

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207131Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 7-20-15

Date Company Submitted Document: 10-16-14 and 1-16-15
CDER Date Received: 10-16-14 and 1-16-15
Received for Review: 10-16-14 and 1-16-15
Date Assigned: 10-16-14 and 1-16-15
Reviewer: Kerian Grande Roche

NAME AND ADDRESS OF SPONSOR

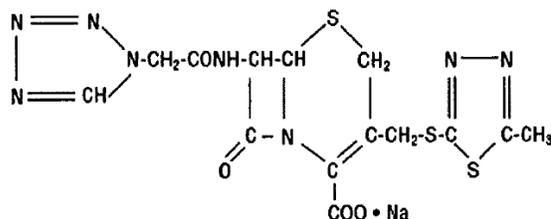
Celerity Pharmaceuticals, LLC
9450 W. Bryn Mawr Ave, Suite 640
Rosemont, Il 60018

CONTACT PERSON

Brent Yurschak
Senior Regulatory Affairs Manager
Phone: 847-999-0492

DRUG PRODUCT NAME

Proprietary Name: None
Established Name/Code Name(s): Cefazolin Injection, USP
Chemical Name:
Sodium (6R,7R)-3-[[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[2-(1H-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
Chemical Structure:



DRUG CATEGORY:

Antibiotic

PROPOSED INDICATION(S)

(b) (4)

DIVISION OF ANTI-INFECTIVE PRODUCTS
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**PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION,
STRENGTH AND DURATION OF TREATMENT**

See table 1 below.

Table 1. Product Comparison – B. Braun and Celerity 2 g Drug Products

Applicant	B. Braun (Listed Drug)	Celerity (Proposed Drug)
Product	Cefazolin for Injection USP and Dextrose Injection USP in Duplex® Container	Cefazolin Injection, USP in GALAXY plastic container
Active Ingredient	Cefazolin Sodium, USP	Cefazolin, USP ^a
Total Drug Content	2.0 g	2.0 g
Diluent	3% Dextrose, USP	4% Dextrose, USP ^b
Other Inactive Ingredients	none listed	Sodium Bicarbonate, USP
Volume	50 mL in Duplex® Container	100 mL in GALAXY plastic container
Strength	2.0 g (2 g base/vial)	2.0 g (2 g base/100 mL)



Source: Pre-NDA submission.

DISPENSED:
Rx

DIVISION OF ANTI-INFECTIVE PRODUCTS

CLINICAL MICROBIOLOGY REVIEW

Date review completed: 7-20-15

RELATED DOCUMENTS:

NDA 050461

NDA 050779

ANDA 065226

REMARKS

The Applicant submitted a 505(b)(2) NDA for cefazolin injection, USP (2 gram strength), and a labeling amendment for review on 10-16-14 and 1-16-15, respectively. In the labeling amendment, the indication was changed to (b) (4). Besides the (b) (4) indications, this product is not substantially different from that of the RLD holder from a clinical microbiology perspective.

CONCLUSIONS

This reviewer recommends approval, however, the microbiology subsection 12.4 should be updated according to the Agency's proposed labeling below:

RATIONALE FOR LABELING CHANGES

The Agency recommends changes to the Applicant's proposed labeling because the indication for this 505(b)(2) product is (b) (4), which differs from the indication of the RLD holder, which includes (b) (4) as well. Because (b) (4) are not in the labeling for the 505(b)(2) product proposed here, the microbiology subsection 12.4 has been updated by the removal of information that pertains (b) (4). This includes methods for susceptibility testing, susceptibility test interpretive criteria, and quality control parameters. Information was retained in subsection 12.4 of the labeling that is informative and useful to prescribing physicians.

DIVISION OF ANTI-INFECTIVE PRODUCTS
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**AGENCY'S PROPOSED LABELING (ONLY MICROBIOLOGY SUBSECTION
12.4 IS SHOWN)**

12.4 Microbiology

Mechanism of Action

Cefazolin is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.

Mechanism of Resistance

Predominant mechanisms of bacterial resistance to cephalosporins include the presence of extended-spectrum beta-lactamases and enzymatic hydrolysis.

Antimicrobial Activity

Cefazolin has been shown to be active against most isolates of the following microorganisms:

Gram-positive Bacteria

Staphylococcus aureus (methicillin-susceptible isolates only)

Streptococcus agalactiae

Streptococcus pyogenes

Gram-negative Bacteria

Escherichia coli

Proteus mirabilis

Most isolates of indole positive *Proteus* (*Proteus vulgaris*), *Enterobacter* spp., *Morganella morganii*, *Providencia rettgeri*, *Serratia* spp., and *Pseudomonas* spp. are resistant to cefazolin.

