

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211413Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Summary Review

Date	Refer to electronic signature date
NDA #	211413
Applicant	HQ Specialty Pharma Corporation
Date of Submission	11/8/2022 (SDN #32)
PDUFA Goal Date	5/8/2023
Proprietary Name / Established (USAN) names	Cefazolin for Injection*
Dosage forms/Strength	Powder for Injection, 2 gram/vial
Proposed Indication	Perioperative prophylaxis in adults (b) (4)
Approved Indication	Perioperative prophylaxis in adult patients
Regulatory Action	Approval

*No proprietary/trade name was proposed for the drug product.

1. Background

Cefazolin is a semi-synthetic, first-generation cephalosporin antibacterial drug that has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections, including gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*), and gram-negative bacteria (*Escherichia coli*, and *Proteus mirabilis*).

This 505(b)(2) NDA provides for Cefazolin for Injection, 2 gram/vial. The listed drugs (LDs) are Cefazolin for Injection, USP and Dextrose Injection, USP in Duplex® Container (NDA 050779) and Ancef® (cefazolin for injection) (NDA 050461). No clinical trials were conducted by the Applicant to support this NDA. The Applicant intends 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.

NDA 211413 was, originally submitted on December 21, 2017, received a Complete Response (CR) letter on October 19, 2018, due to several deficiencies, including insufficient information to adequately quantify or characterize leachables, unspecified impurities above the identification and qualification thresholds, and in-use stability data (refer to the October 19, 2018, Division Director and Cross-Discipline Team Leader review by Drs. Sumathi Nambiar and Elsbeth Chikhale, and October 19, 2018, CR letter). The NDA resubmission dated July 2, 2019, provided a complete response to the action letter and included adequate responses to the deficiencies for the unspecified impurities and in-use stability data; however, the deficiency related to quantifying and characterizing leachables in the drug product was not satisfactorily addressed.

Therefore, a second CR letter was issued for NDA 211413 on December 26, 2019 (refer to OPQ Review dated December 17, 2019, and Unireview dated December 26, 2019, in DARRTS). The Applicant resubmitted their NDA on July 9, 2020. It provided a complete response to the December 26, 2019, action letter and included additional characterization and qualification information for leachables identified in the leachable studies. However, the Pharmacology/Toxicology review team determined that insufficient information was submitted to adequately qualify the identified leachables in the proposed cefazolin drug product and recommended that the Applicant conduct a new nonclinical study to qualify the identified leachables. Therefore, the Applicant was issued a third CR letter on January 8, 2021 (refer to Pharmacology/Toxicology Review dated January 5, 2021, and the NDA Summary review and CR letter dated January 8, 2021, in DARRTS). The Applicant resubmitted NDA 211413 on November 8, 2022, in response to the January 8, 2021, CR letter and this submission was determined to be a complete response to these deficiencies as discussed in the current review.

2. Current Submission

Nonclinical:

The nonclinical deficiencies identified in the CR Letter regarding the qualification of detected leachables have been adequately addressed. Leachables associated with the (b) (4) rubber stopper enclosure (b) (4) were evaluated for safety in an intravenous 14-day repeated-dose toxicity study in dog. Findings from the study indicate exposures to the detected leachables were well tolerated at (b) (4)-fold safety margins (based on body surface area comparisons) and are therefore unlikely to pose any safety concerns. This is further supported by the information provided in the revised toxicological risk assessment that was submitted by the Applicant. From a pharmacology/toxicology perspective, the NDA is recommended for approval.

Clinical:

The submission references several literature reports on adverse reactions associated with cefazolin use, including thrombocytopenia, coagulopathy, serum-sickness like reactions, arthralgia, nephrotoxicity, increases in liver function tests, and anemia.

The prescribing information of the product was updated with the following warning, which has already been included in the PI of the LD (NDA 50461):

5.5 Prothrombin Activity

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

The other adverse reactions described in the provided references have already been reflected in the prescribing information.

Product Quality/CMC:

The current NDA resubmission (SDN#32) includes only minor updates to the previously submitted Product Quality information, which include the leachable data for the lot used in the leachable qualification study, and a revision to the drug product endotoxin acceptance criterion. In addition, all manufacturing facilities remain in adequate status and an overall “Approve” recommendation was entered by the Office of Pharmaceutical Manufacturing Assessment (OPMA) in Panorama on April 10, 2023. Based on the assessment of the overall information submitted in the NDA, including the current resubmission, this NDA is recommended for approval from the Product Quality perspective. For details, refer to the Office of Pharmaceutical Quality (OPQ) Review entered into DARRTS on April 14, 2023.

Labeling:**Prescribing Information**

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI. The finalized PI was compared to the Applicant’s draft PI submitted on November 8, 2022 (see the table below). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

FULL PRESCRIBING INFORMATION Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
2. DOSAGE AND ADMINISTRATION	Removed the statement (b) (4) (b) (4) (b) (4) from section 2 (Dosage and Administrations) and subsection 8.4 (Pediatric Use) of the PI. This change was made because the 2g vial could be used to measure out smaller amounts of drug for administration after reconstitution and dilution. Clarified that Cefazolin for Injection is not for intravenous bolus administration or intramuscular administration in subsection 2.1 (Important Administration Instructions) of the PI. In subsection 2.2 (Dosage for Perioperative Prophylaxis) the dose administered half hour to 1 hour prior to the start of surgery was changed (b) (4) to “1 gram (g) to 2g” for consistency with the dose in the PI for the listed drug, Cefazolin for Injection, USP and Dextrose Injection, USP in Duplex® Container (NDA 050779)

	(b) (4)
	Refer to the Product Quality/CMC section of the Summary Review for additional information.
5 WARNINGS AND PRECAUTIONS	Warnings and Precautions subsection 5.5, regarding Prothrombin Activity has been added. Refer to the Clinical section of the Summary Review for additional details.
8 USE IN SPECIFIC POPULATIONS	(b) (4)
11 DESCRIPTION	Removed the statement (b) (4) (b) (4) (b) (4) Summary Review for additional details.
12 CLINICAL PHARMACOLOGY	Included additional subheadings for Distribution, Elimination, and Excretion. Information relating to the half-life moved to the Elimination subheading.
16 HOW SUPPLIED/STORAGE AND HANDLING	Removed the statement (b) (4) (b) (4) because the acceptance criteria for the appearance of contents is “white to cream powder”. There was no description of the product darkening during the stability (b) (4). Refer to the Product Quality/CMC section of the Summary Review for additional details. Included a cross-reference to the (b) (4) storage conditions of the reconstituted and diluted solution in subsection 2.4.

(b) (4) . As recommended by the Division of Pediatric and Maternal

Health (DPMH) in consultation with other components, the following regulatory disclaimer has been added to the PI: *“Pediatric use information is approved for B. Braun Medical’s Cefazolin for Injection and Dextrose for Injection. However, due to B. Braun Medical’s marketing exclusivity rights, this drug product is not labeled with that pediatric information.”*

The 505(b)(2) Committee has cleared this 505(b)(2) application for an approval action.

Carton and Container Labeling Changes

The revisions applied to the carton and container labeling are based on the recommendations of the Division of Medication Error Prevention and Analysis 1 (DMEPA-1) and Office of Pharmaceutical Quality (OPQ). Please see the OPQ and DMEPA reviews for further details. DMEPA reviews were signed into DARRTS on August 28, and September 12, 2018, August 9, and 30, 2019, and March 3, and 14, 2023.

- 3. Regulatory Action:** This New Drug Application (NDA 211413) for Cefazolin for Injection, 2gram/vial, indicated for perioperative prophylaxis in adult patients will receive an approval action.

Reviewers:

Nonclinical Reviewer: Kelly Brant, PhD, MPH, DABT

Nonclinical Team Leader (CDTL): Terry Miller, PhD

CMC: Shalini Anand, PhD

CMC Team Leader: Dorota Matecka, PhD

Clinical: Alma Davidson, MD

Clinical Team Leader: Dmitri Iarikov, MD, PhD

Associate Director for Labeling: Abimbola Adebowale, MS, PhD

Deputy Division Director: Dmitri Iarikov, MD, PhD

Division Director: Peter Kim, MD, MS

Signatures: *{See appended electronic signature page}*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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NDA Summary Review

Date	December 21, 2020
NDA #	211413
Applicant	HQ Specialty Pharma Corporation
Date of Submission	July 9, 2020 (SDN # 27)
PDUFA Goal Date	January 8, 2021
Proprietary Name / Established (USAN) names	Cefazolin for Injection*
Dosage forms/Strength	Powder for injection, 2 gram/vial
Proposed Indication(s)	Perioperative prophylaxis in adult patients
Regulatory Action:	Complete Response

* No proprietary/trade name was proposed for the drug product

1. Background

Cefazolin is a semi-synthetic, first generation cephalosporin antibacterial agent that has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections including Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*), and Gram-negative bacteria (*Escherichia coli*, and *Proteus mirabilis*).

This 505(b)(2) NDA provides for Cefazolin for Injection, 2 gram/vial. The listed drugs (LDs) are Cefazolin for Injection, USP and Dextrose Injection, USP in Duplex® Container (NDA 050779) and Ancef® (cefazolin for injection) (NDA 050461). No clinical trials were conducted by the Applicant to support this NDA. The Applicant intends 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.

The NDA, originally submitted on December 21, 2017, received a Complete Response (CR) letter on October 19, 2018, due to several deficiencies, including leachables/extractables study, unspecified impurities above the identification and qualification thresholds, and in-use stability data (refer to the October 19, 2018, Division Director and Cross-Discipline Team Leader review by Drs. Sumathi Nambiar and Elsbeth Chikhale, and October 19, 2018, CR letter). The NDA resubmission dated July 2, 2019, provided a complete response to the action letter and included adequate responses to the deficiencies for the unspecified impurities and in-use stability data; however, the deficiencies related to the leachable studies were not addressed satisfactorily. Therefore, another CR letter was issued for this NDA on December 26, 2019 (refer to OPQ Review dated December 17, 2019, and Unireview dated December 26, 2019, in DARRTS).

2. Current Submission

The current resubmission (SDN#27), a complete, class 2 response, addresses the deficiencies listed in the December 26, 2019, CR letter and includes additional characterization and qualification information for leachables identified in the leachable studies.

From the Product Quality perspective, characterization data provided to identify leachables, has been found adequate. In addition, the updated overall recommendation of "Approve" was entered by the Office of Pharmaceutical Manufacturing Assessment (OPMA) into Panorama on July 13, 2020 (refer to the OPQ Review # 4 dated December 4, 2020, in DARRTS). However, the Applicant has not provided adequate information to qualify the identified leachables in their cefazolin drug product. The Applicant's safety qualification approach for leachables > (b) (4) mcg/day does not provide adequate information to characterize the toxicity of the identified leachables. While no mutagenicity concerns have been identified, the 14-day toxicity study conducted in rats did not achieve clinically relevant leachables exposures.

In response to the November 30, 2020, teleconference held with the Agency, the Applicant submitted an additional read-across assessment with surrogate compounds to qualify leachables safety. The CDER Computational Toxicology Consult Service (CTCS) reviewed the surrogate compounds chosen by the Applicant and found some of the surrogates to be not acceptable. Alternate surrogates were proposed by CTCS based on structural similarity and available toxicity information. However, the available toxicity information for the surrogates chosen by the Applicant and CTCS is not sufficient to allow for an adequate read-across assessment. Feasibility issues preventing adequate characterization of the structures of the (b) (4) also add additional uncertainty to the Applicant's read-across approach. Dr. Brant, the pharmacology-toxicology reviewer notes that an additional nonclinical study in which adequate systemic exposures are achieved is needed to qualify the leachables for safety. Dr. Brant also recommends that the Applicant provide a leachables assessment plan and/or justification that the leachables in the drug product to be administered to the animals is qualitatively and quantitatively similar to those identified in the Applicant's leachables assessment (Study Report TE190276). The NDA is recommended for a complete response from a Pharmacology/Toxicology perspective (refer to the review dated January 5, 2021, in DARRTS).

The clinical review of the Applicant's safety update associated with this resubmission did not identify any new safety information related to cefazolin in general or specifically related to its use for perioperative prophylaxis. The following safety-related updates to the proposed product labeling are recommended to align with the recently approved labeling of Cefazolin for Injection USP and Dextrose Injection USP in Duplex Container (NDA 050779): (1) inclusion of a new Postmarketing Experience

subsection 6.2 to add “serum sickness-like reaction” and “acute tubulointerstitial nephritis”; (2) revision to the Warnings and Precautions subsection 5.2 regarding seizures in patients with renal impairment to specifically associate the adverse reaction with Cefazolin for Injection and to provide mitigation language; and (3) addition of patient counseling information related to seizures in section 17. Several other recommendations were made by the review team regarding the labeling. Due to the complete response action, the labeling will be finalized in the next review cycle.

3. Regulatory Action

Since the Applicant has not provided adequate information to qualify the leachables in the drug product, the NDA will receive a complete response action.

