CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211413Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality (OPQ) Review

NDA 211413

OPQ Assessment # 5

Review Date:	April 14, 2023
Submission:	NDA 211413 Resubmission (Class 2); SDN#32
Submission date:	November 8, 2022
OND Division:	Division of Anti-Infectives (DAI)
Product Name:	Cefazolin for Injection, 2 gram/vial
Applicant:	HQ Specialty Pharma Corporation

Executive Summary:

NDA 211413 originally submitted on December 21, 2017, was recommended for Complete Response (CR) by the OPQ Review Team due to several Drug Product related issues, including extractable/leachable and in-use stability studies (refer to the Addendum to OPQ Review dated October 3, 2018, in Panorama). The first NDA resubmission dated July 2, 2019 (SDN#21) addressed several of the product quality issues included in the CR letter (dated October 19, 2018). However, characterization and qualification information for several identified leachables was found inadequate (refer to the OPQ Assessment # 3 dated December 17, 2019, in DARRTS) and this NDA was issued a second CR letter dated December 26, 2019. The NDA was resubmitted again on July 9, 2020 (SDN#27) and included additional information regarding the characterization of the leachables, which was found acceptable from the Product Quality perspective (refer to OPQ Assessment # 4 dated December 4, 2020, in DARRTS). However, the qualification information of the identified leachables was not found adequate by the Pharmacology/Toxicology review team; therefore, the NDA was issued another CR letter on January 8, 2021.

The current NDA resubmission (SDN#32) includes only minor CMC updates, such as updated leachable data generated for the lot used in the leachable qualification study, and a revision to the endotoxin acceptance criterion (for details refer to the Drug Product and Microbiology reviews, respectively, below). The leachable qualification information was reviewed and found acceptable by the P/T review team. The quality related sections of the Package Insert and the container/carton labels were assessed previously (refer to the Labeling Review, attached to this review, below). Furthermore, the overall recommendation for manufacturing facilities of "Approve" was entered by the Office of Pharmaceutical Manufacturing Assessment (OPMA) in Panorama on April 10, 2023.

Recommendation:

Based on the OPQ assessment of the overall information submitted in the NDA, (including the current resubmission), this NDA is recommended for approval from the Product Quality perspective.

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M E M O R A N D U M

U.S. FOOD & DRUG ADMINISTRATION

DATE: March 2nd, 2023

TO: NDA-211413-ORIG-1-RESUB-32

FROM: Erin A. Wall, Ph.D.
Pharmaceutical Scientist
CDER/OPQ/OPMA/DMA II/Branch 6

THROUGH: Erika A. Pfeiler, Ph.D.
Supervisory Microbiologist; Branch Chief
CDER/OPQ/OPMA/DMA II/Branch 6

SUBJECT: **NDA-211413-ORIG-1-RESUB-32**
Submission Date: 11/8/2023
Drug Product: Cefazolin Powder for Injection 2g vial
Applicant: HQ Specialty Pharma

The endotoxins levels in NDA 211413 Cefazolin Powder for Injection were originally found adequate for a 2g dose administered to 70kg adults within 1 hour by quality microbiology in N211413MR01.pdf (7/24/2018, adequate).

(b) (4)

M E M O R A N D U M

The applicant did not update their P.8 stability section. The previously submitted stability section simply lists the timing of the tests that will be performed throughout the drug product shelf life and refers to the document in P.5.1 Specifications and P.5.2 Analytical Procedures documents for information about the tests and acceptance criteria. Therefore, the updated release specification provided in P.5.1 is adequate to cover the P.8 section. Therefore, the totality of the provided information meets regulatory expectations.

ADEQUATE

Erin Wall

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Erika Pfeiler

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NDA 211413 LABELING

IQA Review Guide Reference

{For NDA Only}

Note- The Complete Response was issued to the NDA in the past 3 review cycles, therefore Agency's labelling recommendations were not communicated to the Applicant. The same recommendations as suggested in the previous Quality labelling reviews (i.e. review 001, 002, 003) are included in the sections below.

I. Package Insert

Highlights of Prescribing Information

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name and established name	Cefazolin for injection	Adequate
Dosage form, route of administration	Injection, for intravenous use - For intravenous infusion only. Not for intravenous bolus or intramuscular administration	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths		
Summary of the dosage form and strength	2 gram per vial	*Recommended Text :* *For Injection: 2 grams of cefazolin as a powder in a single-dose vial for reconstitution* *(refer DP labelling review #2 dated 09/08/2018 for details)*
Controlled drug substance symbol (if applicable)	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose,	Not included	*Recommended Text :* *For Injection: 2 grams of cefazolin as a powder in a single-dose vial for reconstitution*

multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

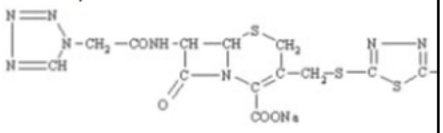
Section 2 Dosage and Administration –

Item	Information Provided in NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	2 g of cefazolin is reconstituted with 5 mL of sterile WFI. The reconstituted Cefazoline for injection will be further diluted with 50-100 mL of sodium chloride injection, USP or 5% dextrose injection USP. After reconstitution. Cefazoline for injection is stable for 4 hours at (b) (4) room temperature (b) (4) or 3 days if stored under refrigeration (2°C to 8°C or 36°F to 46°F)..	Adequate -The reconstitution instructions and stability information of the reconstituted solution are in line with the information provided in the quality sections of the NDA.

Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA	Assessor's Comments
Available dosage forms	Cefazolin for Injection	
Strengths: in metric system	2 grams	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not expressed in terms of salt.	Not expressed in terms of salt. (refer the previous drug product labelling review dated 09/08/2018 or the discussion below
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	*Not Included*	*Recommended Text :* *Cefazolin For Injection: Supplied in 2 grams of cefazolin per single-dose vial as a white to cream powder for reconstitution.*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not included Proposed Text- (b) (4)	*Recommended Text :* *Cefazolin For Injection: Supplied in 2 grams of cefazolin per single-dose vial as a white to cream powder for reconstitution.*

Section 11 Description-

Item	Information Provided in NDA	Assessor's Comments
Proprietary name and established name	Cefazolin for Injection USP	Adequate
Dosage form and route of administration	Cefazolin for injection, for (b) (4) administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Not expressed in terms of salt	Adequate (refer the drug product labeling review dated 09/08/2018 or the discussion below)
For parenteral, otic, and ophthalmic dosage forms, include the name and quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not Included	Adequate There are no inactive ingredients in the drug product. The drug product is cefazolin powder filled in the vials only.
Statement of being sterile (if applicable)	…sterile white to cream powder supplied in vials	Adequate
Pharmacological/ therapeutic class	Semi-synthetic cephalosporin	Adequate
Chemical name, structural formula, molecular weight	Sodium salt of 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]oct2- ene-2-carboxylic acid. Its empirical formula is C14H13N8NaO4S3, with a molecular weight of 476.5,. Its structural formula is: 	The structure and name of cefazolin is the same in this labeling as in the Ancef labeling. This is acceptable.
If radioactive, statement of important nuclear characteristics.	None	
Include information about child-resistant packaging	Not included	The product will be used only in the clinical settings.
Other important chemical or physical properties (such as pKa or pH)	The pH of the reconstituted solution is between 4 and 6.	Adequate

Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA	Assessor's Comments
Available dosage form(s)	Cefazolin for Injection	Adequate
Strength of dosage form	2 grams cefazolin per vial	Adequate
Available units (e.g., bottles of 100 tablets)	2 grams per vial (carton of 25)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not included	Recommended text- Cefazolin for Injection is available in a single-dose vial containing 2 grams of cefazolin as a white to cream powder for reconstitution.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Injection: Single-dose vial	Adequate
Storage conditions	(b) (4) store at 20°C to 25°C (68°F to 77°F)[see USP Controlled Room Temperature]. PROTECT FROM LIGHT.	Adequate The proposed storage conditions are in accordance with the information provided in section 3.2.P.8.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Include information about child-resistant packaging	Not included	The product will be used only in the clinical settings.

Manufacturer/distributor name (21 CFR 201.1(h)(5))	WG Critical Care	Adequate The applicant responded on 06/13/2018 that WG Critical Care is the distributor for this product. Refer to quality labelling review dated 09/18/2018 for additional details.

Reviewer's Assessment of Package Insert:

1. ***Salt Equivalency Statement-*** The following information is included in the quality labelling review -002, dated 09/08/2018.