Kerian Grande Roche, Ph.D.
Clinical Microbiology Reviewer

Kerry Snow, MS
Clinical Microbiology Team Leader
20 July 2015

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

/s/

KERIAN K GRANDE ROCHE
07/20/2015

KERRY SNOW
07/20/2015

Product Quality Microbiology Review

MAY 27, 2015

NDA: 207131

Drug Product Name

Proprietary: N/A

Non-proprietary: Cefazolin Injection, USP

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
October 16, 2014	October 16, 2014	November 15, 2014	December 1, 2014
June 19, 2015	June 19, 2015	Amendment	June 19, 2015

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor

Name: Celerity Pharmaceuticals, LLC

Address: 9450 W. Bryn Mawr Ave, Rosemont, IL 60018

Representative: Brent Yurschak, Sr. RA Manager

Telephone: Ambareen Sheriff, Vice President RA & QA
(847)-999-0129

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
 2. **SUBMISSION PROVIDES FOR:** Cefazolin Injection, USP (b) (4) the RLD in drug content but for different indication in a 100 mL presentation.
 3. **MANUFACTURING SITE:** Baxter Healthcare Corporation, Round Lake, IL 60073.
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 2g/100mL in GALAXY Container for intravenous use.
 5. **METHOD(S) OF STERILIZATION:** Aseptic Fill.
 6. **PHARMACOLOGICAL CATEGORY:** Indicated for (b) (4).
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF (b) (4), Baxter LOA dated July 11, 2014.
- C. **REMARKS:** The subject original NDA submission is for an ant-microbial drug product manufactured by Baxter [DMF (b) (4)] using an (b) (4) (b) (4) in the Review Section P.5, information pertaining to (b) (4) has been added based on the amendment received on June 9, 2015 in response to Agency's email dated June 8, 2015. This information was included in the original NDA submission. This is an electronic submission.

filename: N207131R1

Executive Summary

I. Recommendations

- A. Recommendation on Approvability - Recommend Approval**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product in GALAXY (PL 2040) plastic container is manufactured by Baxter’s** (b) (4)
- B. Brief Description of Microbiology Deficiencies - None**
- C. Contains Potential Precedent Decision(s) - Yes No**

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O ^(3, 4, 5)	Severity of Effect (S)	Detect. (D)	Risk Priority Number ⁶ (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	9		5	5	225	Ensure system is closed
Endo		4		4	4	64	

1 = (b) (4)
 2 = (b) (4)

3 = Anti-Microbial Formulation (e.g., meets USP <51>), modifies O (-1) [less emphasis on in process hold times]
 4 = Post-Constitution/-Dilution Hold Times in Labeling, modifies O (+1) [emphasize Labeling instructions for administration, dosing, storage conditions, and specified diluents. Microbial challenge studies supporting label recon/dilution/storage instructions (b) (4)]
 5 = Components derived from animal sources, modifies O (+1) [emphasize Component bioburden, TSE/BSE-free documentation (TS and AP), viral inactivation studies (AP), bioburden reduction processes.]
 6 = RPN = O (after modification when applicable) ×S×D
 RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

B. Final Risk Assessment - Low

IV. Administrative

- A. Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, DMA/OPQ

- B. Endorsement Block** _____
Stephen E. Langille, Ph.D., Acting Chief, Branch III, DMA/OPQ

- C. CC Block**
N/A

Product Quality Microbiology Assessment

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA**

S DRUG SUBSTANCE – Non-sterile

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – The proposed antibiotic drug product is a frozen, premixed, iso-osmotic, sterile, non-pyrogenic solution packaged in Baxter’s GALAXY container system (2 g cefazolin/100 mL).
- Drug product composition – The drug product composition is provided in Table 1 (copied from Table 2, Section 3.2.P.1).

Table1. Composition of Dosage Form

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

- Description of container closure system – A description of the container closure system for the finished dosage form and a general summary of the container closure manufacturing were provided in Module 3.2.P.7 Container Closure System. The manufacture of the container closure system is described in detail in Baxter’s DMF (b) (4), *Production of (b) (4) Plastic Container.* Finished GALAXY containers, consisting of a bag comprised of PL 2040 film and (b) (4)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – Container closure integrity test was performed after an alternate polymer PL2040 was used for the Galaxy (b) (4). The containers were subjected to worst case gamma irradiation and the integrity test was found acceptable per Microbiology review of DMF (b) (4) dated August 2012.