NDA 211413/Cefazolin for Injection 2 gram/vial

Reviewers:

Clinical: Alma Davidson, MD

Clinical Team Leader: Peter Kim, MD, MS

Cross-Discipline Team Leader: Dorota Matecka, PhD

Division Director: Sumathi Nambiar, MD, MPH

Signatures: *{See appended electronic signature page}*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Memo to the Division File

NDA 211413 (S-0026; SN27, S-0027; SN28, S-0028; SN29)

Cefazolin for Injection, USP 2g/vial (HQ Specialty Pharma Corp.)

From: Kelly Brant, MPH, Ph.D., DABT, Pharmacology/Toxicology reviewer

Through: Terry Miller, PhD, Pharmacology/Toxicology supervisor

To: Jacquelyn Rosenberger, RPh, PharmD

Subject: Complete Response Recommendation

Date: December 29, 2020

Reviewer Recommendation:

The current NDA is recommended for a Complete Response from a pharmacology/toxicology perspective. The Applicant has not provided adequate information to qualify the identified leachables in their cefazolin drug product. The Applicant's safety qualification approach for leachables > (b) (4) mcg/day does not provide adequate information to characterize the toxicity of the identified leachables. While no mutagenicity concerns have been identified, the 14-day toxicity study conducted in rats did not achieve clinically relevant leachables exposures. In response to the November 30, 2020 teleconference held with the Agency, the Applicant submitted an additional read-across assessment with surrogate compounds to qualify leachables safety. The CDER Computational Toxicology Consult Service (CTCS) reviewed the surrogate compounds chosen by the Applicant and found some of the surrogates to be not acceptable. Alternate surrogates were proposed by CTCS based on structural similarity and available toxicity information. However, the available toxicity information for the surrogates chosen by the Applicant and CTCS are not sufficient to allow for an adequate read-across assessment. Feasibility issues preventing adequate characterization of the structures of the (b) (4) also adds additional uncertainty to the Applicant's read-across approach (please see the drug product review by Dr. Shalini Anand in the Platform).

Nonclinical Deficiency Comment to Applicant:

Unless otherwise justified, nonclinical studies conducted to qualify the safety of leachables should be designed such that the identified leachables are administered in a clinically relevant manner at levels that are equivalent to or greater than what patients would be administered when incorporating interspecies allometric scaling. Upon further review, the weight-of-evidence based on information provided in your resubmission [including the Position Paper on the qualification of the Cefazolin Leachables profile for (b) (4), the Toxicological Assessment (Annex 5), the August 20, 2020 response to the IR, the 14-Day Toxicity Study in rat (Final GLP Report: 19-02803-G1), and the additional calculations and read-across approach submitted on December 8, 2020], does not adequately qualify the safety of the identified leachables detected with your drug product:

1. The 14-day toxicity study in rat does not achieve clinically relevant leachables exposures, with animals receiving (b) (4) of the leachables/day when compared with the maximum estimated daily leachables exposure to patients. While the evaluation of analyzed concentrations in leachable study TE190276 in comparison with the 14-day toxicity study TE192771 based on the GC/MS analysis is informative, it does not address the observed differences in daily exposures to

the animals versus maximum estimated daily exposures in humans when accounting for interspecies allometric scaling.

2. You have proposed an acceptable intake of (b) (4) mcg/day for the identified (b) (4) leachables (Toxicological Assessment Annex 5). As previously noted, while it is recognized that PQRI-PODP has proposed higher qualification threshold levels for leachables, the FDA recommends 5 mcg/day as the qualification threshold for non-genotoxic leachables.
3. You applied a (b) (4) to calculate acceptable intake for the (b) (4) that would allow for sufficient safety margins. However, this approach is not considered adequate as the application (b) (4) has not been considered for regulatory decisions on the qualification of leachables (or impurities) for safety.
4. You applied (b) (4) to estimate that the total exposure in rat during the 14-day tox study is approximately (b) (4) times what a patient would receive following administration of 8g in a single day and proposed a change in labeling (b) (4). Given the unknown toxicity of the identified leachables, it cannot be assumed that multiple-lower dose leachables exposures in rat would adequately address the safety concerns of the leachables exposures associated with an 8g dose in a single day.
5. The surrogates chosen for use in your read-across analysis with worst-case scenario substances (submitted December 8, 2020) do not contain sufficient toxicology information to qualify the identified leachables for safety. In consultation with our internal CDER computational toxicology experts, the (b) (4) surrogates included in the read-across assessment were not considered acceptable and there are insufficient toxicity data available for (b) (4) to predict any potential leachables toxicity. Because the (b) (4) cannot be fully characterized, there is considerable uncertainty regarding the structural similarity of the chosen surrogate compounds (i.e., active pharmaceutical ingredient [API] and (b) (4) which further limits the utility of the read-across approach.

Information needed to resolve the deficiency

Given the absence of sufficient toxicity information surrounding the identified leachables, and the feasibility issues precluding adequate structural characterization of the (b) (4), we recommend that you conduct an additional general toxicity study, in an appropriate animal species, for any leachable that exceeds the safety qualification threshold of 5 mcg/day. Such a study should be designed to achieve leachables exposures that are clinically relevant. The potential challenge(s) of the API masking potential toxicity associated with the leachables exposure are acknowledged, but we believe it is feasible to design a nonclinical study that will allow for an adequate safety assessment of the leachables and/or identify any leachables-related shifts in the toxicity profile associated with the API. For example, you may consider conducting a toxicity study of 14-day duration in a larger animal species that would allow for a larger volume of the drug product containing leachables from the (b) (4) rubber stopper to be administered. As indicated in the teleconference held on November 30, 2020, we strongly recommend that you submit a draft study protocol for the Agency to review and provide feedback prior to initiating any additional nonclinical studies. By providing a draft protocol for comment, the Agency will be better able to work with you in designing a study that can best inform on the safety of the identified leachables when administered at clinically relevant exposures. We also recommend that you submit a leachables assessment plan and/or justification that the leachables in the drug product to be administered to the animals is qualitatively and quantitatively similar to the identified leachables described in Study Report TE190276. Upon any

additional leachables characterization or further testing, should there be any revised structures and/or identification of any new structures of leachables compared with those identified in your previous leachables assessment (TE 190276) needing qualification, plan to conduct additional (Q)SAR evaluation(s) for bacterial mutagenicity. A follow-up Ames test (bacterial reverse mutation assay) is recommended to qualify leachables that exceed 120 mcg/day with identified structural alerts for genotoxic potential.

Background:

The Agency issued a Complete Response (CR) Letter for NDA 211413: Cefazolin for Injection USP, 2 g/vial (in DARRTS submitted 12/26/2019), citing inadequate support was provided for the assigned structures of the leachables. The structures, molecular weights and/or levels of the identified leachables could not be confirmed based on the information submitted by the Applicant. It was recommended to the Applicant that given the lack of available toxicity information regarding the identified leachables, they conduct a general toxicity study for any leachable that exceeds the safety qualification threshold of 5 mcg/day. In addition, an Ames test and in vitro mutagenicity and/or mammalian chromosomal aberration assay (i.e., Mouse Lymphoma Assay) were recommended to qualify leachables that exceed 120 mcg/day with identified structural alerts for genotoxic potential.

Response to FDA CR Letter (July 9, 2020, S-0027; SN26): The Applicant provided (1) the final study report for a 14-day repeated dose toxicity study in rats with IV cefazolin prepared using the same rubber stopper enclosure as used in the leachables assessment; (2) an Ames test with the (b) (4) leachable, (3) a position paper on the qualification of the Cefazolin Leachables profile for (b) (4); and (4) a revised risk assessment for the identified leachables.

Study Title: 14-Day Toxicity Study Via Intravenous Injection in Sprague Dawley Rats with 14-Day Recovery/Study No. 19-02803-G1 Second Amended

Key Study Findings

- No differences in test-article related findings were observed between rats intravenously administered cefazolin sodium in a vial with rubber stopper compared to blank cefazolin for 14 days.
- The estimated daily exposures of the identified leachables associated with the rubber enclosures (b) (4) rubber stopper, (b) (4) in rats were less than the estimated clinical exposures.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes (21 CFR Part 58)

Methods

Dose and frequency of dosing:	4.0 mL/kg (160 mg/kg) of cefazoline sodium solution prepared in vial with rubber stopper LOT F2000665 0002D5 ¹ (test article) daily for 14 days
Route of administration:	Intravenous
Formulation/Vehicle:	Blank cefazolin (prepared using (b) (4) cap)
Species/Strain:	<i>Rattus norvegicus</i> /Sprague Dawley
Number/Sex/Group:	10/sex/group (main study)

¹ Lot 002D5 was also tested in the leachables assessment conducted by (b) (4)

Age:	At least 5 weeks old at start of dosing
Satellite groups/ unique design:	5/sex/group for recovery
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control (blank cefazolin)

Parameters	Major findings
Mortality	Control animals (cefazolin prepared in vial with Teflon cap): 1 animal died on Day 4 post dose (#1105); 1 animal found dead on Day 7 (#1022) Test animals (cefazolin prepared in vial with rubber stopper): 1 animal found dead on Day 6 (#2108). Necropsy for animals #1022 and #2108 noted liver, kidney, pancreas, and thymus as soft, mottled and deep red to purple in color. Cause of death could not be determined. No necropsy data was recorded for control animal #1105. No abnormalities were noted at gross necropsy for any other test or control animals.
Clinical Signs	None
Body Weights	None
Ophthalmoscopy	None
Hematology	Male test animals had higher mean MCV and longer PT at end of main study period and higher platelet concentration at recovery; female test animals had higher RBC, Hb concentration and hematocrit and lower platelet concentration at end of main study period. However, the means of all hematologic parameters in test and control animals fell within laboratory historical reference intervals.
Clinical Chemistry	Male test animals had higher Cl concentration at end of main study period and higher albumin and total protein concentration at recovery. Female test animals had higher ALP concentration at end of main study period. However, the means of all clinical chemistry parameters in test and control animals fell within laboratory historical reference intervals.
Urinalysis	None
Gross Pathology	None
Organ Weights	Male test animals had greater absolute brain weights at end of main study period and lower relative heart weights at end of recovery but fell within laboratory historical intervals. Female test animals had greater relative adrenal weights that were slightly above historical intervals (0.075% versus 0.02-0.051%, respectively). Observed changes in organ weights were without histologic correlates.

Histopathology Adequate battery: Yes	None; observations described as 'background findings' observed in both test and control article-treated animals included cytoplasmic vacuolation in adrenal glands; minimal mononuclear and/or PMN cell infiltration in duodenum, jejunum, ileum, rectum, colon, cecum; mononuclear cell infiltration in kidney interstitium and renal (kidney) tubular mineralization; PMN cell infiltration (minimal) in submucosa/mucosa of the stomach; hepatocyte/perivascular mononuclear cell infiltration and hepatocyte cytoplasmic vacuolation (in liver); congestion, edema and hemorrhage and perivascular PMN or mononuclear cell infiltration in lungs; mononuclear cell infiltration (minimal) in vagina; cervix epithelial degeneration (minimal) and distention of uterine lumen; neovascularization in peripheral cornea and minimal mononuclear cells in iris.
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-: indicates reduction in parameters compared to control.

Test and control articles were prepared as follows:

For the control article: For each 5 mL volume required for dosing, add 2.1 g of the lyophilized powder, which contains 2 g of the API, into a (b) (4) glass bottle with (b) (4) screw cap. Reconstitute the powder using 5 mL of sterile water for injection (SWFI). After reconstituting the powder, incubate the solution for 4 hours $\pm$ 10 minutes at $25 \pm 2^\circ\text{C}$ / 60 % R.H. Dilute the solution to a volume of 50 mL.

For the test article: Take one vial, containing 2.1 g of lyophilized powder, which contains 2 g of the API, and remove the red flip-off cap. Add 5 mL of SWFI volume to the vial with a glass syringe with needle inserted through the rubber stopper. Shake the vial for 2 ± 1 minute until the content of the vial has dissolved. After reconstituting the powder, incubate the solution at an inverted position for 4 hours $\pm$ 10 minutes at $25 \pm 2^\circ\text{C}$ / 60 % R.H. After incubating, remove the aluminum cap and the stopper from the vial. Transfer the contents of the needed number of vials to a (b) (4) glass bottle with (b) (4) screw cap. Transfer the contents of the needed amount of solution from the (b) (4) glass bottles with (b) (4) screw caps to an appropriate container and dilute to 50 mL.

The final report for Study No. 19-02803-G1 notes "the test article does not appear to demonstrate any systemic signs of toxicity when injected intravenously in rats for 14 days." An Information Request was sent to the Applicant to provide a justification of their selected MTD, and why a higher dose was not selected. The Applicant was also asked to provide a rationale for the once daily dosing used in the study as opposed to multiple daily doses that would better mimic daily clinical exposures. The Applicant responded that single dosing is considered to lead to highest serum or plasma peak and AUC values and thus provides a worst-case scenario, citing pharmacokinetic studies in a small number of patients demonstrating a higher serum and plasma AUC values following a single daily dose of cefazolin compared with repeated daily dosing (i.e., every 4 to 8 hr). In addition, the Applicant states that multiple daily IV administrations are technically difficult and may lead to complications.