The original labeling was not consistent with the salt policy guidance. The following information request was sent on 5/23/2018:
The salt equivalency statements in the labeling for the carton, container and PI are not consistent with the recommendations in the FDA Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances. The salt equivalency statement should describe the amount of the cefazolin sodium, not only sodium. Refer to the Guidance for the recommended format of this statement. Update the carton and container labeling with the correct salt equivalency statement.
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm 379753.pdf

The applicant responded via e mail on 06/04/2018 and acknowledged the Salt Policy Guidance.They requested that the product not be updated according to the Salt Policy Guidance because all of the approved cefazolin products currently list the strength of cefazolin based on the salt.

Please refer the drug product labeling review dated 09/08/2018 and 12/17/2020. for additional details regarding CMC recommendations for the packaging insert.

II. Labels:

1. *Container and Carton Labels*

Images of the Container label submitted on 02-27-2023, Sequence- 0033

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

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	CEFAZOLIN for Injection, USP	CEFAZOLIN for Injection, USP
Dosage strength	2 grams	2 grams
Route of administration	For intravenous infusion only	For intravenous infusion only
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each vial contains cefazolin sodium equivalent to 2 grams of cefazolin. The sodium content is approximately 48 mg (2.1 mEq) per gram of cefazolin sodium.	Each vial contains cefazolin sodium equivalent to 2 grams of cefazolin. The sodium content is approximately 48 mg (2.1 mEq) per gram of cefazolin sodium.
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	44567-840-01	44567-840-25
Lot number and expiration date (21 CFR 201.17)	Space designated for lot and Expiration date (EXP)	Space designated for lot and Expiration date (EXP)
Storage conditions	Before reconstitution, store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. After Reconstitution- stable for 4 hours at (b) (4) room temperature (b) (4) or 3 days (b) (4) refrigeration (2°C to 8°C (b) (4) 36°F to 46°F).	Before reconstitution, store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. After Reconstitution- stable for 4 hours at (b) (4) room temperature (b) (4) or 3 days (b) (4) refrigeration (2°C to 8°C (b) (4) 36°F to 46°F).
Bar code (21CFR 201.25)	Space designated for bar code	Space designated for bar code
Name of manufacturer/distributor	The distributor name is included: WG Critical Care	WG Critical Care
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	Yes

When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	None	None
And others, if space is available	Single-dose vial. Discard unused portion.	Single-dose vial. Discard unused portion.

Reviewer's Assessment of Labels: Adequate

The salt equivalency statement on the container/ carton label and in USPI is in accordance with the statement on RLD.

List of Deficiencies:

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, Ph.D. 03/07/2023

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Dorota Matecka, Ph.D.

Shalini Anand

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Dorota Matecka

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Office of Pharmaceutical Quality (OPQ) Review

NDA 211413

OPQ Assessment # 4

Review Date:	December 4, 2020
Submission:	NDA 211413 Resubmission (Class 2); SDN#27
Submission date:	July 9, 2020
OND Division:	Division of Anti-Infectives (DAI)
Product Name:	Cefazolin for Injection, 2 gram/vial
Applicant:	HQ Specialty Pharma Corporation

Executive Summary:

NDA 211413 originally submitted on December 21, 2017 was recommended for Complete Response (CR) by the OPQ Review Team due to several Drug Product related issues, including extractable/leachable and in-use stability studies (refer to the Addendum to OPQ Review # 1 dated October 3, 2018 in Panorama). The first NDA resubmission dated July 2, 2019 (SDN # 21) addressed several of the product quality issues included in the CR letter dated October 19, 2018 in DARRTS. However, the characterization and qualification information for several identified leachables was found inadequate (refer to the OPQ Assessment dated December 17, 2019. Therefore, this NDA was issued a second CR letter dated December 26, 2019. The current NDA resubmission (SDN#27) provides additional information regarding the characterization of the leachables, which has been found adequate (refer to the Drug Product Review, Attachment I). In addition, although no new labeling information was submitted, a labeling review of the previously assessed product quality related sections of the Package Insert and the container/carton labels, is also attached to this review (refer to the Labeling Review, Attachment II). Based on the assessment of the information submitted in the current NDA resubmission and the overall recommendation of "Approve" entered by the Office of Pharmaceutical Manufacturing Assessment (OPMA) into Panorama on July 13, 2020, this NDA can be now recommended for approval.

Recommendation:

The outstanding characterization issues with regards to leachables have been addressed satisfactorily; therefore, this NDA is recommended for approval from the Product Quality perspective. However, the review of leachable qualification is currently pending (refer to pharm/tox review for details). In addition, the labeling review by the NDA review team is also pending.

Attachments

Attachment I (Drug Product - Dr. Shalini Anand)

Attachment II (Labeling - Dr. Shalini Anand)

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NDA 211413 LABELING

IQA Review Guide Reference

{For NDA Only}

The NDA holder has not submitted any new labeling information/updates after 08/27/2019. The last DP labeling review (DP labeling review -003) was finalized on 12-18-2019 (Panorama), so there is no new labeling information to review in the current review cycle.

I. Package Insert

1. *Highlights of Prescribing Information – No new Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Cefazolin for injection
Dosage form, route of administration	Injection, for intravenous Infusion only
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	*Recommended Text :* *For Injection: 2 grams of cefazolin as a powder in a vial (single-dose vial) for reconstitution* *(refer DP labelling review #2 for details)*

2. *Section 2 Dosage and Administration – No new Information*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	2 g of cefazolin is reconstituted with 5 mL of sterile WFI. The reconstituted Cefazoline for injection will be further diluted with 50-100 mL of sodium chloride injection, USP or 5% dextrose injection USP. After reconstitution. Cefazoline for injection is stable for 4 hours at (b) (4) room temperature (b) (4) or 3 days if stored under refrigeration (2°C to 8°C or 36°F to 46°F). The supporting in-use stability data is provided in quality submission dated 07/02/2019.

3. *Section 3 Dosage Forms and Strengths -No New Information*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	2 grams per vial
Strengths: in metric system	2 grams
Active moiety expression of strength with equivalence statement (if applicable)	Not expressed in terms of salt. (refer the previous drug product labelling review dated 09/08/2018)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	*Recommended Text :* *For Injection: 2 grams of cefazolin as a powder in a vial (single-dose vial) for reconstitution* *(refer DP labeling review #2 for details)*

4. ***Section 11 Description- No New Information***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Cefazolin for Injection USP
Dosage form and route of administration	Cefazolin for injection, for parenteral administration
Active moiety expression of strength with equivalence statement (if applicable)	Not expressed in terms of salt (refer the previous drug product labeling review dated 09/08/2018)
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	There are no inactive ingredients in the drug product. The only component is cefazolin.
Statement of being sterile (if applicable)	Yes. The product is described as a sterile white to cream powder supplied in vials
Pharmacological/ therapeutic class	Semi-synthetic cephalosporin
Chemical name, structural formula, molecular weight	sodium salt of 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]oct2- ene-2-carboxylic acid. The structure and name of cefazolin is the same in this labeling as in the Ancef labeling. This is acceptable.
If radioactive, statement of important nuclear characteristics.	None
Other important chemical or physical properties (such as pKa or pH)	The pH is listed

5. ***Section 16 How Supplied/Storage and Handling - No New Information***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	2 grams cefazolin per vial
Available units (e.g., bottles of 100 tablets)	2 grams per vial (carton of 25)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	2 gram Single dose Vial- 44567-840-25-01 (recommended text- single-dose vial, refer DP) Carton of 25- 44567-840-25 (Updated the NDC number, as per Agency's recommendation, previously the NDC number on both the vial and the carton were same
Special handling (e.g., protect from light)	(b) (4) store at 20°C to 25°C (68°F to 77°F) {See USP Controlled Room Temperature). Protect from Light
Storage conditions	See above
Manufacturer/distributor name (21 CFR 201.1(h)(5))	WG Critical Care

Reviewer's Assessment of Package Insert:

The NDA holder has not submitted any new labeling information/updates after 08/27/2019. The last DP labeling review (DP labeling review -003) was finalized on 12-18-2019 (Panorama), so there is no new labeling information to review in the current review cycle.

The supporting in-use stability studies to support reconstitution and dilution for cefazoline for injection, was provided in quality submission dated 07/02/2019. The provided information was found to be satisfactory in DP labeling review #3 (dated 12/17/2019).

Please refer the drug product labeling review dated 09/08/2018 and 12/17/2020. for the detailed assessmeny and list of CMC recommendations for the packaging insert.

