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RESEARCH**

APPLICATION NUMBER:

207131Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 207-131	Submission Date(s): 10/16/2014
Drug	Cefazolin
Trade Name	Cefazolin Injection, USP
OCP Reviewers	Kunyi Wu, Pharm.D.
OCP Team Leader	Kimberly L. Bergman, Pharm.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	Celerity Pharmaceuticals LLC
Relevant IND(s)	None
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	GALAXY™ Plastic Container: Cefazolin 2g/100 mL, frozen, premixed, iso-osmotic, sterile solution
Indication	(b) (4)
Dosage and Administration	<p align="center">Adult dose: Use Cefazolin injection in patients who require the entire 2 gram dose and not any fraction of it.</p> <p align="center">Adults with Renal Impairment: Use Cefazolin injection only in patients with creatinine clearance greater than or equal to 35 mL/min.</p> <p align="center">(b) (4)</p>

Background

Cefazolin sodium is a semi-synthetic cephalosporin that specifically targets bacterial cell wall synthesis and demonstrates bactericidal activity against most strains of gram-positive aerobes including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, as well as gram-negative aerobes such as *Escherichia coli* and *Proteus mirabilis*. Cefazolin has been approved by the FDA and is indicated in the treatment of the following infections caused by susceptible isolates of the designated microorganisms: respiratory tract infections; urinary tract infections; skin and skin structure infections; biliary tract infections; bone and joint infections; genital infections; septicemia; endocarditis and perioperative prophylaxis.

Celerity submitted a 505(b)(2) New Drug Application (NDA) on 10/16/2014 for a frozen, premixed, iso-osmotic, sterile, non-pyrogenic solution of cefazolin packaged in Baxter's GALAXY container for the indication of (b) (4). The Sponsor is seeking approval for 2 g cefazolin in GALAXY container (2 g as free acid/100 mL of diluent in each bag). Dextrose, USP is added to adjust the osmolality. The pH is adjusted with sodium bicarbonate (b) (4) to a range of 4.5 – 7.0. The proposed Cefazolin Injection, USP product is intended for intravenous use only after thawing at room temperature or under refrigeration. Baxter Healthcare Corporation currently markets a 1 g/50 mL cefazolin with the same excipients under ANDA 63002 (also a frozen premix in a GALAXY plastic container). The Sponsor has hired Baxter to manufacture and package their proposed 2 g/100 mL cefazolin product.

The Sponsor lists CEFAZOLIN FOR INJECTION USP AND DEXTROSE INJECTION USP IN DUPLEX® CONTAINER (NDA 50779 by B. Braun) as the reference listed drug (RLD) for this 505(b) (2) NDA submission. However, different from the RLD, this proposed product is only for one indication which is (b) (4). Moreover, since this product is a premixed solution, it should be used only in patients who require the entire 2 gram dose and not any fraction thereof. Table 1 provides a comparison between the proposed product and the RLD.

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 for (b) (4) ^a
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) 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 ^d	Iso-osmotic (approx. 290 mOsmol/kg)	Iso-osmotic
pH ^e	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

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)

^d See Section 1.3.

^e See Section 1.4.

The Sponsor intends to rely upon the Agency's findings for safety and efficacy and information provided in the approved labeling for the RLD. No new clinical pharmacology information was submitted in this application, and the Sponsor has submitted a request for waiver of the regulatory requirement for bioavailability as outlined in 21 CFR 320.22. Please refer to the Office of Product Quality (OPQ) Biopharmaceutics review for further evaluation of the request for waiver of bioavailability requirements. The scope of this review will be limited to edits on the proposed labeling.

Clinical Pharmacology Assessment of Proposed Labeling:

Reviewer's recommended revisions appear in underlined bold BLUE font, and/or strikethrough.

~~2.3~~ 2.2 **Patients with Renal Impairment**

Use Cefazolin injection only in patients whose creatinine clearance is greater than or equal to 35 mL/min and require the entire 2 gram dose and not any fraction of it.

(b) (4)

[Redacted]

[Redacted] (b) (4)

7 DRUG INTERACTION

- [Redacted] (b) (4)
-The renal excretion of cefazolin is inhibited by probenecid.
Co-administration of probenecid with cefazolin is not recommended.

Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the application, and no new clinical pharmacology information was submitted. The application is acceptable from a clinical pharmacology standpoint, following incorporation of the labeling edits above and attached in the Agency's proposed label.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KUNYI WU
07/17/2015

KIMBERLY L BERGMAN
07/17/2015

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 207131	Primary Reviewer: Kelly M. Kitchens, Ph.D.	
Submission Date:	October 16, 2014		
Division:	Division of Anti-Infective Products	Secondary Reviewer: Tapash Ghosh, Ph.D.	
Applicant:	Celery Pharmaceuticals, LLC		
Trade Name:	N/A	Date Assigned:	October 17, 2014
Established Name:	Cefazolin Injection, USP	Date of Review:	June 5, 2015
Indication:	(b) (4)		Type of Submission: New Drug Application 505(b)(2)
Formulation/ strengths	Sterile solution for Injection/ 2 g/100 mL		
Route of Administration	Intravenous infusion		
Type of Review:	Amendment to Biopharmaceutics review dated March 13, 2015		
<u>SUMMARY:</u>			
<p>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), and is indicated for treatment of the following infections caused by susceptible isolates of the designated microorganisms:</p> <ul style="list-style-type: none"> • (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), which has the same indication as Cefazolin Injection, USP.

The Applicant requested a biowaiver for their proposed drug product 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.

The Biopharmaceutics review dated March 13, 2015 recommended that the biowaiver be granted for the proposed drug product, Cefazolin Injection, USP.¹ However, the recommendation included a typo that stated the Cefazolin Injection, USP strength as 1 g/vial; therefore, this amendment to the Biopharmaceutics review is to correct the Cefazolin Injection, USP strength to 2 g/100 mL. The recommendation to grant the biowaiver remains.

RECOMMENDATION:

The waiver for in vivo bioavailability/bioequivalence studies for Cefazolin Injection, USP, 2 g/100 mL, is granted. From the Biopharmaceutics perspective, NDA 207131 for Cefazolin Injection, USP, 2 g/100 mL, is recommended for approval.

Signature

**Kelly M.
Kitchens -S**

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Kelly M. Kitchens, Ph.D.
Acting Quality Assessment Lead
Division of Biopharmaceutics
Office of New Drug Products

Signature

**Tapash K.
Ghosh -S**

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Tapash Ghosh, Ph.D.
Acting Branch Chief
Division of Biopharmaceutics
Office of New Drug Products

cc. PSeo.

¹ Panorama: NDA 207131-Orig1-New – Expedited Review, Biopharmaceutics Primary Quality Assessment by Kelly Kitchens, Completed March 13, 2015

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 207131	Primary Reviewer: Kelly M. Kitchens, Ph.D.	
Submission Date:	October 16, 2014		
Division:	Division of Anti-Infective Products	Secondary Reviewer: Tapash Ghosh, Ph.D.	
Applicant:	Celerity Pharmaceuticals, LLC		
Trade Name:	N/A	Date Assigned:	October 17, 2014
Established Name:	Cefazolin Injection, USP	Date of Review:	March 11, 2015
Indication:	Treatment of the following infections caused by susceptible isolates of the designated microorganisms: <ul style="list-style-type: none"> •  (b) (4) 	Type of Submission: New Drug Application 505(b)(2)	
Formulation/ strengths	Sterile solution for Injection/ 2 g/100 mL		
Route of Administration	Intravenous infusion		
Type of Review:	Biowaiver Request		
<u>SUMMARY:</u>			
<i>Background:</i> 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), and is indicated for treatment of the following infections caused by susceptible isolates of the designated microorganisms: <ul style="list-style-type: none"> •  (b) (4) 			

(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), (b) (4) as Cefazolin Injection, USP.

Submission: The Applicant requests a biowaiver for Cefazolin Injection, USP (1 g/vial) 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 (b) (4)
- The dosage form, route of administration and dosing regimen for the proposed drug are the same as the reference product.

Review: The Biopharmaceutics review is focused on the evaluation and approvability of the information submitted to support the biowaiver request.

RECOMMENDATION:

The waiver for in vivo bioavailability/bioequivalence studies for Cefazolin Injection, USP, 1 g/vial, is granted. From the Biopharmaceutics perspective, NDA 207131 for Cefazolin Injection, USP 1 g/vial, is recommended for approval.