The Applicant also noted that the dose level of 160 mg/kg in rats was selected to be equivalent to the maximum human dose of 8 g (160 mg/kg rated at 50 kg) and that higher dosages (e.g., 250 mg/kg) would lead to excessive peak concentrations that might lead to toxicity masking the known effects of the API.

Reviewer assessment of 14-day toxicity study in rat (Study No. 19-02803-G1).

The Applicant did not account for allometric scaling when determining a rat dose equivalent to maximum recommended human dose (MRHD) of 8 g. The human equivalent dose (HED) of the

maximum tested dose of 160 mg/kg in rats is 25.6 mg/kg (based on a body surface area comparison [BSA]), equivalent to a 1.5 g dose for a 60 kg person. The equivalent rat dose (based on BSA comparison) for the 8 g MRHD in patients is 831 mg/kg, approximately 5 times greater than the highest dose in rats. Given the lack of systemic toxicity observed between the control cefazolin (b) (4) cap) and cefazolin prepared using the rubber stopper, it is unlikely that the 160 mg/kg dose in rats represents the MTD. Multiple daily IV administration in rats is feasible and a study designed to allow for repeat daily dosing may provide greater leachables exposures than what was achieved in the 14-day study (see general toxicity of identified leachables discussion below).

The leachables exposure achieved in the rat study are not adequate to qualify the leachables when considering the estimated daily leachables exposures associated with an 8 g dose of cefazolin to patients. This holds true when comparisons are made using values obtained by GC-MS analysis from the same Batch F20006650002D5 stopper used in the TE190276 leachables assessment and the 14-day rat study (leachables present at levels > (b) (4) mcg/day safety threshold are highlighted in grey):

Leachable	Mcg/unit as analyzed by GC-MS (Batch F20006650002D5)		Daily exposure (mcg)		% Exposure achieved*
	TE 190276	TE 192771	Human ¹	Rat ²	
					(b) (4)

*Adjusted for body surface area comparison

¹ Maximum exposure is 4 units (vials) for 8 g total daily dose

²Exposures take into account Method Suitability Test (MST) correction or factor of 2 if no MST applied, as reported by Applicant in TE190276 and TE192771

This also holds true for comparisons made between leachables values obtained in the rat study using GC-MS analysis against the worst-case scenario for maximum human exposure calculated using the highest reported leachable levels (mcg/unit) in 3 batches of rubber stopper as reported in TE190276 by HS-GC/MS, GC-MS, and HRAM UPLC/MS²:

Leachable	Daily exposure (mcg)		% Exposure achieved*
	Human ¹	Rat ²	
			(b) (4)

*Adjusted for body surface area comparison. NR, not reported

² As reported in Table 4 of the Toxicological Assessment Annex 5

¹ Maximum exposure is 4 units (vials) for 8 g total daily dose

²Exposures take into account MST correction or factor of 2 if no MST applied, as reported by Applicant in TE190276 and TE192771

(b) (4)

It is of note that there are leachables identified in Study Report TE190276 (i.e., (b) (4)) that are not reported in the leachables assessment conducted as part of the rat study as these were detected using HS-GC/MS and/or HRAM-UPLC/MS. The Applicant provided a rationale for using GC-MS as the analytical technique for the rat study along with a re-evaluation of the leachables concentrations in the rat study and leachables report as analyzed by GC-MS in their December 8, 2020 submission (S-0028; SN29), highlighting the semi-quantitative nature of the results. From a CMC perspective, the profile of the leachables in the rat study match with the leachable study samples (please see the drug product review by Dr. Shalini Anand in the Platform).

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title: Salmonella Typhimurium Reverse Mutation Assay on (b) (4)

Study no.:	TE191525
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes (OECD)
Drug, lot #, and % purity:	(b) (4)
	Batch# ACF-E10353-054-8
	95.01%

Methods

Strains:	<i>S. typhimurium</i> strains TA98, TA100, TA102, TA1535, and TA1537
Concentrations in definitive study:	(b) (4)
Basis of concentration selection:	0.25 mg is recommended dose for genotoxic impurities by the "Genotoxic Impurities Task Force" ^{3*}
Negative control:	Dimethyl sulfoxide
Positive control:	<u>-S9</u> : TA98, 2-nitrofluorene (2 mcg/plate); TA100, TA1535, sodium azide (2.5 mcg/plate); TA102, mitomycin C (0.5 mcg/plate); TA1537, 9-aminoacridine (100 mcg/plate) <u>+S9</u> : TA98, benzopyrene (20 mcg/plate); TA100, TA102, TA1535, and TA1537, 2-aminoanthracene (1, 20, 2, and mcg/plate, respectively)
Formulation/Vehicle:	Dimethyl sulfoxide
Incubation & sampling time:	37 ± 2 degrees C; 48 - 72 hours
Comment on Study Validity:	All test strains were checked for spontaneous mutation frequencies; solvent treated controls were within the historical laboratory range and mutant frequency of positive controls were 2- to 3-times the frequency of the negative controls.

Results

The (b) (4) was not mutagenic to *S. typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 when tested in the absence and presence of S9 up to the highest concentration of (b) (4) mg/plate, under the conditions of the test. No test item toxicity or precipitation was observed in the TA100 strain (toxicity and precipitation were not evaluated in tester strains TA98, TA1535 or TA1537).

Reviewer comment: Tables 9 through 13 of the study report indicate the estimated concentrations are (b) (4) mcg/plate. Results from the dose formulation analysis notes that the averaged measured concentration of (b) (4) by gas chromatography/flame ion detector in the stock solution was (b) (4) mg/L; one hundred mL of stock solution was added to the plate making the highest concentration tested ~ (b) (4) mcg/plate. From Tables 9-13, it is estimated that the neat stock solution was diluted 1:3, 1:10, 1:30, and 1:100. Dose formulation analyses on the serial dilutions were not performed. Based on the average concentration calculated for the neat stock solution, the actual concentrations tested per plate were (b) (4) mcg/plate.

Reviewer Assessment of the Genotoxic Potential of Identified Leachables

Overall there are no mutagenicity concerns for any of the identified leachables. CDER's Computational Toxicology Service (CTCS)⁴ reviewed the Applicant's (Q)SAR predictions for mutagenicity and provided in-house (Q)SAR predictions to assess the mutagenic potential of the leachables. CTCS noted that it was

³Kenyon, M.O., et. al. 2007. *An evaluation of the sensitivity of the Ames assay to discern low level mutagenic impurities*. Regulatory Toxicology and Pharmacology 48: 75-86

* The 0.25 mg dose cited by Genotoxic Impurities Task Force (Kenyon et al. 2007) is based on a literature survey of approximately 450 mutagens in which an estimated 85% of mutagens were detected at concentrations of 250 microg/plate or less.

⁴ Division of Applied Regulatory Science within CDER Office of Clinical Pharmacology, Office of Translational Sciences

not clear if the Applicant analyzed the leachables using a statistical-based and an expert rule-based system in parallel, that the Applicant used (b) (4), which is not an acceptable model, and that outdated versions of (Q)SAR software were used. In-house evaluation of the leachables for bacterial mutagenicity was conducted using the most recent versions of three (Q)SAR models: Derek Nexus 6.1.0 (DX), Leadscope Model Applier version 3.0.2-4 Bacterial Mut v2 model (LMA), and CASE Ultra version 1.8.0.2 GT1_BMUT model (CU). CTCS predicted (b) (4) and (b) (4) to be positive for bacterial mutagenicity.

In the submitted position paper, the Applicant states that the positive (Q)SAR predictions for mutagenicity for (b) (4) should be overruled by means of the findings from the submitted Ames assay. Of note, the maximum human daily exposure for the (b) (4) (tested in the Ames assay) is roughly (b) (4) mcg/day⁵ and the maximum daily exposure for (b) (4) is (b) (4) mcg/day, below the 120 mcg/day threshold for leachables with genotoxic potential, and therefore are of no concern.

The identified leachables with an estimated maximum exposure of $\geq$ (b) (4) mcg/day (b) (4) yielded no structural alerts for mutagenicity based on both the (Q)SAR reports previously submitted (S-0021; SN22 submitted July 9, 2019, see UniReview in DARRTS 12/26/2019) and by CTCS evaluation.

Reviewer Assessment of the General Toxicity of Identified Leachables:

Overall, the Applicant has not provided adequate information to qualify the identified leachables in their cefazolin drug product. The Applicant considers there to be no safety concern for the identified leachables. The submitted position paper and risk assessment note that the (b) (4) (b) (4) leachables are considered qualified as they are below a threshold of (b) (4) mcg/day, as the Applicant considers the latest PQRI limit of (b) (4) mcg/day to be too conservative. In consultation with an FDA expert who serves on the PQRI Leachables and Extractables Working Group, the recommended qualification threshold for leachables found in parenteral drug products is 5 mcg/day. It should be noted that the FDA has not yet adopted the less conservative, higher limits of (b) (4) mcg/day, or (b) (4) mcg/day currently proposed by PQRI. The Applicant also applied (b) (4) in (b) (4) estimated acceptable daily leachables intake, (b) (4)

(b) (4) the appropriateness (b) (4) for the qualification of non-genotoxic impurities remains to be established⁶ and has not been adopted by the Agency.

Because the leachables exposure in rats were significantly below the estimated clinical exposure, the 14-day toxicity study is not considered adequate to qualify the safety of the identified leachables. Administration of a higher dose of cefazolin prepared with the rubber enclosures may yield exposures that are more clinically relevant. The animals used in the 14-day repeated-dose toxicity study weighed

⁵ The Applicant classifies (b) (4) as possible isomer(s) and was assigned separate ToxIDs: (b) (4) (b) (4) for a cumulative maximum daily exposure of (b) (4) mcg/day.

⁶ https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-qualification-non-genotoxic-impurities_en.pdf

~350 g at the initiation of dosing. Per good practice guidelines, and general Institutional Animal Care and Use Committee (IACUC) recommendations, rats can be safely administered up to 5 mL i.v. bolus, with larger amounts administered as continuous slow infusion (to 4 mL/kg/h)⁷. Administration of 5 mL of a 40 mg/mL solution equates to 200 mg cefazolin (571 mg/kg) and would allow for the rats to be exposed to a greater concentration of leachables but would not cover clinically relevant exposures for all of the leachables (i.e., animal exposure to (b) (4) would be ~ (b) (4) %). It is unknown whether the rats can tolerate the 200 mg (571 mg/kg) dose of cefazolin and if any API-mediated toxicity(ies) would mask any leachables toxicity(ies). However, a study may qualify the leachables provided no significant shift(s) in API toxicity profile are observed. The Applicant also stated that higher exposure of leachables levels were not feasible as the drug product could not be concentrated nor can the leachables be spiked. The Agency communicated the outstanding concerns regarding the approaches used by the Applicant to qualify the leachables safety on November 30, 2020. An IR was subsequently issued requesting the Applicant provide all of the final data, including any read-across and exposure calculations, to support safety of the identified leachables.

December 8, 2020 Response to IR (S-0028; SN 29). The Applicant proposed a change in labeling and submitted a final read-across assessment for the identified leachables.

Proposed change in labeling

(b) (4)

Reviewer's Assessment of the Applicant's Read-Across Approach

General principles adopted by ECHA⁸ and OECD⁹ for read-across include identifying a structurally similar surrogate (analogue) with the hypothesis that different compounds have the similar effects. That is, the surrogate structures would have similar toxicological properties as the identified leachables. The utility of read-across also depends on whether the chosen surrogate contains sufficient information for general toxicity endpoints that can be used to predict the same toxicity endpoints for the identified leachables.

The Applicant submitted a read-across assessment in their December 8, 2020 response and Toxicological Assessment (Annex 5) to help qualify the safety of the leachables using the following surrogates for extrapolation of the toxicity information to the identified leachables:

- (b) (4)

⁷ Turner et al. Administration of Substances to Laboratory Animals: Routes of Administration and Factors to Consider. J Am Assoc Lab Anim Sci. 2011 Sep; 50(5): 600–613. PMID: 22330705

⁸ European Chemical Society Read-Across Assessment Framework (RAAF) 2017 DoI: 10.2823/619212
https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a

⁹ [Guidance Document for using the OECD \(Q\)SAR Application Toolbox to develop Chemical Categories according to the OECD Guidance on Grouping of Chemicals](#), Series on Testing and Assessment No. 102, 2009

The Applicant stated in their December 8, 2020 submission that it was “very difficult to find data-rich neighbor substances.” CTCS was consulted to evaluate the leachables and surrogates proposed by the Applicant and propose alternative surrogates to assess general toxicity where the Applicant’s surrogates are unsuitable.