II. Labels:

1. ***Container and Carton Labels***

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	CEFAZOLIN for Injection, USP	CEFAZOLIN for Injection, USP
Dosage strength	2 grams	2 grams
Net contents	2 grams per vial	2 grams per vial
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	44567-840-01	44567-840-25
Lot number and expiration date (21 CFR 201.17)	Space designated for lot and Expiration date (EXP)	Space designated for bar code
Storage conditions	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. After Reconstitution- stable for 4 hours at (b) (4) room temperature (b) (4) or 3 days (b) (4) refrigeration (2°C to 8°C (b) (4) 36°F to 46°F).	Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. After Reconstitution- stable for 4 hours at (b) (4) room temperature (b) (4) or 3 days (b) (4) refrigeration (2°C to 8°C (b) (4) 36°F to 46°F).
Bar code (21CFR 201.25)	Space designated for bar code	Space designated for bar code
Name of manufacturer/distributor	The distributor name is included: WG Critical Care	WG Critical Care
And others, if space is available	"protect from light"	"protect from light"

Reviewer's Assessment of Labels:

The revised container label and carton labeling are acceptable from a medication error perspective (Labeling review dated 08/03/2019)

List of Deficiencies:

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, Ph.D.

11/22/2020

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Thomas F. Oliver, Ph.D.

Shalini Anand

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Thomas Oliver

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 211413
Assessment # 3

Drug Product Name	Cefazolin for Injection
Dosage Form	Powder for Injection
Strength	2 g/vial
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	HQ Specialty Pharma
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0020	07/02/2019	NDA resubmission (all)
eCTD 0021	07/29/2019	Quality
eCTD 0022	08/27/2019	Labeling
eCTD 0023	10/15/2019	Quality
eCTD 0025	12/05/2019	Pharm/tox and Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	
Drug Product	Shalini Anand	Thomas Oliver
Manufacturing	N/A	
Microbiology	N/A	
Biopharmaceutics	Mei Ou	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika E. Englund	
Laboratory (OTR)	N/A	
Environmental	N/A	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	Refer to Review #1	
	III			Adequate	Refer to Review #1	
	III			Adequate	Refer to Review #1	

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

Document	Application Number	Description
pIND	131420	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology		CR- Refer to Pharm/tox Review		
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

This NDA, as amended, has **not** provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for a **complete response** by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on August 15, 2019. However, the drug product review found the NDA inadequate. Therefore, this NDA is recommended for a CR from a CMC perspective.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This review covers the resubmission of NDA 211-413. During the review of the original NDA, manufacturing process, biopharmaceutics, drug substance and quality micro reviewers recommended approval of the NDA as documented in Review #1 on 9/11/2018. However, there were pending issues in the drug product review concerning the leachables/extractables and in-use stability data. An addendum to Review #1 was completed on 10/03/2018 and recommended the NDA for a Complete Response (CR). The CMC deficiencies concerned the leachables/extractables study, unspecified impurities above the identification and qualification thresholds, and in-use stability data. This NDA received a CR letter on 10/19/2018.

NDA 211413 was resubmitted on 07/02/2019. The applicant's responses to the deficiencies for the in-use stability, and impurities above the identification threshold were found acceptable. The applicant performed a new leachables study, and identified different leachables from those described in CMC Reviews #1 and #2. Some of these leachables were above the threshold for toxicological concern, but the characterization and qualification of these leachables is considered inadequate. Refer to the pharm/tox review concerning the qualification of these leachables. This NDA is recommended for a CR from a CMC perspective.

Proposed Indication(s) including Intended Patient Population	Cefazolin for Injection is a cephalosporin antibacterial indicated in perioperative prophylaxis

Duration of Treatment	1 to 2 grams administered ½ hour to 1 hour prior to the start of surgery; 500 mg to 1 gram during surgery for lengthy procedures; 500 mg to 1 gram every 6 to 8 hours for 24 hours postoperatively
Maximum Daily Dose	8g/day (4 vials)
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Per the 7/5/2019 e mail from Suong Tran, no drug substance review was necessary for this NDA resubmission. There was no new drug substance information submitted since CMC Review #1, and no new information was submitted to the referenced DMF (b) (4) that needed drug substance review. Therefore, no separate drug substance review was conducted for this NDA.

Drug Product: Inadequate

Cefazolin for injection is a sterile powder in a vial that is proposed to be initially reconstituted with Water for Injection, followed by dilution with (b) (4) NaCl or 5% dextrose. In the quality submission dated 07/02/2019, the sponsor has addressed the concerns related to in-use stability studies by restricting the number of diluents to only (b) (4) NaCl or 5% dextrose, compared to previously proposed (b) (4) diluents. The sponsor has also tightened the proposed storage time of the cefazolin injection after dilution to 4 hours at 25°C and 3 days at 5°C (from previously proposed time frame (b) (4)). The in-use stability data is in compliance with proposed drug product regulatory specifications.

However, the responses to the deficiencies related to extractable/leachable studies are still inadequate. Inadequate supportive information is provided to confirm the proposed structures of the identified leachables. The stopper is not acceptable for use from the CMC perspective until the identity of the leachables has been established, and the safety profile of the leachables is considered acceptable from a nonclinical perspective.

For additional details, refer to the drug product review by Shalini Anand.

Labeling: Adequate

The labeling recommendations were communicated to the OND PM. Some of the labeling changes since CMC Review #1 include the reduced number of diluents described in the PI, and reduced in-use storage time.

Manufacturing: Adequate

No manufacturing deficiencies were included in the complete response letter, and no new manufacturing information was submitted with the resubmission. The overall manufacturing inspection recommendation was approve on 8/15/2019.

Biopharmaceutics: Adequate

The Biopharmaceutics review for the original NDA submission focused on the evaluation of the in vitro bridging between the proposed drug product and the listed drugs (LDs) and reference standard (RS) product, Cefazolin for Injection, under ANDA 065226 by Hospira. Per 21 CFR 320.24(b)(6), the in vitro bridging was established between the proposed product and the LDs for IV infusion (1-2 gram) (b) (4) Therefore, the original NDA 211413 was recommended for approval from a Biopharmaceutics perspective, provided that the label will be changed to indicate administration by IV infusion (1-2 gram) (b) (4)

The Applicant resubmitted the current NDA 211413-ORIG-1-RESUB-21 on July 2, 2019 and provided the responses to all the deficiencies listed in the COMPLETE RELEASE (CR) letter issued on October 19, 2018. Specifically, in order to address the clinical deficiency #1, the Applicant responded that they have removed (b) (4) from the proposed package insert. Although the newly proposed labeling and package insert is under purview of clinical team, the above response for deficiency #1 is acceptable from a Biopharmaceutics perspective based on the recommendation for the original NDA.

For additional details, refer to the review by Mei Ou.

Microbiology (if applicable): Adequate

No microbiology deficiencies were included in the complete response letter, and no new microbiology information was submitted with the resubmission.

C. Risk Assessment

Refer to Review #1

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

Refer to Drug Product Deficiencies

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

1. In quality submission dated October-15-2019, you stated that the same (b) (4) rubber stopper (b) (4)), as used for NDA 211413, Cefazolin for Injection drug product (2g), has also been used for Cefazolin for Injection 500 mg and 1 g (ANDA 065303). However, you have identified several leachables (especially the (b) (4) above the AET threshold for NDA 211413 cefazolin drug product. As recommended earlier, qualify all leachables for the proposed Cefazolin drug product and provide supporting data to justify the safety of the (b) (4) rubber stoppers. Refer the toxicology section of the Complete Response letter for additional details.

2. We acknowledge your statement that (b) (4) could not be detected by HC-GC-MS analysis, when pharmaceutical matrix was spiked with (b) (4) (MST study), (b) (4) (b) (4)

It is not clear why the proposed analytical method can detect the level of (b) (4) µg/unit for bromomethane in neat sample, but not for the MST samples, (b) (4). With the above -mentioned limitation of the analytical method, we are concerned about the accuracy of maximum reported levels of the (b) (4) for the neat extractable study samples. We recommend that you further evaluate the suitability of the proposed analytical method and define the LOD and LOQ levels for (b) (4) testing (both for neat samples and for the pharmaceutical matrix). Additionally, as appropriate, evaluate alternate analytical methodologies for detection and quantification of (b) (4) in the leachable study samples.

3. Regarding characterization data of (b) (4) (Annex 2, quality submission dated October-15-2019), we have the following concerns:

a. The total ion chromatograms for leachable study samples and MST samples, in figure 1, do not show any clear peak between retention time (b) (4) (b) (4)

b. (b) (4) (b) (4) (b) (4) The chromatograms appear to be individual chromatograms of MST samples or leachable study samples instead of overlaid chromatograms.

c. You have not provided comparative mass spec (or any other structure specific characterization data) with standards to confirm the structure of these two leachables.
Based on the data submitted, the structure of these two leachables remains uncertain and should be confirmed. Please re-evaluate the suitability of your proposed GC/MS method for qualification of these two leachables. Provide appropriate comparative characterization data for the standards and leachable study samples to confirm the structure of the compounds with (b) (4). The complete analytical method details i.e. sample preparation, analytical conditions, raw characterization data etc. for both analytical standards and leachable study samples should be submitted. Additionally, provide the overlaid spectra of standards and samples with clear and legible peak patterns.