Signature

Kelly M.
Kitchens -S

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Kelly M. Kitchens, Ph.D.
Primary Biopharmaceutics Reviewer
Office of New Drug Products

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Tapash Ghosh, Ph.D.
Secondary Biopharmaceutics Reviewer
Office of New Drug Products

cc. PSeo.

BIOPHARMACEUTICS ASSESSMENT

Drug Product:

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, Hydrus ^c	USP	Osmolality adjuster	4 grams
(b) (4)			
Sodium Bicarbonate	USP	pH adjuster	pH adjustment ^a
Component	Quality Standard	Function	Component Quantity
			Per 100 mL ^a
Water for Injection	USP	Drug vehicle	QS

USP = United States Pharmacopeia; QS = Quantity Sufficient

^a Labeled volume: 100 mL. Fill volume: (b) (4)

^b The dosage form is formulated with a (b) (4)

^c Dextrose is weighed for formulation (b) (4) Dextrose, Hydrus. The (b) (4)

Biowaiver Request:

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?

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.

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

¹

(b) (4)

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 for the treatment of the following (b) (4) (b) (4)
Active Ingredient	Cefazolin sodium	Cefazolin sodium
Total Drug Content	2 g (as cefazolin)	2 g (as cefazolin)
Tonicity Adjuster	3% w/v Hydrus Dextrose, USP (1.5 g/50 mL)	4% w/v Hydrus 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

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)

^c See Section 1.3.

^d See Section 1.4.

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.

Biopharmaceutics Reviewer comments:

The properties of the proposed and reference products are similar, except for the following:

Tonicity adjuster/Hydrous Dextrose, USP:

- Applicant’s justification: Since the drug concentration in the proposed drug product is less than in the reference product, the concentration of dextrose (4%)

required to achieve an iso-osmotic solution in the proposed drug product is greater than the concentration of dextrose (3%) in the reference product. The concentration of dextrose in the proposed drug product (4%) is identical to the concentration of dextrose in Baxter's currently marketed 1 g/50 mL drug product under ANDA 063002. Moreover, the original GSK pharmacy bulk pack under NDA 050461 (since withdrawn) as well as the currently marketed Hospira pharmacy bulk pack under ANDA 065247, are labeled for reconstitution with several diluents, including 5% or 10% dextrose solution. As summarized in the following table, it is evident that dextrose amounts ranging from 3-10% are acceptable for clinical practice, and the difference between the proposed and reference drug products does not present a risk to clinical safety and efficacy.

Table 2. Dose Volumes for Cefazolin Drug Products

Manuf.	Concentration of Cefazolin	1 g Dose	2 g Dose	Infusion Rate	Concentration of Dextrose
Celerity	2 g/100 mL	Not Applicable	100 mL	Infusion over approximately 30 minutes: 200 mL/hr	4%
B. Braun ^a	1 g/50 mL 2 g/50 mL	50 mL	50 mL	Infusion over approximately 30 minutes: 100 mL/hr	4% (1G) 3% (2G)
Baxter ^b	1 g/50 mL	50 mL	Not Applicable	Not specified	4%
GSK ^c	10 g/51 mL 10 g/102 mL	5 mL 10 mL	10 mL 20 mL	Not specified	5% or 10%
Hospira ^d	10 g/51 mL 10 g/102 mL	5 mL 10 mL	10 mL 20 mL	Not specified	5% or 10%

^a B. Braun Package Insert, Cefazolin for Injection USP and Dextrose Injection USP in DUPLEX[®] Container, for intravenous use (revised 4/2012).

^b Baxter Package Insert, Cefazolin Injection, USP in GALAXY Container (PL 2040 Plastic) (revised 3/2014).

^c GSK Package Insert, ANCEF[®] Cefazolin for Injection approved on 06/02/2004 for NDA 050461.

^d Hospira Package Insert, Cefazolin for Injection, USP (revised November 2011).