A summary of findings from the consult report and follow-up e-mail communication with the Computational Toxicology team (December 23, 2020) are as follows:

- (b) (4) was an acceptable surrogate because its alert was in the same chemical environment and toxicity data is available. While it is not perfect, the toxicity profile of (b) (4) would provide a conservative/worse-case assessment.
- (b) (4) is structurally similar, but was not acceptable, because there is no toxicity data available. The read-across (e.g., EpiSuite and EPA TEST) approach to assess (b) (4) and extrapolate to the (b) (4) leachables is not an acceptable approach.

- (b) (4) was not an ideal surrogate. It shares some structural similarity but also contains (b) (4) while the (b) (4) leachables contain (b) (4). As there was nothing else better in the literature and CTCS expects (b) (4) to be more “toxic” than (b) (4) leachables, (b) (4) was considered as acceptable surrogate. The toxicity profile of (b) (4) would provide a conservative/worse-case assessment.
- (b) (4) was not acceptable because better surrogates that are more structurally similar to (b) (4) are available. (b) (4) were selected because they are (b) (4) with similar features (b) (4) and have a more complete toxicological profile.

- (b) (4) is an acceptable surrogate and has some toxicity data (e.g., fish) available.
- (b) (4) is an acceptable surrogate because it contained the (b) (4) and the leachables are not expected to be more toxic than cefazolin.
- (b) (4) was suggested because it is structurally similar to (b) (4) and has more complete toxicological profile.
- (b) (4) was suggested because it contains the (b) (4). These features combined are represented in (b) (4). The (b) (4) will affect the absorption and physical chemical properties. As such (b) (4)

(b) (4) is the best surrogate available for assessing the toxicity of (b) (4)

Reviewer's Assessment of the Applicant's Read-Across Approach

Overall, the Applicant's submitted read-across approach does not adequately qualify the leachables. The available toxicity information for the surrogates chosen by the Applicant that were deemed acceptable by CTCS, along with CTCS-proposed alternate surrogates, were evaluated and are summarized in Table 1 below. Much of the available toxicity data comes from carcinogenicity studies conducted by the National Toxicology Program (NTP) or combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) that were conducted to comply with ECHA Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations. No repeated-dose toxicity information was found for the surrogate compounds when administered intravenously.

- The available toxicity data for (b) (4) suggest the (b) (4) leachables are non-carcinogenic and may be irritants. The Applicant extrapolated from ICH M7 limit of 120 mcg/day for < 1 month to a staged acceptable intake of (b) (4) mcg/day based on same interval spacing. No justification or rationale was provided for this approach and no general toxicity endpoint data are available for (b) (4) that could be used in calculating a more appropriate acceptable intake value.
- The Applicant extrapolated a permissible daily exposure (PDE) of (b) (4) mcg/day for (b) (4) using an oral (dietary) NOAEL of (b) (4) mg/kg in rat estimated for the surrogate (b) (4) using ICH Q3 assessment factors as follows: 5 for rat to human, 10 intraspecies factor, 1 for duration (short term exposure), 5 for absence of developmental tox and 1 for use of NOAEL:

$$\text{PDE} = \frac{(b) (4) * 50 \text{ kg}}{5 \times 10 \times 1 \times 5 \times 10} = (b) (4) \text{ mg/day}$$

Assuming 50% oral absorption, a PDE IV of (b) (4) mg/day or (b) (4) mcg/day was derived. It is unclear why the applicant chose factor 5 for absence of developmental toxicity as ICH Q3C guidelines would suggest using factor 1 due to absence of severe toxicity¹⁰. The adequacy of extrapolating an oral (dietary) NOAEL of (b) (4) (b) (4) surrogate to predict an acceptable daily intake of the (b) (4) leachables following intravenous exposure is uncertain in the absence of available surrogate toxicokinetic and/or ADME data. The reviewer estimates a PDE of (b) (4) mcg/day using the following factors: 5 for rat to human, 10 for variability between individuals, 1 for duration, 1 for toxicity severity, 10 for use of a surrogate, and 10 for bioavailability (absorption unknown):

$$\text{PDE} = \frac{(b) (4) * 50 \text{ kg}}{5 \times 10 \times 1 \times 10 \times 10} = (b) (4) \text{ mcg/day}$$

The estimated daily exposure of (b) (4) are (b) (4) mcg/day, approximately (b) (4)-fold less than PDE estimated for the surrogate. However, as noted by CTCS the surrogate shares some structural similarity but also contains (b) (4) while the (b) (4) leachables contain (b) (4).

- The alternate surrogates proposed by CTCS for (b) (4) are limited in available toxicity information. Both alternate surrogates show evidence of skin

¹⁰ Guidance for Industry Q3C Impurities: Residual Solvents <https://www.fda.gov/media/71736/download>

sensitization. The ECHA dossier for (b) (4) consists of summaries of preliminary, non-GLP, repeated-dose oral (dietary) toxicity study and a 14-week GLP inhalation (whole-body exposure) toxicity study in rat. Additional 3-month inhalation toxicity studies were conducted in rats and mice by NTP. The absence of toxicokinetic and/or ADME data for the (b) (4) (b) (4) surrogates following oral/dermal/inhalation exposure preclude any meaningful extrapolations to potential toxicity that may occur following intravenous exposure to the (b) (4) leachables.

- CTCS considers the (b) (4) impurity to be acceptable surrogates for the (b) (4). Although (b) (4) has been qualified as an impurity per ICH Q3B, there is limited toxicity information available to predict any potential toxicity associated with the (b) (4). In addition, there is considerable uncertainty using the (b) (4) impurity as surrogates for the (b) (4) given the structures of the (b) (4) cannot be adequately characterized due to technical feasibility issues. The characterization uncertainty for the (b) (4) also limits any toxicity information that can be derived from the (b) (4) alternate surrogates proposed by CTCS.

Summary and Conclusions

Overall, the weight of evidence provided by the applicant does not adequately qualify the leachables for safety. The 14-day toxicity study conducted in rats did not achieve clinically relevant leachables exposures. The read-across assessment provided by the Applicant did not contain adequate toxicity information on the identified surrogate compounds and is limited in regard to the (b) (4) given the structures of these adducts have not been adequately characterized (please see the drug product review by Dr. Shalini Anand in the Platform). Because of this, an additional non-clinical study in which adequate systemic exposures are achieved is the best approach to qualify the leachables for safety. Such a study could be designed by administering higher doses (volume) of the cefazolin when reconstituted in the rubber stopper enclosure system in rodents, stressing the stoppers in a way that would allow for a greater concentration of leachables within the reconstituted drug product, or by conducting a study in a larger species (e.g., dog). It is recommended that the Applicant submit a draft study protocol for review and comment prior to initiation of the nonclinical study. It is also recommended that the Applicant provide a leachables assessment plan and/or justification that the leachables in the drug product to be administered to the animals is qualitatively and quantitatively similar to the identified leachables described in Study Report TE190276.

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/s/

KELLY A BRANT
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NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number	211413
Priority or Standard	Standard
Submit Dates	12/21/2017 (original); 07/02/2019 (complete response)
Received Dates	same as above
PDUFA Goal Date	01/02/2020
Division/Office	Division of Anti-Infectives (DAI)
Review Completion Date	12/23/19
Established/Proper Name	Cefazolin for Injection USP
(Proposed) Trade Name	Cefazolin for Injection USP, 2 gm/vial
Pharmacologic Class	Cephalosporin antibacterial
Code name	N/A
Applicant	HQ Specialty Pharma Corp
Doseage form	Powder for Injection
Applicant proposed Dosing Regimen	• 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
Applicant Proposed Indication(s)/Population(s)	Perioperative prophylaxis/adult patients
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	N/A
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Perioperative prophylaxis/adult patients
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N/A
Recommended Dosing Regimen	• 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

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Reviewers of Multi-Disciplinary Review and Evaluation

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Clinical Reviewer	Alma Davidson, MD
Clinical Team Leader	Peter Kim, MD, MS
Cross-Disciplinary Team Leader	Erika Englund, PhD
Division Director (DAI)	Sumathi Nambiar, MD, MPH

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

NDA 211413 Multi-disciplinary Review and Evaluation
Cefazolin Powder for Injection

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Kelly Brant, PhD, MPH, DABT	OID/DAI	Sections: 5, 11	Select one: ☒ Authored ☐ Approved
	Signature: Kelly A. Brant -S Digitally signed by Kelly A. Brant -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kelly A. Brant -S, 0.9.2342.19200300.100.1.1=2001539497 Date: 2019.12.23 12:22:03 -05'00'			
Nonclinical Supervisor	Terry Miller, PhD	OID/DAI	Sections: 5, 11	Select one: ☐ Authored ☒ Approved
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Regulatory Project Manager	Jacquelyn Rosenberger, PharmD, RAC	ORO/DRO-ID	Section: 3	Select one: ☐ Authored ☒ Approved
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Chief, Regulatory Project Management Staff	Maureen Dillon- Parker, MS	ORO/DRO-ID	Section: 3	Select one: ☐ Authored ☒ Approved
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NDA 211413 Multi-disciplinary Review and Evaluation
Cefazolin Powder for Injection

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Alma Davidson, M.D.	OID/DAI	Sections: 1-3, 6-9, 11	Select one: ☒ Authored ☐ Approved
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Clinical Team Leader	Peter Kim, M.D., M.S.	OID/DAI	Sections: 1-3, 6-9, 11	Select one: ☐ Authored ☒ Approved
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OPQ Team Leader (acting)	Erika Englund, Ph.D.	OPQ/ONDP/DNDPI/NDPI/NDPB2	Sections: 1, 4	Select one: ☒ Authored ☒ Approved
	Signature: Erika E. Englund -S Digitally signed by Erika E. Englund -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000532787, cn=Erika E. Englund -S Date: 2019.12.23 10:40:55 -05'00'			
Division Director	Sumathi Nambiar, MD, MPH	OID/DAI	Section: 7	Select one: ☐ Authored ☒ Approved
	Signature: {See electronic signature page in DARRTS}			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information

NDA 211413 Multi-disciplinary Review and Evaluation
Cefazolin Powder for Injection

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

The proposed product is a single strength of cefazolin for injection (2g/vial) for the proposed indication of perioperative prophylaxis. The Applicant originally submitted this 505(b)(2) NDA for Cefazolin 2g/vial on December 21, 2017. The listed drugs (LDs) were Cefazolin for Injection USP and Dextrose Injection USP in Duplex Container (NDA 050779) and Ancef (NDA 050461). The NDA received a Complete Response (CR) Letter on October 19, 2018, and was resubmitted on July 2, 2019. The product description, indication, and LDs are the same as in the original NDA. Refer to the October 19, 2018 Division Director and Cross- Discipline Team Leader review by Drs. Sumathi Nambiar and Elsbeth Chikhale for additional details regarding the product background. No new clinical trials were conducted by the Applicant to support this submission.

In the original NDA, the Applicant proposed to administer the product intravenously as (b) (4) an infusion or as a bolus over 3- 5 minutes. In the October 19, 2018 CR letter, the Applicant was informed that (b) (4)

During the review of the original NDA, manufacturing process, biopharmaceutics, drug substance and quality microbiology reviewers recommended approval of the NDA. However, there were drug product deficiencies concerning the leachables/extractables study, unspecified impurities above the identification and qualification thresholds, and in-use stability data. These deficiencies were included in the October 19, 2018 CR letter. The Applicant submitted adequate responses to the deficiencies for the unspecified impurities and in-use stability data in the complete response; however, the drug product and pharmacology/toxicology reviewers identified deficiencies with the leachables study.

The same stopper is used as described in the original NDA (b) (4) rubber stopper). The Applicant performed a new leachables study, and identified leachables different from those described in the CMC and nonclinical reviews of the original NDA. Some of these new leachables were above the threshold for toxicological concern, but the characterization and qualification of these leachables was considered inadequate. Since the structures and quantities of some of the leachables could not be confirmed, the safety of these leachables could not be established. Refer to the deficiencies from the nonclinical and OPQ teams for further details.

1.1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 211413, the Applicant seeks approval of Cefazolin for Injection USP, 2 gm/vial for perioperative prophylaxis in adult patients. No new clinical trials were conducted by the Applicant to support this 505(b)(2) NDA. The Applicant is relying solely on the Agency's previous findings of safety and efficacy for the listed drug, BBraun's NDA 050779, for the indication of perioperative prophylaxis.

Cefazolin is a semi-synthetic, first generation cephalosporin antibacterial agent with *in vitro* activity against Gram-positive and a limited number of Gram-negative bacteria. It shares the same mechanism of action as other beta-lactam antibacterials, namely inhibition of cell wall biosynthesis mediated by binding to penicillin-binding proteins. Cefazolin was originally approved for use in the United States in 1973 under NDA 050461 (ANCEF®, GlaxoSmithKline). There are other approved indications for cefazolin for treatment of bacterial infections.

The most common adverse reactions associated with cefazolin are: gastrointestinal (nausea, vomiting, diarrhea), and allergic reactions (anaphylaxis, urticaria, skin rash).