4. (b) (4) (b) (4) (b) (4) Please clarify what is the spiked concentration (and % recovery) of the standards for the MST study, for these provided chromatograms. We recommend you spike the MST study samples with higher concentration of the standards and then provide overlay of total ion-chromatograms for MST samples and leachable study samples. Please list the studied concentration of MST samples in the total ion- chromatograms. Also, establish the LOD and LOQ values for all the reported leachables for the proposed GC/MS and HS-CG/MS analytical methods to confirm that the proposed analytical methods are suitable to detect all the leachables at the reported levels.

5. The retention time for the leachable [redacted] in the MST samples does not match with the leachable study samples [redacted] We recommend you further evaluate the suitability of the proposed analytical methodologies for characterization of [redacted] and provide adequate supporting characterization data to confirm the structure of [redacted].

6. [redacted] Please provide the complete mass spec data to confirm the identification of [redacted] compound in the leachable study samples.

7. [redacted] Provide details of the calculation and discuss how the recovery correction factors for all the leachables were calculated.

8. We acknowledge that you have provided additional mass spectra using different analytical techniques (GC-MS, GC-EI-QTOF and GC-CI(CH4)-QTOF MS) [redacted]. However, the data only confirms the molecular weight or fragmentation pattern of these [redacted] but does not confirm the structures. As recommend earlier in the information request letter dated September-24-2019, please obtain the analytical standard of [redacted] and perform detailed characterization studies of analytical standards and leachable study samples using various analytical technologies (i.e. HPLC, MS and NMR)

to confirm the structure of [redacted] (b) (4) as potential leachables. Provide complete analytical method details (e.g. sample preparation, analytical conditions, raw characterization data, etc.) for both analytical standards and leachable study samples. Also, provide the overlaid spectra of standards and samples with clear and legible peak pattern.

9. You have proposed to apply the ICH Q3B limits to justify the safety of cefazolin [redacted] (b) (4) [redacted] (b) (4) ICH Q3B limits do not justify the safety of any of the leachables or [redacted] (b) (4). Provide appropriate data to justify the safety of these [redacted] (b) (4) [redacted] (b) (4). Refer to the pharmacology/ toxicology section of the Complete Response letter for additional details.

4. Labeling Deficiencies

N/A

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

N/A

Application Technical Lead Name and Date:

Erika E. Englund

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CHAPTER VI: BIOPHARMACEUTICS

NDA: 211413-ORIG-1-RESUB-21 [505(b)(2)]
Drug Product Name/Strength: Cefazolin for Injection USP, 2 g/vial
Route of Administration: IV Injection
Proposed Indication: Cefazolin for injection is a cephalosporin antibacterial indicated in perioperative prophylaxis
Applicant Name: HQ Specialty Pharma Corporation
Submission Date: 07/02/2019
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Elsbeth Chikhale, Ph.D.

BIOPHARMACEUTICS REVIEW

The original NDA 211413 for the proposed drug product, Cefazolin for Injection USP, 2 g/vial, was submitted on December 21, 2017, under the 505(b)(2) pathway. The listed drugs (LDs) are Cefazoline for Injection USP and Dextrose Injection USP in Duplex® Container (NDA 050779) and Ancef® (NDA 050461). The Applicant intended to rely solely on the Agency's previous findings of safety and efficacy for NDA 050779 for the perioperative prophylaxis indication and not for the other approved indications of the listed drug. No clinical trials were conducted by the Applicant to support this NDA.

The Biopharmaceutics review for the original NDA submission focused on the evaluation of the in vitro bridging between the proposed drug product and the LDs and reference standard (RS) product, Cefazolin for Injection, under ANDA 065226 by Hospira. Per 21 CFR 320.24(b)(6), the in vitro bridging was established between the proposed product and the LDs for IV infusion (1-2 gram) (b) (4) Therefore, the original NDA 211413 was recommended for approval from a Biopharmaceutics perspective[1], provided that the label will be changed to indicate administration by IV infusion (1-2 gram) (b) (4)). However, the original NDA was issued a COMPLETE RESPONSE (CR) by the FDA on October 19, 2018, due to the clinical, non-clinical and drug product quality reasons[2].

The Applicant resubmitted the current NDA 211413-ORIG-1-RESUB-21 on July 2, 2019 and provided the responses to all the deficiencies listed in the above CR letter. Specifically, in order to address the clinical deficiency #1, the Applicant responded that they have removed (b) (4) from the proposed package insert. Although the newly proposed labeling and package insert is under purview of clinical team, the above response for deficiency #1 is acceptable from a Biopharmaceutics perspective based on the recommendation for the original NDA.

[1] Biopharmaceutics Review for original NDA 211413 dated 08/28/2018:
http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881bae6d0
[2] NDA 211413-ORIG-1 Complete Response Letter dated 10/19/2018:
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804be8f8&_afrRedirect=912983237066219

CONCLUSION:

A detailed review by the Division of Biopharmaceutics for the current NDA 211413-ORIG-1-RESUB-21, Cefazolin for Injection USP, 2 g/vial, is not needed, considering there are no additional Biopharmaceutics issues that need to be addressed.

Mei Ou

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Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 10/17/2019 03:08:29PM
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/s/

ERIKA E ENGLUND
12/17/2019 06:30:51 PM

Recommendation: Complete Response

NDA 211413
Addendum to Review # 1
Oct 3, 2018

Drug Name/Dosage Form	***Cefazolin for Injection USP***
Strength	*2g / vial*
Route of Administration	*Powder for Injection*
Rx/OTC Dispensed	*Rx*
Applicant	*HQ Specialty Pharma Corporation*
US agent, if applicable	*NA*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*12/21/2017*
Amendment	*4/2/2018*
Amendment	*5/11/2018*
Amendment	*5/17/2018*
Amendment	*6/6/2018*
Amendment	*6/7/2018*
Amendment	*7/3/2018*
Amendment	*7/19/2018*
Amendment	*8/9/2018*
Amendment	*9/14/2018*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Gene Holbert	Charles Jewell
Drug Product	Erika Englund	Balajee Shanmugam
Microbiology	Koushik Paul	Elizabeth Bearr
Biopharmaceutics	Mei Ou	Elsbeth Chikhale
Process	Ying Wang	Upinder Atwal
Facility	Ying Wang	Derek S. Smith
Regulatory Business Process Manager	Anh-Thy Ly	NA
ORA Lead	NA	NA
Laboratory (OTR)	NA	NA

Environmental Assessment (EA)	Erika Englund	Balajee Shanmugam

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status[1]	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	7/18/2018	LoA: 6/12/2017 Reviewed by Gene Holbert
	Type III			NA		LoA: 9/29/2017
	Type III			Adequate	9/8/2018	LoA: 10/2/2017 Reviewed by Erika Englund

[1]NA (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
pIND	131420	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Pending		9/10/2018	Terry Miller
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

Manufacturing process, biopharmaceutics, drug substance and quality micro reviewers have recommended approval of the NDA as documented in Review #1. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 2/1/2018.

As documented in this review, the applicant submitted an Amendment on 9/14/2018 which provided responses to the drug product deficiencies including in-use stability and toxicological assessment of the leachables covered in Review #1. However, the responses to the deficiencies are inadequate, and drug product upholds the Complete Response recommendation. Therefore, NDA 211413 is recommended Complete Response from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

The following CR comments should be included in the CR letter:

1. *Inadequate support was provided for the assigned structures of the leachables. The original program assigned both leachables CAS numbers which could not be found in the literature or databases. The IR response on 09/14/2018 confirmed that the program used in the leachables study erroneously provided those CAS numbers, and that both leachables do not have CAS numbers. However, no discussion was included regarding the validity of the assigned structures of the leachables from this program. Since neither of these leachables could be found in the literature, it is not clear how the structures of these leachables were assigned. Additional characterization data should be submitted to support the structures of these leachables. Refer to USP <1663> and USP <1664>.*

2. *The proposed stopper is not acceptable for use from a CMC perspective until the identity of the leachables has been established, and the safety profile of the leachables is considered acceptable from a nonclinical perspective.*

3. *The drug product specifications in the 09/14/2018 amendment, with the unspecified impurities above the identification and qualification thresholds, is considered inadequate. The in-use stability data will be evaluated during the next review cycle after the drug product specification deficiency is addressed.*

4. *The proposed drug product specifications are not considered acceptable because three of the impurities (RRT (b) (4)) are above the identification and qualification thresholds. The referenced ANDA Guidance is not applicable to this*

NDA. Qualification data should be submitted for all impurities above the qualification threshold.

