) (4)
Vehicle	Water for Injection, USP	Water for Injection, USP
Volume	50 mL in DUPLEX [®] plastic container	100 mL in GALAXY plastic container
Strength	2 g (2 g base in powder form)	2 g (2 g base/100 mL)
Concentration	40 mg/mL (2 g/50 mL)	20 mg/mL (2 g/100 mL)
Dosage Form	Injectable; sterile lyophilized dry powder packaged with dextrose solution (ready to mix)	Injectable; frozen, iso-osmotic, sterile solution (premixed)
Container Closure System	Dual-chamber (DUPLEX [®]), single-use plastic container for sterile reconstitution of dry powder and diluent for injection	Single-use plastic container (GALAXY) for frozen, premixed, iso-osmotic, sterile solution

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Table 1. Side-by-Side Comparison of Proposed and Reference Listed Drug Products

Parameter	Reference Listed Drug	Proposed Drug Product
Instructions for Use	Do not use directly after storage by refrigeration, allow the product to equilibrate to room temperature before patient use. Unfold the DUPLEX® container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber. Agitate the liquid-powder mixture until the drug powder is completely dissolved.	Thaw frozen container at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). (DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.)
Short-Term Stability	After admixing: 7 days under refrigeration or 24 hours stored at room temperature	After thaw: 30 days under refrigeration and 48 hours at room temperature (proposed)
Route of Administration	Injection: Intravenous infusion	Injection: Intravenous infusion
Dosing Regimen	2 g dose infusion over approximately 30 minutes	2 g dose infusion over approximately 30 minutes
Dosing Volume	50 mL	100 mL
Infusion Rate	100 mL/hour	200 mL/hour

(b) (4)

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

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