In this submission, the Applicant has not provided adequate analysis or characterization information for the leachables that may be associated with the rubber stopper in the proposed commercial drug product container closure system. The structures, molecular weights and/or levels of the identified leachables cannot be confirmed based on the information submitted by the Applicant. In addition, the Applicant has not provided adequate information to qualify the identified leachables in their cefazolin drug product. The Applicant's safety qualification approach for leachables with levels (b) (4) mcg/day does not provide adequate information to characterize the toxicity of the identified leachables.

A complete response action will be taken based on the OPQ/CMC and Nonclinical Pharmacology/Toxicology assessments of the submitted information.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Surgical site infections (SSI) are serious complications and account for 21.8% of all nosocomial infections the United States. They cause significant morbidity, mortality, readmissions, and prolong the duration of hospitalization. - Perioperative antibacterial drug administration has been shown to decrease the incidence of SSI. The antibacterial drugs used for prophylaxis are site specific, but most commonly target Gram-positive cocci such as <i>Staphylococcus</i> spp. - Broader coverage and longer durations of therapy than are recommended have not been shown to reduce the incidence of SSI.	- Prophylaxis is indicated for procedures associated with high infection rates, e.g., those involving implantation of prosthetic material, and those in which the consequences of infection are serious. - The present IDSA guidelines recommend narrow-spectrum antibiotic therapy selected according to the surgery performed. - The administration of this antibiotic is to be limited to one dose or continued for less than 24 hours post-surgery.
Current Treatment Options	There are other approved antibacterial agents for perioperative prophylaxis including cefoxitin, cefuroxime, cefotetan, ceftriaxone, and ertapenem.	Cefazolin is a commonly used antibacterial drug for perioperative prophylaxis in the U.S.
Benefit	Cefazolin for perioperative prophylaxis can be effective in certain surgical patients in whom infection at the operative site would present serious risk (e.g., open-heart surgery and prosthetic arthroplasty).	Cephalosporins (such as cefazolin) are appropriate first line agents for most surgical procedures, targeting the most likely organisms while avoiding broad-spectrum antibacterial therapy that may lead to the development of antibacterial resistance.
Risk and Risk Management	The most common adverse reactions associated with cefazolin are gastrointestinal (nausea, vomiting, diarrhea), and allergic reactions (anaphylaxis, urticaria, skin rash).	- The safety profile of cefazolin is well-established through decades of use. - Most patients are treated with a single dose during the perioperative period.

2 Therapeutic Context

2.1. Analysis of Condition

Perioperative prophylactic use of antibacterial drugs following surgeries is a common practice in the U.S. and has been shown to reduce the incidence of surgical site infections. However, the organisms to be targeted for such prophylaxis are site specific, and most commonly Gram-positive cocci such as *Staphylococcus* spp. Broader coverage and coverage given for longer longer durations of time than recommended have not been shown to reduce the incidence of SSIs. The present IDSA guidelines recommend narrow-spectrum antibacterial therapy selected according to the surgery performed.

In addition, the administration of Cefazolin for Injection USP is to be limited to one dose or continued for less than 24 hours post-surgery.

2.2. Analysis of Current Treatment Options

There are other FDA approved antibacterial drugs for perioperative prophylaxis as listed in the following table:

Table 1: Summary of Treatment Armamentarium Relevant to Perioperative Prophylaxis Indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
Cefoxitin	Prophylaxis in patients undergoing uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, or cesarean section.	1978	Adults: 2 grams administered intravenously just prior to surgery (approximately one-half to one hour before the initial incision) followed by 2 grams every 6 hours after the first dose for no more than 24 hours. Pediatric Patients: 30 to 40 mg/kg doses may be given at the times designated above. Cesarean Section Patients: For patients undergoing cesarean section, either a single 2 gram dose administered IV as soon as the umbilical cord is clamped OR a 3-dose regimen	The most common adverse reactions have been local reactions (thrombophlebitis) following intravenous injection.	Use in adults and pediatric patients (3 months and older).

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			consisting of 2 grams given IV as soon as the umbilical cord is clamped followed by 2 grams 4 and 8 hours after the initial dose is recommended.		
Cefotaxime	Prophylaxis for surgical procedures (e.g., abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated.	1981	Single 1 gram IM or IV administered 30 to 90 minutes prior to start of surgery. Cesarean Section Patients: The first dose of 1 gram is administered IV as soon as the umbilical cord is clamped. The second and third doses should be given as 1 gram IV or IM at 6 and 12 hours after the first dose.	The most frequent adverse reactions (greater than 1%) are: Local (4.3%) - Injection site inflammation with IV administration. Pain, induration, and tenderness after IM injection. Systemic AEs: Hypersensitivity (2.4%) - Rash, pruritus, fever, eosinophilia. Gastrointestinal (1.4%) - Colitis, diarrhea, nausea, and vomiting.	Use in adults and pediatric patients (neonates, infants, and older).
Cefuroxime	For patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. For prevention of infection during open heart surgery.	1983	For preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5-gram dose administered IV just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg IV or IM every 8 hours when the procedure is prolonged. For preventive use during open heart surgery, a 1.5-gram dose administered IV at the induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.	The most common adverse effects have been local reactions following IV administration.	Use only in adult patients.
Ceftriaxone	For patients undergoing surgical procedures classified as contaminated or potentially contaminated (e.g., vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not	1984	Single 1 gm dose	Local reactions: pain, induration and tenderness was 1% overall. Phlebitis was reported in <1% after IV administration. Most common systemic reactions (incidence > 2% incidence): diarrhea, eosinophilia, thrombocytosis, leukopenia, and elevations of enzymes.	Use only in adult patients.

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	requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (eg, during coronary artery bypass surgery).				
Cefotetan	In surgical procedures classified as clean-contaminated or potentially contaminated (e.g., cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, gastrointestinal surgery).	1985	1 or 2 g I V , 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.	Most common adverse reactions (incidence > 1%): Gastrointestinal, including diarrhea. Hematologic abnormalities. Hepatic enzyme elevations; Hypersensitivity reactions.	Use only in adult patients.
Ertapenem	Prevention of surgical site infection following elective colorectal surgery.	2001	1 g Single intravenous dose given 1 hour prior to surgical incision	The most common adverse reactions (≥5%) in patients treated with ertapenem were diarrhea, nausea, headache and infused vein complication. In the prophylaxis indication the overall adverse experience profile was generally comparable to that observed with ertapenem in other clinical trials.	Use only in adult patients.

Reviewer's Comment: *There are alternative antibacterial drugs used empirically for perioperative prophylaxis particularly in patients who have an allergy to beta-lactam antibacterial drugs, as well as for MRSA coverage (i.e., vancomycin for injection).*

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The New Drug Application (NDA) 211413 was originally submitted on December 21, 2017 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the indication of perioperative prophylaxis in the adult population. The Applicant is relying solely on the Agency's previous findings of safety and efficacy for the listed drug, BBraun's NDA 050779, for the perioperative prophylaxis indication and not for the other approved indications of the listed drug.

On October 19, 2018, this application received a CR action because of nonclinical and product quality issues including leachables and impurities and insufficient information to support the safety of 2-gram cefazolin (b) (4).

On July 02, 2019, the Applicant submitted a complete response to the Agency's October 19, 2018 CR letter. In this submission, the Applicant submitted new information regarding product quality, removal of (b) (4) from the current proposed Cefazolin package insert and a clinical safety update.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Product Quality

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 (CR) 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.

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 the original NDA. Some of these new leachables were above the threshold for toxicological concern, but the characterization and qualification of these leachables is considered inadequate. For example, (b) (4) was identified in the extractables studies, but the analytical method could not detect (b) (4) in the leachables study samples. Therefore, the level of (b) (4) in the leachables study could not be confirmed. The structures of some of the other leachables

could not be confirmed. For example, the structures of (b) (4) could not be confirmed due to uncertainties about the retention times in the GC/MS results, and no comparative characterization data. Refer to the December 17, 2019 Integrated Quality Review in DARRTS for additional details regarding the deficiencies for the leachables/extractables studies. In addition, refer to the Pharmacology/Toxicology section of this review concerning the qualification of these leachables. This NDA is recommended for a CR action from a CMC perspective.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The original program assigned CAS numbers to both leachables that could not be found in the literature or databases. In the Applicant's response dated September 14, 2018, they confirmed that the program used in the leachables study erroneously provided the CAS numbers, and that both leachables do not have CAS numbers. In addition, no information was provided regarding the validity of the assigned structures of the leachables from this program. It was conveyed to the Applicant in the CR letter that in the absence of valid, reliable structures for the two leachables that exceed the safety qualification threshold of 5 mcg/day, the results obtained using the computational QSAR methodology and read across toxicology assessments with structurally similar compounds and hydrolysis products were of questionable utility. The Applicant was asked to provide: 1) additional characterization data to support the structures of two leachables that exceeded the safety qualification threshold of 5 mcg/day, and 2) conduct additional QSAR evaluation(s) and revised comprehensive toxicological assessment(s) to justify the safety of the identified compounds as needed.

After review of the Applicant's response to the CR letter, the Nonclinical Pharmacology/Toxicology team recommends a CR for the July 2, 2019 resubmission. The Applicant has not provided adequate information to qualify the identified leachables in their cefazolin drug product. The structures, molecular weights and/or levels of the identified leachables cannot be confirmed based on the information submitted by the Applicant. In addition, the Applicant's safety qualification approach for leachables > (b) (4) mcg/day does not provide adequate information to characterize the toxicity of the identified leachables. The Applicant is relying on computational toxicology methods (i.e., quantitative structure–activity relationship (QSAR) models) for general toxicity endpoints, which is not considered to be of sufficient quality on which to base a final regulatory decision regarding safety. The Applicant conducted no new toxicology studies and did not submit any published literature of nonclinical studies to qualify the safety of the identified leachables.

5.2. Review of NDA Resubmission/Response to CR Letter

The Applicant conducted a “new, more accurate extractables and leachables study” (E/L) in a new external lab (b) (4). The Applicant did not submit the requested information regarding the leachables analysis conducted previously by (b) (4) as the Applicant reported that analysis did not include a blank control matrix, used an unreliable identification system, and the potential impurities observed by (b) (4) were not observed in their new E/L study conducted by (b) (4). The Applicant states that (b) (4) performed a method suitability test (MST) to prove that the target compounds could be analyzed in the actual matrix solution at the relevant concentration level (Analytical Evaluation Threshold, AET). However, there were differences in the analytical methods used:

Table 2. Comparison of leachable strategy

Items	(b) (4)	
Lots	0001 D5 0002 D5 0003 D5	0001 D5
Position	Upright and inverted	Upright and inverted
Age Cefazolin for injection 2 g	Approx. 30 months 25°C (April 2019)	Approx. 24 months 25°C (August 2018)
Primary solution	2 g in 5 ml of WFI	2 g in 5 ml of WFI
In use conditions	4 h at 25°C*	24 h at 25°C** 10 days at 2-8°C**
Potential impurities/ Analytical method****	Volatile (HS-GC/MS) Semi-volatile (GC/MS) Non-volatile (HRAM-UPLC/MS) Elemental impurities (ICP-OES; ICP-MS)	Volatile(HS-GC/MS) Semi-volatile(HS-GC/MS) Non-volatile (LC-UV/MS) Elemental impurities (ICP MS) (b) (4)

*According to the new revised PI

**According to previous PI

***The analytical methods in use in the two laboratories are totally different and therefore not comparable.

Source: Applicant’s Table 1 in NDA 211413 SN0020: Reviewer’s Guide

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The new E/L study was conducted with 4h at 25°C in-use conditions whereas the in-use conditions from the previous study were 24h at 25°C and 10 days at 2-8°C.

Reviewer comment: The difference in analytical methods used and in-use conditions may contribute to the differences observed in leachables/potential impurities by (b) (4) and (b) (4). Per communication with CMC Reviewer (Dr. Shalini Anand), the Applicant in the current resubmission, has not provided sufficient information (raw data such as NMR spectra, mass, etc.) to ascertain any level of confidence in the identity of the provided structures.

Review of the E/L Study Findings: Eight substances were identified above the AET and evaluated in the toxicological risk assessment provided in Annex 5. The identified substances, maximum exposure levels, safety margins and Applicant calculated acceptable daily intake (ADI)s are presented in Tables 2 and 3 below:

Table 3. Identified substances to be toxicologically qualified

Substance	CAS/ID No.	Structure	FIT scr. class	Max µg/unit (Method) – (Batch No.)	MST reco-very	Max. exposure **
(b) (4)						

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Source: Applicant's Table 4 in NDA 211413 SN0020: 3.2.P.7 Annex 5

Table 4. Safety margins after maximal exposure

No.	Name	CAS No. /ID	Max. exposure µg/day *	Acceptable Intake (µg/day)	Safety margin
Individual substances					
(b) (4)					

Source: Applicant's Table 11 in NDA 211413 SN0020: 3.2.P.7 Annex 5

The Applicant provided a summary of the available literature to qualify Substance 1, (b) (4). For substances 2 through 8, the Applicant provided a revised comprehensive toxicological assessment based solely on QSAR evaluations (i.e., DEREK Nexus and MultiCASE) of the newly identified leachables. In addition, based on structural alerts for skin sensitization observed in the QSAR reports, a GLP local lymph node assay (LLNA) in mice was conducted on the (b) (4) (substances 2, 3 and 5). The Applicant concludes that the toxicological assessment on the eight substances demonstrate no safety concerns for the identified leachables.