5. *No characterization data or description of laboratory studies demonstrating efforts to identify the structures were submitted for the specified unidentified impurities in the drug product specifications. The only information provided for these impurities was the relative retention time (RRT). This is not adequate since the impurities are above the identification threshold. Submit the characterization data for the unidentified specified impurities above the identification threshold in the drug product specifications.*

6. *The analytical procedures were updated to describe the measurement of the 3 specified unidentified impurities, but the method was not validated for the measurement of these unspecified impurities. The analytical methods should be validated for the measurement of the specified impurities in the drug product specifications.*

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	For the treatment of perioperative prophylaxis in adults.
Duration of Treatment	1 to 2 grams administered ½ hour to 1 hour prior to the start of surgery. See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

Refer to Review #1.

ii. Drug Product Quality Summary

Refer to review #1 and the attached drug product review #2. In the quality amendment dated 9/14/2018, the applicant did not submit the requested additional time points for the in-use stability data. The applicant revised the drug product regulatory specifications with the addition of three new impurities above the

qualification threshold, which corresponded to impurities measured during the in-use stability studies. Information submitted to characterize, analyze and qualify these impurities is inadequate. The applicant confirmed that the CAS numbers for the two leachables are not correct and that the CAS numbers are not available. No additional data is provided to support the structures of the two leachables. Pharma/Tox reviewer Dr. Terry Miller has not found the toxicological assessment of the leachables acceptable. Therefore, the use of the proposed stopper is not considered acceptable from a CMC perspective. Therefore, NDA 211413 remains a Complete Response recommendation from a drug product perspective.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site[3]	H	(b) (4)	L	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	L		L	
Assay (API), stability	Formulation Container closure[1] Raw materials	L		L	
Reconstitution time	Formulation	L		L	

Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	**M**	(b) (4)	**L**	
Extractables and Leachables	Formulation Container closure[1] Process parameters Scale/equipment	**M**		**H**	
Particulate matter	Formulation Container closure[1] Process parameters Scale/equipment	**M**		**L**	

[1]Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

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Chunchun Zhang

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Recommendation: Complete Response

NDA 211413
Review # 1
Sep 11, 2018

Drug Name/Dosage Form	***Cefazolin for Injection USP***
Strength	*2g / vial*
Route of Administration	*Powder for Injection*
Rx/OTC Dispensed	*Rx*
Applicant	*HQ Specialty Pharma Corporation*
US agent, if applicable	*NA*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*12/21/2017*
Amendment	*4/2/2018*
Amendment	*5/11/2018*
Amendment	*5/17/2018*
Amendment	*6/6/2018*
Amendment	*6/7/2018*
Amendment	*7/3/2018*
Amendment	*7/19/2018*
Amendment	*8/9/2018*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
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Biopharmaceutics	Mei Ou	Elsbeth Chikhale
Process	Ying Wang	Upinder Atwal
Facility	Ying Wang	Derek S. Smith
Regulatory Business Process Manager	Anh-Thy Ly	NA
ORA Lead	NA	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Erika Englund	Balajee Shanmugam

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status[1]	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	7/18/2018	LoA: 6/12/2017 Reviewed by Gene Holbert
	Type III			NA		LoA: 9/29/2017
	Type III			Adequate	9/8/2018	LoA: 10/2/2017 Reviewed by Erika Englund

[1]NA (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
pIND	131420	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Pending		9/10/2018	Terry Miller
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

Satisfactory information and responses have been submitted to support the quality of the drug substance, biopharmaceutics, process and quality micro aspects. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 2/1/2018.

At the current time, there are several unresolved product quality issues related to extractable/leachable assessment and in-use stability study and due to these deficiencies, the drug product reviewer recommends a Complete Response. In agreement with the above recommendation, NDA 211413 is recommended Complete Response from Product Quality perspective at this time. Once the responses to the IR on the in-use stability and toxicological assessment of the leachables are received and evaluated, a final recommendation from OPQ will be documented in an addendum before the PDUFA date.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	For the treatment of perioperative prophylaxis in adults.
Duration of Treatment	1 to 2 grams administered ½ hour to 1 hour prior to the start of surgery. See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance, Cefazolin sodium, is a white or almost white powder. It is manufactured by (b) (4) The drug substance referenced in DMF (b) (4) was found adequate by Gene Holbert on 7/18/2018.

ii. Drug Product Quality Summary

Cefazolin for Injection USP, 2g/vial is indicated to treat perioperative prophylaxis in adults. The drug product is provided in a 20 mL (b) (4) clear glass vial and a rubber stopper with an aluminum/plastic flip off overseal. The product is initially reconstituted with Water for Injection and then will be further diluted in the proposed (b) (4) diluents.

No excipient is used in the drug product formulation. The drug product specification includes tests for appearance, identification, assay, impurities (specified, unspecified and total), pH, water, optical rotation, sterility, constituted solution, reconstitution time, particulate matter, uniformity of dosage units and container closure integrity. Evaluation of the risk assessment of the elemental impurities indicates the levels are lower than the permitted daily exposure (PDE) as noted in USP<232>. The proposed specification is acceptable to ensure quality of the product over its expiration period. All analytical methods are described in reasonable detail and have been adequately validated.

Two leachable compounds exceed the safety concern threshold (SCT) of 1.5 mcg/day. The applicant has not submitted the toxicological assessment of the leachables as of this review date. For details concerning the leachables profile of the stopper, please refer to the deficiency comments communicated by nonclinical. The stopper will not be acceptable for commercial use from a CMC perspective if the safety of the leachables is not determined to be acceptable from a nonclinical perspective.

The proposed commercial scale is (b) (4) vials. Batch analyses are provided for 3 registration batches on scale of about (b) (4) vials and manufactured in the commercial site. All batches complied with the proposed specification.

Drug product stability data is available to 12 months at long term storage 25°C/60%RH and 6 months at 40°C/75%RH for three registration batches. The tested attributes are within proposed specifications. The shelf life of (b) (4) months when stored at 20°C-25°C is granted. The storage statement is "Store at 20°C to 25°C (68°F to 77°F)"] and will be finalized at the OND's labeling meeting. The applicant has provided in-use stability data for the reconstituted product in all the proposed (b) (4) diluents. However, several specified impurities were out of specification when the product was tested in (b) (4) a diluent while the unspecified impurities were out of specification for most of the other diluents. Several information requests, and one teleconference was held with the applicant to discuss this issue. However, the information received to support the stability of the product in the labeled diluents has been incomplete and inadequate.

Biopharmaceutics has found the in vitro bridging established between the proposed product and the list drug products (NDA 50779 and NDA 50461) for IV infusion 1-2 gram (b) (4)

The proposed drug product manufacturing process is (b) (4) . During the NDA review several information requests regarding to container closure integrity test, process validation, endotoxin method, and reconstitution microbiology study were conveyed to and addressed by the applicant. The overall information regarding the sterility assurance provided in the NDA submission and subsequent amendments was found acceptable.

All the facilities are acceptable based on the profiles. No pre-approval inspection is required at this review cycle. Therefore, the overall recommendation of "Approve" was entered for the NDA into Panorama by OPF on 2/1/2018.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site[3]	**H**	(b) (4)	**L**	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	**L**		**L**	
Assay (API), stability	Formulation Container closure[1] Raw materials	**L**		**L**	

			(b) (4)		
Reconstitution time	Formulation	L		L	
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	M		L	
Extractables and Leachables	Formulation Container closure[1] Process parameters Scale/equipment	M		H	
Particulate matter	Formulation Container closure[1] Process parameters Scale/equipment	M		L	

[1]Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

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MICROBIOLOGY

Product Background: Used for surgical prophylaxis.

NDA: 211413

Drug Product Name / Strength: Cefazolin for Injection USP, 2 g/vial [Single-dose vial].

Route of Administration: IV Injectable

Applicant Name: HQ Specialty Pharma Corporation

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): (b) (4) **validation**

Justification (ANDA only): N/A

Review Summary: The (b) (4) drug substance (Cefazolin Sodium (b) (4)) is (b) (4) filled into (b) (4) 20ml vials to obtain the final drug product (Cefazolin for Injection USP, 2 g/vial).

List Submissions Being Reviewed: 12/21/2017, 04/04/2018, 06/07/2018, and 07/19/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

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

Concise Description Outstanding Issues Remaining: None.

Supporting Documents:

> DMF # (b) (4) (b) (4) is reviewed and found adequate (b) (4) (b) (4).

> DMF # (b) (4) (b) (4) is reviewed and found adequate (b) (4).

> The manufacturing facility, environmental monitoring, and actions concerning product when media fills fail is already reviewed from the same facility and found adequate in Microbiology review (b) (4).

List Number of Comparability Protocols (NDA only): Comparability Protocol is not included with the application.