- Preservative Effectiveness – N/A

ADEQUATE

REVIEWER COMMENT – The Galaxy Container Closure system is currently used for several FDA approved cephalosporin products. The container closure integrity has been tested and found acceptable in 2012 per microbiology review of DMF (b) (4).

P.3 Manufacture

P.3.1 Manufacturers – Baxter Healthcare Corporation, Roundlake IL 60073.

P.3.3 Description of the Manufacturing Process and Process Controls



ADEQUATE

REVIEWER COMMENT – The applicant meets the regulatory expectations with regard to the design of the stability program to support the drug product’s microbiological quality throughout its shelf life.

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

A. PACKAGE INSERT

The conditions of use, prescribed, recommended or suggested in the labeling proposed for Cefazolin Injection, USP have been previously approved for the reference listed drug (RLD) Cefazolin for Injection USP and Dextrose Injection USP marketed by B. Braun Medical Inc. under NDA 050779. No drug product manipulation or pharmacy compounding is indicated. Labeling meetings will be scheduled in July 2015.

ADEQUATE

REVIEWER COMMENT – The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

**3. LIST OF MICROBIOLOGY DEFICIENCIES AND
COMMENTS:**

None

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300151299,
cn=Vinayak B. Pawar -A
Date: 2015.06.22 13:34:02 -04'00'

Stephen E. Langille -A

Digitally signed by Stephen E. Langille -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
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Date: 2015.06.29 11:30:05 -04'00'

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 5-27-14

Date Company Submitted Document: 3-14-14 CDER Date Received: 3-26-14
Received for Review: 5-22-14 Reviewer: Kerian Grande Roche
Date Assigned: 5-22-14

NAME AND ADDRESS OF SPONSOR

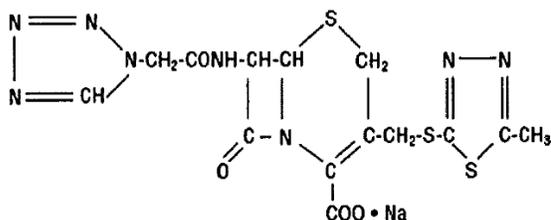
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Rosemont, Il 60018

CONTACT PERSON

Brent Yurschak
Senior Regulatory Affairs Manager
Phone: 847-999-0492

DRUG PRODUCT NAME

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Established Name/Code Name(s): Cefazolin Injection, USP
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Chemical Structure:



DRUG CATEGORY:

Antibiotic

PROPOSED INDICATION(S)

(b) (4)

**PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION,
STRENGTH AND DURATION OF TREATMENT**

See table 1 below.

DISPENSED:

Rx

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 5-27-14

RELATED DOCUMENTS:

NDA 050461
NDA 050779
ANDA 065226

REMARKS

The Sponsor would like to discuss with the FDA their plans to seek a waiver of the bioequivalence requirement for a premixed 2 g cefazolin injection, USP drug product.

CONCLUSIONS

The changes to this product are not substantially different from the RLD from a clinical microbiology perspective. The Sponsor should proceed with the submission of their NDA. There are no clinical microbiology comments for the Sponsor at this time, however, the Sponsor may need to re-evaluate the appropriateness of their breakpoints in the near future, particularly if there is a change to the breakpoints with the RLD holder.

COMMENTS FOR SPONSOR

None

DIVISION OF ANTI-INFECTIVE PRODUCTS

CLINICAL MICROBIOLOGY REVIEW

Date review completed: 5-27-14

Table 1. Product Comparison – B. Braun and Celerity 2 g Drug Products

Applicant	B. Braun (Listed Drug)	Celerity (Proposed Drug)
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Other Inactive Ingredients	none listed	Sodium Bicarbonate, USP
Volume	50 mL in Duplex® Container	100 mL in GALAXY plastic container
Strength	2.0 g (2 g base/vial)	2.0 g (2 g base/100 mL)



(b) (4)

Source: This submission.

Kerian Grande Roche, Ph.D.
Clinical Micro. Reviewer/HFD520

Kerry Snow, MS
Clinical Microbiology Team Leader
27 May 2014

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

/s/

KERIAN K GRANDE ROCHE
05/27/2014

KERRY SNOW
05/27/2014