Review of the Comprehensive Toxicological Risk Assessment:

- Characterization of the identified leachables
 - With the exception of (b) (4), CAS numbers were not provided for the leachables.
 - With the exception of retention time, Substance #6 has not been characterized.
 - Two of the leachables identified (Substances #2 and #3; (b) (4)) were assigned different ToxIDs by the Applicant but have the same structure. The Applicant notes these Substances could be possible isomers.
- General Toxicity. All of the identified substances exceed the safety threshold of 5 mcg/day. The risk assessment provided does not adequately qualify the identified substances for the following reasons:
 - For Substances Nos 2 through 8, the Applicant relied heavily on structural activity alerts from QSAR analysis (Derek™ and CASE Ultra™) to qualify the leachables. However, the Applicant has not provided all of the QSAR reports for review. Of note, there are no data for classification in ECHA Registered Substances or Classification & Labeling Databases or the published literature for

the structures provided, nor are the structures recognized by the ChemIDPlus TOXNET database¹.

Reviewer comment: Per communication with Marlene Kim and Lidiya Stavitskaya in the FDA computational toxicology consulting group (CDER Modeling & Simulation in the Office of Translational Sciences), QSAR assessments for general toxicity endpoints (i.e., respiratory/skin sensitization), hepatotoxicity, phototoxicity, hERG, etc.) are typically not of sufficient quality on which to base a final regulatory decision regarding the safety of the identified leachables. Therefore, the Applicant's use of these models to determine the safety of the identified leachables is not adequate to qualify their safety for these endpoints.

- o A semi-quantitative method was applied to calculate maximum exposure, considering a maximum daily dose (4 vials), method suitability test (MST)² correction (if applicable) or factor of 2 (if no MST was applied), which the Applicant indicates might overestimate exposure.
- o The ADIs calculated by the Applicant for the identified substances are of uncertain value:
 - For Substance No 1. (b) (4), the Applicant based the ADI on EPA's oral reference dose (RfD) of (b) (4) mcg/day for (b) (4)³. However, the Applicant did not make any adjustments to account for uncertainty(ies) associated with route-to-route extrapolation.
 - The ADI for Substances 2, 3 and 5 was based on negative findings from an LLNA sensitization assay conducted in mice. However, the Applicant did not submit the full LLNA study report for review.
 - For Substance No 4, the Applicant applied (b) (4) (b) (4) noting that PQRI PODP best practices recommendation provide a rationale that the qualification threshold for chemicals without known or suspect genotoxicity, sensitization, or irritation potential is (b) (4) mcg/day⁴. However, this approach is not considered to be valid given that there is no toxicity information to support the Applicants classification of (b) (4) (b) (4), a more recent PQRI approach has adopted a threshold level of (b) (4) mcg/day for (b) (4), and

¹ <https://chem.nlm.nih.gov/chemidplus/>

² Method suitability tests were prepared from the blank matrix (19-B0808) which was spiked with the respective target compounds for the particular method, followed by the same preparations and treatments as regular analytical samples.

⁴ Ball DJ Presentation on 'Threshold Establishment and rationale'. PQRI Workshop on Safety Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products, February 22-23, 2011, Bethesda, US

finally the Agency has not yet adopted the proposed PQRI thresholds of (b) (4) mcg/day.

- Substances Nos. 6, 7 and 8 contained fragments (b) (4). The Applicant conducted a comparative QSAR of Substance No. 8 against the API and noted that Derek Nexus demonstrated that less toxicity alerts were predicted for the (b) (4) and therefore a lower systemic toxicity profile is most likely. The Applicant therefore calculated a toxicological ADI of (b) (4) mcg/day (derived from a NOEL of (b) (4) mg/kg based on maternal toxicity in an oral rat teratology study)⁵. This approach and use of the calculated (b) (4) mcg/day ADI is not considered to be valid given that the Applicant did not fully characterize Substance No. 6 and there is no available toxicity information on Substance Nos. 6, 7, and 8 that supports the Applicant's comparative toxicological assessment against the API.
- Genotoxicity: The maximum exposure of Substance Nos. 4 and 6-8 are above the acceptable intake of 120 mcg/day as outlined in ICH M7. The Applicant states Substance No. 4 and Substance No. 8 both were predicted negative for bacterial mutagenicity by Derek™ and CASE Ultra™. However, full QSAR reports were not provided for review.

An Information Request (IR) was sent on July 23, 2019 asking the Applicant to provide additional characterization data for the leachables, the complete, comprehensive QSAR reports for results generated by CASE Ultra™ and Derek Nexus™ for leachable Substance Nos. 2 through 8 and the complete report for the LLNA mouse study conducted with the (b) (4). In addition, the Applicant was asked to provide any additional toxicity information they may have regarding the identified leachables, in particular for Substance Nos. 2 through 8 and was informed that if this information is not available, general toxicology studies will be needed for leachables that exceed the safety qualification threshold of 5 mcg/day, with additional genotoxicology studies for leachables that exceed 120 mcg/day.

In their response to the July 23, 2019 IR, the Applicant provided the requested final LLNA study report and QSAR reports and conducted additional QSAR analysis for the identified leachables that exceed 120 mcg/day. Not all of the QSAR analyses were conducted using the current versions of the software (e.g., some of the identified structures were run through QSAR models using Knowledge Base(s) from 2014). In addition, a QSAR analysis for Substance No. 6 was not conducted as the Applicant claims that Substance No. 6 is an isomer of Substance No. 7. A summary of the submitted QSAR reports can be found in Nonclinical Pharmacology/Toxicology Appendix.

⁵ CVMP Cefazolin Summary Report. EMAEA/MRL/0126/96-FINAL, July 1996.

Murine Local Lymph Node Assay with Pre-Screen- OECD 429/STOP-003-CNC

Key Study Findings

- No changes in clinical observations were observed in any of the test or control animals. The Stimulation Index in animals treated with (b) (4) concentration of the test article extracts were not significantly different when compared with control ((b) (4) (b) (4), respectively). The test article is not considered to be a sensitizing agent under the conditions of the assay.

GLP compliance: Yes

Test system: Mice (female CBA/J) were exposed to 25 µl of test article solution (extracts of Stopper (b) (4)), vehicle control (DMSO), or positive control (25% (w/v) Hexyl Cinnamic Aldehyde (HCA)) via topical application to the dorsum of both ears once daily for 3 days. On Day 6, animals were injected with ³[H]-methyl thymidine in PBS and proliferative response of draining auricular lymph nodes measured 5 hours post injection.

Study is Valid: Yes

Reviewer comment: The LLNA study was conducted as a follow-up to the structural skin sensitization alert from QSAR analysis of (b) (4) and (b) (4). In this study, DMSO extracts were obtained from a stopper other than the one proposed for their drug product (Stopper (b) (4) versus (b) (4), respectively). The study report claims an attempted targeted dose of (b) (4) mg/mL of combined (b) (4) and (b) (4) was administered to the animals. Based on the dose formulation analysis, the highest dose ('100%') of extract administered was (b) (4) mg/mL which contained (b) (4) mg/ml (b) (4) and (b) (4) mg/ml (b) (4) (roughly (b) (4) ng per animal).

No additional toxicity information on the identified leachables was provided. The Applicant also noted in their response to the Information Request that they consider Substance Nos. 6, 7, and 8 to be impurities/degradation products (b) (4) based on molecular structure and retention time and would therefore fall under ICH Q3B⁶. Per ICH Q3B, the qualification threshold for the cefazolin with maximum daily dose of 8g is 0.15%, or a total daily intake of (b) (4) mcg/day. The Applicant states that because the estimated intake of these substances is lower than the ICH Q3B qualification threshold, extra toxicological evaluation is not necessary.

Reviewer comment: Per communication with CMC, the 'degradation' products are not the neat degradation product of cefazolin (b) (4). As such, ICH Q3B would not apply to Substance Nos 6, 7, and 8.

In email correspondence dated July 25, 2019, the Applicant informed the Agency that other generic cefazolin drug products used rubber stoppers covered by the same DMF (DMF No.

⁶ <https://www.fda.gov/media/71733/download>

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(b) (4) as that for the current NDA. Given that DMF (b) (4) covers multiple rubber stoppers, and that the Applicant has not provided a Letter of Authorization for the referenced generic drug product holder(s), it cannot be confirmed that the rubber stoppers used in the referenced generic drug products are the same as those used in the current NDA submission.

Another IR was sent to the Applicant on September 24, 2019 seeking clarification on discrepancies noted in the identified leachables as listed in the cover letter versus the leachables identified in the various sections of the leachable screening report TE 1090276 (Table 23) (e.g., (b) (4) were identified in TE 1090276 but not included in the final summary list or comprehensive toxicological risk assessment). The IR also asked the Applicant to provide additional characterization data, the suitability of proposed analytical methodologies for the leachables testing, and comment on the accuracy of the reported maximum levels of various leachables detected in drug product stability samples.

In their response, the Applicant stated that the (b) (4) leachables were not included in the summary list because they are not potential leachables impurities having safety concerns. The Applicant estimates the maximum daily intake of (b) (4) to be (b) (4) mcg/day, respectively. The Applicant also included a toxicological evaluation of these two leachables in their response, noting the following:

- Maximum daily intake levels are below the proposed ADI of (b) (4) mcg/day for (b) (4) and (b) (4) mcg/day for (b) (4)
- QSAR analysis using Derek Nexus and CASE Ultra™ predicted the (b) (4) to be 'negative' for mutagenicity and 'non-sensitizing' and 'equivocal' for nephrotoxicity.

Reviewer comment: The Applicant provided accurate structures and CAS Nos. for the (b) (4). The Applicant did not provide the full QSAR reports and it is noted that the alert for nephrotoxicity is a rapid prototype alert derived using proprietary data set. The maximum daily intake for the (b) (4) was applied using the (b) (4), noting that because the application of Cefazolin for Injection is not lifetime the 'latest PQRI limit of (b) (4) mcg/day is considered too conservative'^{7,8}. The ADI for (b) (4) was calculated based on the systemic NOEL of (b) (4) mg/kg/day in a subcutaneous rat study⁹. Applying safety factors for rat-to-human extrapolation (F1=5), variability between individuals (F2=10), subchronic-to-chronic exposures (F3=5), no indications for severe reproductive & developmental toxicity (F4=1) and available NO(A)ELs (F5=1), a permissible daily exposure of (b) (4) mg/kg/day (eq. (b) (4) mg/day for 50 kg adult) was calculated. Based on the risk assessment provided and given the estimated maximum daily exposure of (b) (4) associated with Cefazolin for Injection use is at the 5 mcg/day safety threshold ((b) (4)

⁷ <http://pqri.org/wp-content/uploads/2018/04/2-PQRI-Paskiet-Final.pdf>

⁸ PDA J Pharm Sci and Tech, 67, 2013, 430-447

⁹ Misumi, J. and Nagano M. *Br J Ind Med* 41, 1984, 526-532.

mcg/day), (b) (4) is considered qualified and does not necessitate additional toxicological evaluation.

Per communication with the CMC Reviewer, the response to the IR does not contain adequate information to confirm the molecular weight and/or structure for some of the identified leachables. Given the lack of confidence in the identified structures and variability in levels of leachables detected across stability batches questioning the reliability of the estimated maximum exposure levels, a determination of which of the identified leachables need to be qualified by additional genotoxicity analysis and/or general toxicity study(ies) cannot be made at this time. Once the Applicant has addressed the deficiencies and the CMC review team has determined the leachables to be adequately characterized, the Applicant will be informed of the type(s) of toxicity studies needed to qualify the identified leachables.

6 Clinical Safety Update

This section only discusses the safety update provided in this submission. Refer to the clinical review of the original NDA submission, signed in DARRTS on September 6, 2018. The Applicant identified 62 papers in total, within Medline, Embase, Scopus, and International Pharmaceutical Abstracts from November 29, 2017 to June 30, 2019 that included information on the clinical use of Cefazolin with (or without) any adverse events. Of these 62 references, two papers were relevant for assessing the postmarketing safety of cefazolin.

1. Xu A, Hyman D, Lu LB. Cefazolin-Related Acute Interstitial Nephritis with Associated Nephrotic-Range Proteinuria: A Case Report. *Drug Saf Case Rep.* 2018 Apr 9;5(1):16.