S Drug Substance-

An LOA dated 06/12/2017 is provided by the (b) (4). on behalf of HQ Specialty Pharma Corporation. Data can be accessed from DMF (b) (4) (b) (4)

The following information request was conveyed to the applicant regarding the DMF (b) (4)

05/21/2018 Information Request: *The DMF (b) (4) has been reviewed and was deemed inadequate. The DMF Holder will be notified.*

06/07/2018 Response: The applicant did not provide adequate information.

Initially, the applicant did not provide adequate information and therefore following additional clarification was requested.

07/16/2018 Information Request: *The DMF (b) (4) has been reviewed and was deemed inadequate. The DMF Holder will be notified.*

07/19/2018 Response: The applicant has provided adequate information.

The applicant's response was acceptable.

Reviewer's Assessment: The DMF was reviewed and found adequate (b) (4) (b) (4)

Acceptable

P.1 Description of the Composition of the Drug Product

- **Description of the Composition of the Drug Product** (*3.2.P.1 Description and Composition of the Drug Product.pdf, and 3.2.P.2 Pharmaceutical Development.pdf)*

- **Description of drug product** – Cefazolin for Injection, USP 2 g/vial is a sterile white or almost white powder for injection containing Cefazolin Sodium sterile (b) (4) lyophilized. The drug product is filled in a (b) (4) glass vial with a rubber stopper and aluminum cap with plastic flip-off. The dry sterile powder should be

dissolved in appropriate media for the reconstitution of the solution for infusion. It is marketed as a single-dose vial (2g/20ml vial).

- **Drug product composition –**
  The formulations used for the manufacturing of the drug product are summarized below (table is copied from *Description and Composition of the Drug Product.pdf, p.1/2*):

Table 1: Theoretical Unit Composition

Ingredient	Dosage	Function	mg/vial	Overfill (%)*
Cefazolin Sodium Sterile (b) (4)	2 g/vial	Active	2000	(b) (4)

- **Description of container closure system –**
  The following container-closure systems are used for the production (table is modified from *3.2.P.7.1 Summary of Container/Closure System,* (b) (4) *and source of supply and suppliers address.pdf*):

Component details/ material code	Manufacturer /address	DMF
20ml (b) (4) clear glass vials (b) (4) (b) (4)	(b) (4)	(b) (4)
20 mm (b) (4) rubber stopper (b) (4)		(b) (4)
20 mm aluminum/plastic flip off (b) (4)		N/A

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

Acceptable

P.2 Pharmaceutical Development

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

sLifecycle Management Considerations

Reviewer's Assessment: Changes to the container closure system, component and equipment (b) (4) could affect microbiological quality of the subject drug product.

List of Deficiencies: *None*

Primary Microbiology Reviewer Name and Date:

Koushik Paul, Ph.D. and 7/24/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Elizabeth Bearr, Ph.D. and 7/24/2018

Koushik Paul

Digitally signed by Koushik Paul
Date: 7/24/2018 12:20:29PM
GUID: 5600522e0069b02f59c7bd85b6b54742

Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 7/24/2018 12:24:33PM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

BIOPHARMACEUTICS

Product Background:

NDA: 211413 [505(b)(2)]

Drug Product Name / Strength: Cefazolin for Injection USP, 2 g/vial

Route of Administration: IV Injectable

Dosage Form: Powder for injection

Applicant Name: HQ Specialty Pharma Corporation

Proposed indication: Cefazolin for injection is a cephalosporin antibacterial indicated in perioperative prophylaxis

Review Recommendation:
From the Biopharmaceutics perspective, NDA 211413 for Cefazolin for Injection USP, 2 g/vial, is recommended for **APPROVAL** when administered by IV infusion 1-2 gram (b) (4)

List of Submissions being reviewed:

12/21/2017	NDA 211413/Original submission
05/17/2018	eCTD-0005/Response to Biopharmaceutics Information Request

1. Background

The Applicant submitted NDA 211413 on 12/21/2017 to seek the approval for the proposed Cefazolin for Injection, USP, 2 g/vial, under the 505(b)(2) pathway. Per the proposed labeling package insert, the proposed drug product is a powder for injection (2 gram), which has to be reconstituted in 5 mL sterile water to a 6 mL solution. This reconstituted solution (b) (4) further diluted with 50 to 100 mL of a variety of diluents and administered as an IV infusion at a concentration of 2 g/56 mL to 2 g/106 mL. The Applicant is relying on two listed drugs (LDs): NDA 050779 and NDA 050461. This Biopharmaceutics Review focuses on the evaluation of the bridging between the proposed drug product and the listed drug products.

2. The proposed drug product, two listed drug products (LDs), and the reference standard (RS) product

The drug substance, Cefazolin Sodium, is a (b) (4) powder, and has high solubility in water, saline, and dextrose solutions. No other excipients are included in the final to-be-marketed formulation.

The side-by-side comparison of the proposed drug product, the two LDs[1] and the RS product are summarized in Table 1. LD #2 is discontinued and not available for comparative in vitro testing. Therefore, the Applicant relies on a generic version/reference standard (RS) of LD #2, approved under ANDA 065226, to provide pH and osmolality information expected to be representative of LD #2. The proposed drug product, the two LDs and RS product have the same active ingredient (cefazolin sodium sterile powder), but they have some differences in strengths, route of administration, solution concentration, diluents and dosing instruction as shown in Table 1.

Table 1: Side-by-side comparison of the proposed drug product, the two LDs and the RS product

	The proposed drug product: Cefazolin for Injection	**LD #1: Cefazolin for Injection and Dextrose Injection**	**LD #2: Ancef® (Cefazolin for Injection)**	**RS product: Cefazolin for Injection**
A/NDA numbers	**NDA 211413**	**NDA 050779** by BBraun, approved on 07/27/2000	**NDA 050461** by GSK, approved on 10/04/1973, discontinued not for safety or efficacy	**ANDA 065226** by Hospira, approved on 04/21/2005
Indications and Usage	Perioperative prophylaxis	Perioperative prophylaxis and others	Perioperative prophylaxis and others	Perioperative prophylaxis and others
Strength	2 g/vial	1 g/vial with 50 mL of 4.0% Dextrose (*Duplex Container*); 2 g/vial with 50 mL of 3.0% Dextrose (*Duplex Container*)	1 g/vial for single-dose vials, 10 g/vial for pharmacy bulk vials	500 mg/vial and 1 g/vial for single-dose vial
Route of Administration	(b) (4) IV infusion	IV infusion	IM injection, IV bolus injection, or IV infusion	IM injection, IV bolus injection, or IV infusion
Active Ingredient	2 g Cefazolin Sodium powder	*Drug Chamber:* 1 g or 2 g Cefazolin Sodium powder *Diluent Chamber:* 3% or 4% Dextrose solution	1 g Cefazolin Sodium powder	500 mg or 1 g Cefazolin Sodium powder
Excipients	None	None	None	None

[1] M.1.1 (356h form) and M.1.2 (Reviewer's Guide) of 02/28/2018 submission: Application 211413 - Sequence 0001 - 356H (SN0001) and Application 211413 - Sequence 0001 - Reviewer's Guide (SN0001)

Diluents	Sodium Chloride Injection, USP 5% (b) (4) Dextrose Injection, USP (b) (4)	N/A (Duplex container contains either 3% or 4% Dextrose solution)	Sodium Chloride Injection, USP 5% or 10% Dextrose Injection, USP 5% Dextrose in Lactated Ringer's Injection, USP 5% Dextrose and 0.9% Sodium Chloride Injection, USP 5% Dextrose and 0.45% Sodium Chloride Injection, USP 5% Dextrose and 0.2% Sodium Chloride Injection, USP Lactated Ringer's Injection, USP Invert Sugar 5% or 10% in Sterile Water for Injection Ringer's Injection, USP 5% Sodium Bicarbonate Injection, USP	Sodium Chloride Injection, USP 5% or 10% Dextrose Injection, USP 5% Dextrose in Lactated Ringers Injection, USP 5% Dextrose and 0.9% Sodium Chloride Injection, USP 5% Dextrose and 0.45% Sodium Chloride Injection, USP 5% Dextrose and 0.2% Sodium Chloride Injection, USP Lactated Ringer's Injection, USP Invert Sugar 5% or 10% in Sterile Water for Injection Ringer's Injection, USP 5% Sodium Bicarbonate Injection, USP