- Reviewer's assessment: The dextrose concentration in the proposed drug product is within IIG levels; the highest dextrose concentration approved for intravenous drug products is 30%.² The different amounts of tonicity adjuster in the proposed and REFERENCE PRODUCT products are acceptable to adjust for the different drug concentrations. The Applicant's justification for using a higher dextrose concentration (4% w/v) than the reference product dextrose concentration (3% w/v) to achieve comparable osmolality with the reference product is acceptable.

pH adjuster/Sodium Bicarbonate, USP:

- Applicant's justification: The proposed drug product contains sodium bicarbonate as an additional inactive ingredient as the product (b) (4). Sodium bicarbonate is additionally used to adjust solution pH. The concentration of sodium bicarbonate in the proposed drug product is approximately 0.4%. Use of sodium bicarbonate in current

² <http://intranetapps.test.fda.gov/scripts/iig/>

preparations of cefazolin drug products (e.g. ANDA 65247, ANDA 63002) supports the lack of impact of this ingredient on the bioequivalence of the drug product. Since currently marketed cefazolin drug products indicate the use of sodium bicarbonate for further dilution at a higher concentration than the proposed drug product formulation, the use of sodium bicarbonate in the proposed drug product does not present a risk to clinical safety and efficacy.

- Reviewer's assessment: The amount of sodium bicarbonate used in the proposed product (b)(4) adjusts the pH of the proposed product to comparable pH levels as the reference product. The amount of sodium bicarbonate in the proposed drug product is within IIG levels; the highest dextrose concentration approved for intravenous drug products is 81.94%.³ The Applicant's justification for using sodium bicarbonate as a diluent and pH adjuster in the proposed drug formulation is acceptable.

Dosing volume:

- Applicant's justification: The administration of a full 2 g dose in 100 mL (proposed drug product) rather than 50 mL (reference product) is expected to have minimal impact on product performance and safety. Generally, a safe range of daily fluid intake is well over 3 liters. Standard IV bags contain 50 mL to 1000 mL of fluid for infusion. Celerity considers the infusion of 100 mL of the proposed drug product to be a safe, common volume for administration of IV medication. Since cefazolin is administered in a hospital setting, the condition of each patient will be considered prior to administration of cefazolin, and there is little risk to the additional volume compared to alternative cefazolin medications available.

Differences in dose volume between cefazolin products is further mitigated due to common medical practice to administer additional IV fluids preceding and immediately following the administration of cefazolin. Prior to the introduction of a 2 g product by B. Braun in January 2012, patients requiring 2 g (or more) cefazolin would likely have received two "piggyback" doses of the B. Braun or Baxter 1 g/50 mL products, therefore representing the same total dose of 2 g/100 mL solution as the proposed drug product.

- Reviewer's assessment: The dosing volume of 100 mL does not pose any safety concerns. In addition, the infusion rate is adjusted to ensure the same amount of cefazolin is delivered at the same rate (i.e. 66.66. mg/minute) as the reference product over the 30 minute infusion period despite the different dosing volumes. The Applicant's justification for the different dosing volume is acceptable.

Infusion rate:

- Applicant's justification: The approved labeling for the reference product and the proposed labeling for the proposed drug product both state that the drug product shall be administered via infusion over approximately 30 minutes. For the reference product with a dosing volume of 50 mL, this equates to an infusion rate

³ <http://intranetapps.test.fda.gov/scripts/iig/>

of approximately 100 mL/hour (66.6 mg/min.); the proposed drug product (100 mL) will be infused at approximately 200 mL/hour (also 66.6 mg/min). This difference is well within the accuracy of hospital infusion pumps, and does not present any additional safety risk to the patient. In terms of efficacy, the same amount of cefazolin will be delivered at the same rate (approximately 66.6 mg/min) over the same infusion period of 30 minutes.

- **Reviewer's Assessment:** The volume infusion rate of the proposed drug product (200 mL/hour for 2 g/100 mL) is adjusted to ensure the same amount of cefazolin is delivered at the same rate (i.e. 66.66 mg/minute) as the reference product over the 30 minute infusion period. The Applicant's justification for the different infusion rate is acceptable.

Reviewer's Overall Assessment:

- The proposed drug product meets the following CFR § 320.22 (b)(1) criterion for a biowaiver:
 - i. The drug product is a parenteral solution intended solely for administration by injection; and
- Although the proposed drug product does not contain the same inactive ingredients in the same concentration as the reference product, the Applicant provided adequate justification for the differences between the proposed drug product and the reference product to support the biowaiver request. Therefore, the waiver for in vivo bioavailability/bioequivalence studies for Cefazolin for Injection, 1 g/vial, is granted.

RECOMMENDATION:

The waiver for in vivo bioavailability/bioequivalence studies for Cefazolin Injection, USP, 1 g/vial, is granted. From the Biopharmaceutics perspective, NDA 207131 for Cefazolin Injection, USP 1 g/vial, is recommended for approval.