This article describes a case of a 67-year-old male with history of well controlled type 2 diabetes mellitus and hypertension who developed acute interstitial nephritis (AIN) with nephrotic-range proteinuria during treatment with cefazolin for methicillin-sensitive *Staphylococcus aureus* and Group B Streptococcus (GBS) bacteremia. The patient received intravenous cefazolin 2 g every 8 h for 4 weeks prior to presentation to the emergency department with abdominal distension, nausea, and vomiting. Investigations revealed a serum ascites albumin gradient of 1.0 with a total protein of 1.8 g/dL suggestive of nephrotic syndrome, which was confirmed with a spot urine protein/creatinine ratio that estimated a loss of 7.95 g of protein per day. Serum creatinine was elevated compared with baseline. Urine studies showed sterile pyuria with 3+ protein and eosinophiluria. The patient was diagnosed with AIN with nephrotic-range proteinuria associated with cefazolin use. Cefazolin was discontinued and, within a couple of days, the patient's creatinine stabilized. He was discharged on prednisone 60 mg once a day for 10 days with a taper over 2 weeks for his AIN. The patient's creatinine and proteinuria slowly decreased over the next couple of weeks; however, neither lab parameter returned to baseline. A Naranjo assessment score of 6 was obtained, indicating a probable relationship between the patient's AIN with nephrotic-range proteinuria and his use of cefazolin.

Reviewer's Comment: Increase in BUN and creatinine levels and renal failure are known adverse reactions of cefazolin as with other cephalosporins. These adverse reactions are mentioned under the "Clinical Trials Experience" section of the cefazolin PI. However, acute interstitial nephritis with nephrotic-range proteinuria associated with cefazolin use is not specifically mentioned in the cefazolin label. The clinical reviewer recommends including this adverse reaction under the Postmarketing Experience subsection of the cefazolin PI. Additionally, the reviewer consulted OSE to search for AIN case reports in FAERS. The OSE review is pending and will be added as an addendum to this review.

2. Mota I, Gaspar Â, Morais-Almeida M. Perioperative Anaphylaxis Including Kounis Syndrome due to Selective Cefazolin Allergy. Int Arch Allergy Immunol. 2018;177(3):269-273.

The aim of this study was to describe a group of patients with immediate reactions to cefazolin, with proven selective hypersensitivity reactions. The authors performed a systematic review of all patients followed at onecenter with cefazolin-related reactions, between January 2012 and December 2016. All patients were investigated according to the European Network for Drug Allergy (ENDA) recommendations through skin testing (major and minor penicillin determinants, penicillin, amoxicillin, cefazolin, cefuroxime and ceftriaxone) and oral challenges tests. Seven patients were included (median age 40 years) with perioperative anaphylactic reactions immediately after cefazolin injection, 4 with hypotension and 1 with Kounis syndrome (KS) type. The presence of a selective IgE-mediated hypersensitivity through positive skin tests to cefazolin was noted in all patients. Two patients experienced systemic reactions during skin testing. Of note, the patients were able to tolerate administration of other beta-lactams. This may be explained by cefazolin's chemical structure which includes an R1 side-chain that is different from other beta-lactams.

Reviewer's Comment: Hypersensitivity and anaphylaxis are listed as adverse reactions in the cefazolin PI.

6.1.1. Conclusions and Recommendations

Acute interstitial nephritis will be added as an adverse reaction under the Postmarketing Experience subsection of the cefazolin PI, after the OPQ/CMC and Nonclinical Pharmacology/Toxicology deficiencies have been satisfactorily addressed. A complete response action will be taken for this 505(b)(2) application, NDA 211413, Cefazolin Powder for Injection, 2 gm per vial based on the OPQ/CMC and Nonclinical Pharmacology/Toxicology assessments of the submitted information.

7 DAI Division Director Comment

I concur with the review team's assessment and recommendations.

8 Appendices

8.1. References

- Dale W. Bratzler, E. Patchen Dellinger, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery: Am J Health-Syst Pharm. 2013; 70:195-283.
- Stijn Willem de Jonge, Sarah L. Gans, Jasper J. Atema, et al. Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection: A systematic review and meta-analysis. Medicine (Baltimore) 2017 Jul; 96(29): e6903.

8.2. Financial Disclosure

No financial disclosure report was provided by the Applicant because no clinical studies were conducted for this application.

8.3. Nonclinical Pharmacology/Toxicology

Substance	Max Exposure (mcg/d)	QSAR Model	Findings
(b) (4)			

¹⁰ Possible isomers

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/s/

JACQUELYN C ROSENBERGER
12/23/2019 02:18:21 PM

SUMATHI NAMBIAR
12/26/2019 11:43:47 AM

Clinical Review of Applicant's Response to CR letter

NDA: 211413

Sequence 0020

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

Applicant: HQ Specialty Pharma Corporation

Date of Submission: July 2, 2019

Re: Complete Response (CR)

Background:

On October 19, 2018, the FDA sent a CR letter to the Applicant after review of NDA 211413, a 505(b)(2) application for Cefazolin for Injection USP, 2 g/vial for perioperative prophylaxis indication. In that letter, the FDA described the reasons for this action and recommendations to address these issues below:

Clinical

1. You have not provided adequate information to support the safety of 2-gram cefazolin

(b) (4)

Applicant's Response (verbatim):

HQSP has removed (b) (4) from the current proposed package insert. Please refer to Module 1.14.1.3.

Reviewer's Comment: *We acknowledge the Applicant's response. The Applicant has updated the proposed Cefazolin for Injection USP, 2g / vial PI with the removal (b) (4). With regard to the Safety update, the adequacy of the submitted safety information will be determined during review of the NDA resubmission.*

Nonclinical and Product Quality

Leachables and Impurities (The reader is referred to the Applicant's response in the CR letter.)

Reviewer's Comment: The clinical reviewer defers to the OPQ and Pharmacology/Toxicology reviewers for the acceptability of the Applicant's response to their deficiency related issues.

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/s/

ALMA C DAVIDSON
07/09/2019 06:41:48 PM

PETER W KIM
07/09/2019 10:32:08 PM

Division Director and Cross-Discipline Team Leader (CDTL) Review

Date	October 18, 2018
From	Sumathi Nambiar, MD, MPH Director, Division of Anti-Infective Products (DAIP) and Elsbeth Chikhale, Ph.D. Biopharmaceutics Team Lead (Acting)/CDTL, Division of Biopharmaceutics, ONDP, OPQ
Subject	Division Director and CDTL Review
NDA	NDA 211413
Type of Submission	NDA
Applicant	HQ Specialty Pharma
Date of Submission	December 21, 2017
PDUFA Goal Date	October 21, 2018
Proprietary Name / Established (USAN) names	Cefazolin for Injection, USP
Dosage forms / Strength	Powder for Injection / 2 gram per vial
Proposed Indication(s)	Perioperative prophylaxis
Regulatory Action	COMPLETE RESPONSE

This DD/CDTL review is based, on the following primary reviews/memos:

DICIPLINE	PRIMARY REVIEWER
Pharmacology/Toxicology	Terry Miller, Ph.D.
Quality Drug Substance	Gene Holbert, Ph.D.
Quality Drug Product	Erika Englund, Ph.D.
Quality Process	Ying Wang, Ph.D.
Quality Facility	Ying Wang, Ph.D.
Quality Microbiology	Koushik Paul, Ph.D.
Quality Biopharmaceutics	Mei Ou, Ph.D.
Quality Overall Summary	Chunchun Zhang, Ph.D.
Clinical Pharmacology	Cristina Miglis, PharmD.
Clinical	Alma Davidson, M.D.
Division of Pharmacovigilance II	Ronald Wassel, PharmD.
Clinical Microbiology	Jalal Sheikh, Ph.D.
Office of Prescription Drug Promotion (OPDP)	David Foss, Pharm.D.
Division of Pediatric and Maternal Health Review	Catherine Roca, M.D.
Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology (OSE)	Deborah Myers, RPh., MBA
Regulatory Project Manager	Jacquelyn Rosenberger, RPh, PharmD

Division Director and Cross Discipline Team Leader Review

1. Introduction

The Applicant submitted this 505(b)(2) NDA for Cefazolin 2 gm/vial on December 21, 2017. The listed drugs (LDs) are Cefazoline for Injection USP and Dextrose Injection USP in Duplex® Container (NDA 050779) and Ancef® (NDA 050461) (see Table 1 for comparison). No clinical trials were conducted by the Applicant to support this NDA. The Applicant intends 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. (b) (4)

(b) (4). The Applicant requested a waiver of the requirement to provide evidence of in vivo bioequivalence of the proposed Cefazolin 2 gm drug product relative to the list drugs.

2. Background

Cefazolin was first approved by the FDA and marketed in the US in 1973 by GlaxoSmithKline (GSK) under the trade name Ancef (NDA 050461). Ancef has been marketed in the strengths of 250 mg/vial, 500 mg/vial, 1 g/vial, 5 g/vial and 10 g/vial. The products are not currently marketed and are listed as discontinued in the Orange Book. Currently, cefazolin is marketed in the US by B Braun Medical Inc. and was approved in the United States under NDA 050779 on July 27, 2000, and has similar indications as Ancef, including peri-operative prophylaxis, although there are some differences in the indicated covered pathogens.

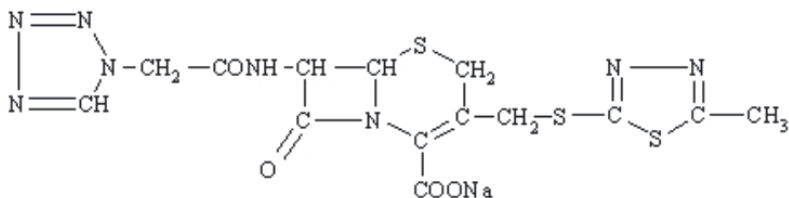
Cefazolin is a semi-synthetic, first generation cephalosporin antibacterial agent with *in vitro* activity against Gram-positive and a limited number of Gram-negative bacteria. It shares the same mechanism of action as other beta-lactam antibacterial drugs, namely inhibition of cell wall biosynthesis mediated by binding to penicillin-binding proteins. Predominant mechanisms of bacterial resistance to cephalosporins include the presence of extended-spectrum beta-lactamases and enzymatic hydrolysis. Cefazolin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections including Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*), and Gram-negative bacteria (*Escherichia coli*, and *Proteus mirabilis*).

3. Product Quality

Drug Substance:

Cefazolin for Injection USP is a semi-synthetic cephalosporin for parenteral administration. It is the 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]oct-2-ene-2-carboxylic acid.

Structure of Cefazolin:



Molecular weight: 476.5

Empirical Formula: C₁₄H₁₃N₈NaO₄S₃

The chemistry manufacturing and controls information for cefazolin drug substance has been provided via reference to DMF (b) (4) which was found adequate by Gene Holbert on July 18, 2018.

Drug Product:

The drug product is provided in a 20 mL (b) (4) clear glass vial with 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 one of the proposed (b) (4) diluents. No excipient is used in the drug product formulation. Two leachable compounds exceed the safety concern threshold (SCT) of 1.5 mcg/day. Reference is made to the nonclinical review by Dr. Terry Miller. The stopper is not acceptable for commercial use from a CMC perspective since the safety of the leachables is not acceptable from a nonclinical perspective. A shelf life of (b) (4) months when stored at room temperature is granted. 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) (b) (4) a diluent while the unspecified impurities were out of specification for most of the other diluents. Several information requests were sent to the Applicant and one teleconference was held with the Applicant on August 03, 2018 to discuss this issue. However, the information received to support the stability of the product in the labeled diluents has been inadequate. For full details refer to the Drug Product reviews by Dr. Erika Englund dated September 08 and 24, 2018 in Panorama.

Drug Product Manufacturing Process:

The proposed drug product manufacturing process is (b) (4). The overall information regarding the sterility assurance provided in the NDA submission and subsequent amendments was found to be acceptable.

Microbiology:

(b) (4) drug substances and the sterile (b) (4) drug product are manufactured (b) (4) in Italy. (b) (4). Based on the information provided, the reviewer has concluded that the Applicant has provided satisfactory summary of the (b) (4) validation data to support the (b) (4) manufacturing process for the drug product. The NDA is recommended for approval from a sterility assurance standpoint per the review by Koushik Paul, Ph.D. dated July 24, 2018.

Biopharmaceutics:

The Applicant requested a waiver for the requirement to provide evidence of in vivo bioequivalence of the proposed cefazolin powder for injection relative to the listed drugs. The Biopharmaceutics review focuses on the evaluation of the bridge between the proposed drug product and the listed drug products/reference standard (RS). A comparison between the proposed drug product and the LDs/RS is summarized in the following table:

	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 SmithKline Beecham d/b/a GSK, approved on 10/04/1973, NDA withdrawn, FR effective May 2009	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	Duplex Container: 1 g/vial with 50 mL of 4.0% Dextrose; 2 g/vial with 50 mL of 3.0% Dextrose	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/ Diluent	2 g Cefazolin Sodium powder (b) (4) diluent per labeling instructions	Drug Chamber: 1 g or 2 g Cefazolin Sodium powder Diluent Chamber: 3% or 4% Dextrose solution	1 g Cefazolin Sodium Powder Use a variety of diluents per labeling instructions	500 mg or 1 g Cefazolin Sodium powder Use a variety of diluents per labeling instructions
Excipients	None	None	None	None
Solution Concentration (calculated by this reviewer based on labeling)	(b) (4)	Not for bolus injection	For IV (bolus) injection (3-5 min): (b) (4)	For IV (bolus) injection (3-5 min): (b) (4)

	For IV infusion (no specific time): (b) (4)	For IV infusion (30 min):	For IV infusion (no specific time):	For IV infusion (no specific time): (b) (4) (b) (4)
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.