Solution Concentration (*calculated by this reviewer based on labeling*[2,3,4,5])	Reconstitute **2 g powder** in 5 mL of sterile water to a 6 mL solution (b) (4) (b) (4) *For IV infusion (no specific time)*: Further dilute above reconstituted solution in 50 to 100 mL of the following diluents to get final conc. = (b) (4)	Duplex Container *For IV infusion (30 min)*: Conc. = 2 g/50 mL = **40 mg/mL** Or Conc. = 1 g/50 mL = **20 mg/mL**	Single-dose vial: Reconstitute **1 g powder** in 2.5 mL of sterile water to a 3 mL solution (b) (4) *For IV (bolus) injection (3-5 min):* Further dilute the reconstituted solution with 5 mL of sterile water (b) (4) *For IV infusion (no specific time):* Further dilute above reconstituted solution in 50 to 100 mL of the following diluents to get final conc. = (b) (4)	Reconstitute **0.5 g** or **1 g** powder in 2 mL or 2.5 mL of sterile water to a 2.2 mL or 3 mL solution (b) (4) (b) (4) *For IV (bolus) injection (3-5 min)*: Further dilute the reconstituted solution with 5 mL of sterile water (b) (4) *For IV infusion (no specific time)*: Further dilute above reconstituted solution in 50 to 100 mL using the following diluents to get final conc. = (b) (4)

[2] The proposed labeling of NDA 211413: Application 211413 - Sequence 0003 - Draft Labeling Text - PI PDF
[3] NDA 050779, labeling dated on 10/08/2015:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050779s025lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/50779lbl.pdf
[4] NDA 050461, labeling dated on 06/02/2004:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50461slr139_ancef_lbl.pdf
[5] ANDA 065226, labeling dated on June 2016: Application 065226 - Sequence 0020 - Cefazolin USPI Novaplus Clean - 948026438 (Jun 2016)

Dosing Instruction	**1 to 2 g** prior to the start of surgery. For lengthy operative procedures (e.g., 2 hours or more), **500 mg to 1 g IV** during surgery. **500 mg to 1 g** IV every 6 to 8 h for 24 h postoperatively.	**1 to 2 g** prior to the start of surgery. For lengthy operative procedures (e.g., 2 hours or more), **500 mg to 1 g IV** during surgery. **500 mg to 1 g** IV every 6 to 8 h for 24 h postoperatively.	**1 g** prior to the start of surgery. For lengthy operative procedures (e.g., 2 hours or more), **500 mg to 1 g IV or IM** during surgery. **500 mg to 1 g** IV or IM every 6 to 8 h for 24 h postoperatively.	**1 g** prior to the start of surgery. For lengthy operative procedures (e.g., 2 hours or more), **500 mg to 1 g IV or IM** during surgery. **500 mg to 1 g** IV or IM every 6 to 8 h for 24 h postoperatively.

3. Comparative pH data

The batch information and the comparative pH data of three registration batches of the proposed drug product (2 g/vial), LD#1 product (NDA 050779, 2 g in Duplex container) and RS product (ANDA 065226, 1 g/vial) after reconstitution and dilution are provided in in M.3.2.P.8.1 and M.3.2.P.8.3 and summarized in the following Table 2-4.

Table 2: Three registration batches of the proposed drug product (Cefazolin for Injection, 2 g/vial)

The proposed drug product	Batch #	Manufacturing Date	Proposed Expiration Date	pH Test Date	Osmolality Provided Date
Cefazolin for Injection, 2 g/vial	0001D5	Jun 2015	Jun 2018	Apr-Nov 2017	May 2018
	0002D5	Jun 2015	Jun 2018	Apr-Nov 2017	May 2018
	0003D5	Jun 2015	Jun 2018	Apr-Nov 2017	May 2018

Table 3: Comparative pH data of the reconstituted and diluted proposed drug product (2 g/vial) and the LD#1 product (2 g in Duplex container) at 40 mg/mL at batch release and after storage at 40°C for 6 months or 25°C for 12 months

Product	Bach #	Reconstitution	Conc.	Storage	Proposed pH range	After 6 Months @ 40°C/75% RH Time (hours)		After 12 Months @ 25°C/60% RH Time (hours)	
						0 h	24 h	0 h	24 h
The proposed drug product	0001D5	Dextrose 5%	40 mg/mL	25°C± 2°C	4.0-6.0	4.6	5.9	4.6	5.9
	0002D5	Dextrose 5%	40 mg/mL	25°C± 2°C	4.0-6.0	4.6	5.9	4.7	5.9
	0003D5	Dextrose 5%	40 mg/mL	25°C± 2°C	4.0-6.0	4.6	5.9	4.6	5.9
LD#1 product	H6A834	Dextrose 5%	40 mg/mL	25°C± 2°C	4.0-6.0	4.8	5.9	4.8	5.9

Product	Bach #	Reconstitution	Conc.	Storage	Proposed pH range	Time (days)		Time (days)	
						0 d	10 d	0 d	10 d
The proposed drug product	0001D5	Dextrose 5%	40 mg/mL	5°C ± 3°C	4.0-6.0	4.6	5.8	4.6	5.7
	0002D5	Dextrose 5%	40 mg/mL	5°C ± 3°C	4.0-6.0	4.6	5.7	4.7	5.7
	0003D5	Dextrose 5%	40 mg/mL	5°C ± 3°C	4.0-6.0	4.6	5.6	4.6	5.6
LD#1 product	H6A834	Dextrose 5%	40 mg/mL	5°C ± 3°C	4.0-6.0	4.8	5.9 (7 days)	4.8	5.6 (7 days)

Table 4: Comparative pH data of the reconstituted (330 mg/mL) and/or diluted (20 or 40 mg/mL) proposed drug product (2 g/vial) and the RS product (1 g/vial) at batch release and after storage at 40°C for 6 months or 25°C for 12 months

Bach #	Tested Diluent	Conc.	Storage	Proposed pH range	After 6 Months @ 40°C/ 75% RH pH Data		After 12 Months @ 25°C/ 60% RH pH Data	
					Time (hours)		Time (hours)	
					0 h	24 h	0 h	24 h
0001D5	Sterile water	330 mg/mL	25°C ± 2°C	4.0-6.0	5.3	5.9	5.2	5.9
0002D5	Sterile water	330 mg/mL	25°C ± 2°C	4.0-6.0	5.2	5.9	5.2	5.9
0003D5	Sterile water	330 mg/mL	25°C ± 2°C	4.0-6.0	5.2	5.9	5.1	5.9
101G054	Sterile water	330 mg/mL	25°C ± 2°C	4.0-6.0	5.1	5.9	5.1	5.8
Bach #	Tested Diluent	Conc.	Storage	Proposed pH range	Time (days)		Time (days)	
					0 d	10 d	0 d	10 d
0001D5	Sterile water	330 mg/mL	5°C ± 3°C	4.0-6.0	5.3	5.9	5.2	5.9
0002D5	Sterile water	330 mg/mL	5°C ± 3°C	4.0-6.0	5.2	5.9	5.2	5.9
0003D5	Sterile water	330 mg/mL	5°C ± 3°C	4.0-6.0	5.2	5.9	5.1	5.9
101G054	Sterile water	330 mg/mL	5°C ± 3°C	4.0-6.0	5.1	5.9	5.1	5.8
Bach #	Tested Diluent	Conc.	Storage	Proposed pH range	Time (hours)		Time (hours)	
					0 h	24 h	0 h	24 h
0001D5	NaCl (b) (4)	40 mg/mL	25°C ± 2°C	4.0-6.0	4.8	5.9	4.5	5.9
0002D5	NaCl	40 mg/mL	25°C ± 2°C	4.0-6.0	4.7	5.9	4.5	5.9
0003D5	NaCl	40 mg/mL	25°C ± 2°C	4.0-6.0	4.7	5.9	4.5	5.9
101G054	NaCl	40 mg/mL	25°C ± 2°C	4.0-6.0	4.7	5.9	4.6	5.9

Product	Bach #	Tested Diluent	Conc.	Storage	Proposed pH range	Time (days)		Time (days)	
						0 d	10 d	0 d	10 d
The proposed drug product	0001D5	NaCl (b) (4)	40 mg/mL	5°C ± 3°C	4.0-6.0	4.8	5.7	4.5	5.9
	0002D5	NaCl	40 mg/mL	5°C ± 3°C	4.0-6.0	4.7	5.7	4.5	5.7
	0003D5	NaCl	40 mg/mL	5°C ± 3°C	4.0-6.0	4.7	5.5	4.5	5.6
RS product	101G054	NaCl	40 mg/mL	5°C ± 3°C	4.0-6.0	4.7	5.6	4.6	5.5

Product	Bach #	Tested Diluent	Conc.	Storage	Proposed pH range	Time (hours)		Time (hours)	
						0 h	24 h	0 h	24 h
The proposed drug product	0001D5	NaCl (b) (4)	20 mg/mL	25°C ± 2°C	4.0-6.0	4.6	5.9	4.5	5.9
	0002D5	NaCl	20 mg/mL	25°C ± 2°C	4.0-6.0	4.5	5.9	4.5	5.9
	0003D5	NaCl	20 mg/mL	25°C ± 2°C	4.0-6.0	4.5	5.8	4.4	5.9
RS product	101G054	NaCl	20 mg/mL	25°C ± 2°C	4.0-6.0	4.6	5.9	4.4	5.9

Product	Bach #	Tested Diluent	Conc.	Storage	Proposed pH range	Time (days)		Time (days)	
						0 d	10 d	0 d	10 d
The proposed drug product	0001D5	NaCl (b) (4)	20 mg/mL	5°C ± 3°C	4.0-6.0	4.6	5.8	4.5	5.7
	0002D5	NaCl	20 mg/mL	5°C ± 3°C	4.0-6.0	4.5	5.5	4.5	5.6
	0003D5	NaCl	20 mg/mL	5°C ± 3°C	4.0-6.0	4.5	5.8	4.4	5.6
RS product	101G054	NaCl	20 mg/mL	5°C ± 3°C	4.0-6.0	4.6	5.6	4.4	5.6

Reviewer's Assessment:

The above pH data showed that the proposed drug product, upon storage at 12 months long term or 6 months accelerated conditions and in-use storage 0 to 10 days, has comparable pH values compared to the LD#1 and the RS products with the pH range of 4.5-5.9 at different reconstitution and dilution concentrations.

4. Comparative osmolality data

The comparative osmolality data of the proposed drug product, LD#1 product and RS product at different drug concentrations after reconstitution and dilution using any two proposed diluents were requested in an information request dated 04/25/2018[6] (*also see Appendix 1 for Biopharmaceutics Information Request*).

The requested comparative osmolality data were submitted on 05/17/2018[7], which are summarized in Table 5. Sterile water was used for the proposed drug product and RS product to get the 330 mg/mL reconstitution solution. (b) (4) NaCl and 5% Dextrose were used to further dilute the above reconstitution solution and get the final solution with

[6] Biopharmaceutics IR conveyed on 04/25/2018: http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881a9af07

[7] M.3.2.P.5.4 of NDA 211413 on 05/17/2018 submission: Application 211413 - Sequence 0005 - Batch Analyses

concentration ranging from 19 to 36 mg/mL. 3% Dextrose was used for the LD#1 product to get the final reconstituted solution at concentration of 20 and 40 mg/mL.

Table 5: Comparative osmolality data of the proposed drug product (2 g/vial), the LD#1 product (2 g in Duplex container) and the RS product (1 g/vial)

Theoretical final concentrations		Osmolality (mOsm/kg)				
		The proposed drug product (2 g/vial)		LD#1 product (2 g/bag)	RS product (1 g/vial)	
[redacted] (b) (4)						
For IV infusion	36 mg/mL	412.0 (b) (4) NaCl)	387.5 (5% Dextrose)	/	/	/
	19 mg/mL	352.0 (b) (4) NaCl)	241.0 (5% Dextrose)	/	349.0 (b) (4) NaCl)	342.5 (5% Dextrose)
	10 mg/mL	/	/	/	296.0 (b) (4) NaCl)	308.0 (5% Dextrose)
	40 mg/mL	/	/	398.0 (3% Dextrose)	/	/
	20 mg/mL	/	/	224.0 (5% Dextrose)	/	/

Reviewer's Assessment:

The osmolality data of the proposed drug product, the LD#1 and the RS products are in the range of 224.0-520.5 mOsm/kg. The normal range of human plasma osmolality is about 275-299 mOsm/kg[8]. An osmolality range of cefazolin injection of about 290 - 636 mOsm/kg[9] is cited in "Trissel Handbook". The Clinical Division had no concerns about the osmolality data of the proposed product as discussed during the mid-cycle meeting (dated on 05/30/2018). In general, osmolality values of up to 500-600 mOsm/kg are not of concern. [redacted] (b) (4)

(b) (4)

5. *In vitro* bridging assessment

(1) The main differences between the proposed drug product vs. LD#1 are:

	The proposed drug product	LD#1 (NDA 050779 by BBraun)
Strength	2 g/vial	2 g/bag
Dose	1 to 2 gram	1 to 2 gram
Route of administration	[redacted] (b) (4) IV infusion	IV infusion
Solution Concentration	[redacted] (b) (4)	

[8] Wikipedia: https://en.wikipedia.org/wiki/Plasma_osmolality

[9] M.3.2.P.5.4 of NDA 211413 on 05/17/2018 submission: Application 211413 - Sequence 0005 - Trissel Handbook

	For IV infusion (no specific time): Approx. conc. range = **19** to **36 mg/mL**.	*For IV infusion (no specific time)*: Specific conc. = **20** or **40 mg/mL**.

As presented in Table 3 above, the proposed product and LD#1 have comparable pH values at the same tested concentration (20 and 40 mg/mL solution). As presented in Table 5 above, the proposed product and LD#1 have comparable osmolality at similar concentration (19 to 40 mg/mL solution) for **IV infusion**. Therefore, the *in vitro* bridging between the proposed product and LD#1 for **IV infusion** is established for the 1 to 2 gram dose.

(b) (4)

(2) The main differences between the proposed drug product vs. LD#2/RS are:

	The proposed drug product	**LD#2 (NDA 050461 by GSK) and RS (ANDA 065226 by Hospira)**
Strength	2 g/vial	1 g/vial
Dose	1 to 2 gram	1 gram
Route of administration	(b) (4) IV infusion	IM injection, IV bolus injection and IV infusion
Solution Concentration	(b) (4)	*For IV bolus injection (3-5 min)*: Approx. conc. range = (b) (4)
	For IV infusion (no specific time): Approx. conc. range = (b) (4)	*For IV infusion (no specific time)*: Approx. conc. range = (b) (4)

(b) (4)

As presented in Table 5 above, the proposed product and RS product have comparable osmolalities in the concentration range of (b) (4) mg/mL for **IV infusion**. Although the concentration of the proposed IV infusion is higher than the concentration of the LD#2 IV infusion, both can be given at the 1 gram dose. Therefore, the *in vitro* bridging between the proposed product and LD#2 product for **IV infusion** is established at the 1 gram dose.

CONCLUSION:

(i) Bridging between the proposed drug product and LD#1 (NDA 050779 by BBraun):

- (b) (4)
- For IV infusion: The bridge is established between the proposed product and NDA 050779 by:
  1) Same total dose: **1 to 2 g** prior to the start of surgery. For lengthy operative procedures (e.g., 2 hours or more), **500 mg to 1 g** IV during surgery. **500 mg to 1 g** IV every 6 to 8 h for 24 h postoperatively.
  2) Comparable drug concentrations of the to-be-infused solutions (approximately 19 to 36 mg/mL vs. 20 to 40 mg/mL). This minor difference is acceptable since the total dose is the same, because the proposed drug product has a slightly larger volume.
  3) Comparable pH and osmolality of the to-be-infused solutions (after reconstitution and dilution): pH 4.6 vs. pH 4.8 and 241-412 mOsm/kg vs. 224-387 mOsm/kg (depending on diluent and concentration).
  4) The absence of excipients that could alter the in vivo drug disposition.
  5) Although the diluent in NDA 050779 is 3% or 4% Dextrose, whereas the proposed drug product has a series of different possible diluents, the difference in diluents is not expected to have an impact on the safety and/or efficacy.

(ii) Bridging between the proposed drug product and LD#2 (NDA 050461 by GSK):

- (b) (4)
- For IV infusion: The bridge is established between the proposed product and NDA 050461 only for the 1 gram dose (not the 2 gram dose), by:
  1) Same 1 gram dose (but not 2 gram dose): The proposed drug product is proposing a starting dose (prior to surgery) of 1 to 2 gram, whereas NDA 050461 has a starting dose (prior to surgery) of 1 gram.
  2) The drug concentrations of the to-be-infused solution of the proposed drug product (19-36 mg/mL) are overlapping with drug concentrations of the to-be-infused solution of NDA 050461 (10-19 mg/mL). For a 1 gram dose, both products can be infused as a 53 mL volume of a 19 mg/mL solution.
  3) Comparable pH and osmolality of the to-be-infused solutions (after reconstitution and dilution), using the reference standard ANDA 065226 instead of NDA 050461 for the measurements, since NDA 050461 is discontinued: pH 4.5-4.7 vs. pH 4.6-4.7 and 241-412 mOsm/kg vs. 296-349 mOsm/kg (depending on diluent and concentration).
  4) The absence of excipients that could alter the in vivo drug disposition.

5) The possible diluent for the proposed drug product and NDA 050461 are the same.

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 211413 for Cefazolin for Injection USP, 2 g/vial, is recommended for **APPROVAL** when administered by IV infusion 1-2 gram (b) (4)

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Biopharmaceutics Reviewer
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