The Applicant has provided acceptable comparative pH and osmolality data on the reconstituted/diluted solutions between the proposed drug product and LD#1 and RS. Since LD#2 is discontinued, the pH and osmolality measurements on the RS were provided instead. This approach was found acceptable. Per 21 CFR 320.24(b)(6), the in vitro bridging is established between the proposed product and the list drug products (NDA 50779 and NDA 50461) for IV infusion (1-2 gram) (b) (4)). From a Biopharmaceutics perspective, NDA 211413 was recommended for approval when administered by IV infusion (1-2 gram) (b) (4). For full details refer to the Biopharmaceutics review by Dr. Mei Ou dated 8/28/2018 in Panorama.

Manufacturing Facilities Review/Inspection:

All the facilities are acceptable based on profiles. No pre-approval inspection is required during this review cycle. Therefore, the overall recommendation of “Approve” was entered for the NDA into Panorama by the Office of Process and Facilities (OPF) on 2/1/2018.

Product Quality overall recommendation: Due to the outstanding drug product deficiencies, from the product quality perspective, NDA 211413 for cefazolin powder for Injection is recommended for **Complete Response (CR)**. For full details refer to the Intergrated Quality Assessment (IQA) review by Dr. Chunchun Zhang dated 9/11/2018 in Panorama. The CR comments are listed at the end of this review.

4. Nonclinical Pharmacology/Toxicology

The Applicant did not submit any new relevant pharmacology / toxicology information in the NDA. The Applicant submitted the final report for the leachable study on July 3, 2018, containing the table of detected leachables below (Table 14 2-4 from the submission).

Table 14.2-4
Semi-Volatile organic leachables: PH-18-010454 (Reverse storage)

			Test A	Test B	Test C
Id. level	Semi-volatile compounds	CAS	µg/vial	µg/vial	µg/vial
(b) (4)					

Considering the proposed maximum recommended human dose for Cefazolin for Injection for perioperative prophylaxis is 2 vials, up to 4 g/day (1 g, 4x daily), two of the leachables (b) (4) detected in their product were found to exceed the safety concern threshold (SCT) of 5 mcg/day originally established by PQRI (Product Quality Research Institute). The Applicant has not provided sufficient safety qualification data on two leachable compounds (presumed originating from the rubber stopper); and insufficient data on three recently identified impurities detected in the in-use stability studies to be above the identification and qualification thresholds, for which no identification or qualification data have been submitted. The Applicant has since modified their drug product specifications to include these three unqualified impurities. The Pharmacology/Toxicology Review concludes that, while the Applicant's approach to determine the genotoxic potential and systemic toxicity profile for the two leachables appears appropriate, there is an underlying concern for the validity of the original structures of both leachables identified by the LabAnalysis Software used by the Applicant. The software determined both the structure and associated CAS# for the leachables, however because the CAS# was later identified to be incorrect, there is uncertainty that the associated structures were correctly identified by the Applicant. Since the QSAR and read-across approaches in toxicology risk assessment is based entirely on the similarities to the proposed structure of the leachable, the lack of certainty of the structure would diminish the interpretability and utility of the risk assessment findings. The Pharmacology/Toxicology review dated October 15, 2018 by Dr. Terry Miller, recommends a Complete Response for NDA 211413.

5. Clinical Pharmacology

Because no new Clinical Pharmacology information was submitted to support this application, the review focused on the labeling recommendations from the Clinical Pharmacology

perspective. The application is acceptable from a Clinical Pharmacology perspective pending labeling revisions. For full details refer to the Clinical Pharmacology review by Cristina Miglis, PharmD, dated August 29, 2018, in DARRTS.

6. Clinical/Statistical – Efficacy and Safety

No new safety or efficacy studies were submitted to support this application. The Applicant provided a safety review of the literature for cefazolin. According to the Applicant, they contracted (b) (4), a global research firm to perform the safety review of the literature. (b) (4) identified 30 papers in total of which eleven were considered by the Applicant's evaluator to be of highest relevance. The reported adverse events in the above articles are listed in the cefazolin label except serum-sickness-like reaction (SSLR) associated with cefazolin. It is notable that serum sickness reaction is mentioned in other cephalosporin package inserts including ceftriaxone, cefuroxime axetil, and cefdinir. Dr. Alma Davidson, Clinical Reviewer, recommends that SSLR be mentioned under a Postmarketing section for this product.

Based on the literature reviewed, cefazolin 2 g appears to be used for surgical prophylaxis. Dosing is commonly a single dose at an appropriate point in the procedure (preoperative period, anesthesia induction, etc.). (b) (4)
(b) (4)

Given that the Applicant's proposed dosing of 500 mg to 1- 2 gm IV as an infusion over approximately 30 minutes is noted in the label for Cefazolin for Injection USP and Dextrose Injection USP in Duplex® Container, NDA 50779, (b) (4)

Because the Applicant has not provided a comprehensive toxicological risk assessment (i.e., local toxicity, systemic toxicity, mutagenicity, carcinogenicity, reproductive toxicity, etc.) for any leachable that exceeds a daily total intake limit of (b) (4) mcg/day, at this time, the Clinical Reviewer recommends a complete response.

7. Clinical Microbiology

No new clinical microbiology data were submitted to the NDA. The Microbiology section (12.4) of the Package Insert has been updated by the Applicant in accordance with the FDA guidance document and the 21st Century Cures Act.

The application is recommended for approval pending acceptance of labeling changes to the MICROBIOLOGY subsection of the Package Insert. For full details, refer to the Clinical Microbiology review by Dr. Jalal Sheikh, dated September 12, 2018.

8. Advisory Committee Meeting

This NDA was not discussed at an Advisory Committee meeting as there were no issues that needed input from the committee.

9. Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. In Pre-NDA meeting minutes dated, August 26, 2016, DAIP noted that HQ Pharma's proposal for cefazolin 2-gram dose would not trigger PREA. (b) (4)

This information will be included in the CR letter. Please see addendum by Dr. Alma Davidson in DARRTS dated October 17, 2018.

10. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI). There are no other relevant regulatory issues with this application.

11. Labeling:

As the NDA will be receiving a complete response, labeling recommendations will be discussed during the next review cycle.

12. Recommendations

A complete response action will be taken for NDA 211413, Cefazolin Powder for Injection, 2 gm per vial. The following deficiencies will be conveyed to the Applicant in the CR letter:

CLINICAL

1. You have not provided adequate information to support the safety of 2-gram cefazolin (b) (4)

NONCLINICAL and PRODUCT QUALITY

Leachables

2. You have not provided adequate support for the assigned structures of the leachables. The original program assigned CAS numbers to both leachables that could not be found in the literature or databases. In your response dated September 14, 2018, you confirmed that the program used in the leachables study erroneously provided the CAS numbers, and that both leachables do not have CAS numbers. Also, no information was provided regarding the validity of the assigned structures of the leachables from this program. Since neither of these leachables are identified in the literature, it is not clear how the structures of these leachables were assigned.

In the absence of valid, reliable structures for the two leachables that exceed the safety qualification threshold of 5 mcg/day, the results obtained using the computational QSAR methodology and read across toxicology assessments with structurally similar compounds and hydrolysis products are of questionable utility.

Information needed to resolve the deficiency

- Additional characterization data should be submitted to support the structures of these leachables. Refer to USP <1663> and USP <1664>.
 - Once you have provided additional characterization data to support the proposed structures of these two leachables or have included revised structures with greater structural certainty, conduct additional QSAR evaluation(s) and revised comprehensive toxicological assessment(s) to justify the safety of these identified compounds as needed.
3. The acceptability of the proposed stopper cannot be determined until the identity of the leachables has been established, and the safety profile of the leachables is considered acceptable from a nonclinical perspective.

Impurities

4. The drug product specifications provided in the September 14, 2018 amendment, with the unspecified impurities (RRT (b) (4)) above the identification and qualification thresholds, are inadequate. The referenced ANDA Guidance is not applicable to this NDA.

Information needed to resolve the deficiency

- Qualification data should be submitted for all impurities above the qualification threshold.
 - Additional nonclinical studies may be needed to qualify any impurities that exceed the safety qualification threshold described in ICH Guidance Q3B(R2) 'Impurities in New Drug Products'.¹
5. No characterization data or descriptions 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, as the impurities are above the identification threshold.

Information needed to resolve the deficiency

- 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 three specified unidentified impurities, but the method was not validated for the measurement of these unspecified impurities.

Information needed to resolve the deficiency

- The analytical methods should be validated for the measurement of the specified impurities in the drug product specifications.

¹

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf>

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/s/

SUMATHI NAMBIAR
10/19/2018

Addendum Clinical Review

NDA 211413 Cefazolin for Injection USP, 2 gm/vial

Re: Cefazolin for Injection, 2gm/vial I.V. (b) (4) injection and PREA requirement

In Pre-NDA meeting minutes dated, 8/26/16, DAIP noted that HQ Pharma's presentation of cefazolin powder in a 2-gram vial would not trigger PREA. Though HQ Pharma is not specifically seeking an indication for pediatric patients for perioperative prophylaxis, based on further consideration, DAIP notes that the proposed drug product would trigger PREA.

NDA 211413, cefazolin powder in 2-gram vials from HQ Pharma, relies on two reference listed drugs: Ancef® (NDA 50461) and 2 g Cefazolin for Injection USP and Dextrose Injection USP in Duplex Container (NDA 50779). Ancef® is no longer marketed and was provided as 250 mg, 500 mg, and 1-gram base/vial. Its labeling included the indication for perioperative prophylaxis with no age restrictions, and the option for direct intravenous (bolus) injection over 3-5 minutes.

The Ancef® label included pediatric dosing recommendations down to 4.5 kilograms, and noted that, "... Since safety for use in premature infants and in neonates has not been established, the use of Ancef® in these patients is not recommended..." Based on this information, one could infer that up to a 1-gram direct intravenous (bolus) injection was approved for use in pediatric patients for perioperative prophylaxis, if so indicated based on the weight of the pediatric patient.

Cefazolin for Injection USP and Dextrose Injection USP in Duplex Container 1-gram and 2-grams base/vial (NDA 50779) includes the indication for perioperative prophylaxis. It is labeled for intravenous administration over approximately 30 minutes, that is, it is not labeled for direct intravenous (bolus) injection over 3-5 minutes. Additionally, the label notes that, "...The 2 grams dose of Cefazolin for Injection USP and Dextrose Injection USP is not recommended for use in pediatric patients...", and, "...Only administer 1-gram Cefazolin for Injection USP and Dextrose Injection USP to pediatric patients where the individual dose is the entire contents of the 1g DUPLEX container and not any fraction of it..."

(b) (4)

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/s/

ALMA C DAVIDSON
10/17/2018

PETER W KIM
10/17/2018

Memo to the Division File

NDA 211413, Submitted 12/21/2017

Cefazolin for Injection USP, 2g/vial (HQ Specialty Pharma Corp.)

From: Terry J. Miller, Ph.D., Pharmacology/Toxicology Reviewer/Supervisor, DAIP

Through: Jacquelyn Rosenberger, RPh, PharmD

Subject: Complete Response Recommendation

Date: 10/1/2018

Review Recommendation:

The current NDA is recommended for a Complete Response from a pharmacology/toxicology perspective. The Applicant has not provided the sufficient safety qualification data on two leachable compounds (presumed originating from the rubber stopper); and insufficient data on three recently identified impurities detected in the in-use stability studies to be above the identification and qualification thresholds, for which no identification or qualification data have been submitted. The Applicant has since modified their drug product specifications to include these three unqualified impurities. The CMC reviewer, Dr. Erika Englund, is similarly recommending a Complete Response for this NDA. Please see the drug product review by Dr. Erika Englund in the Platform for additional information on these deficiencies from a chemistry perspective.

In agreement with Dr. Englund and the CMC review team, I support sending the Applicant the following combined pharmacology/toxicology (in bold) and CMC deficiencies (as described by Dr. Englund in her latest NDA review – amendment to Review #1 submitted to the Platform) to be addressed in their NDA **resubmission**.

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. ***There is a general uncertainty on the accuracy of the structures proposed for the two leachables in question. In the absence of valid, reliable structures for***

the two leachables requiring safety qualification, the results obtained using the computational QSAR methodology and read across toxicology assessments with structurally similar compounds and hydrolysis products are of questionable value and utility. Once you have provided additional characterization data to support the proposed structures of these two leachables or have included revised structures with greater structural certainty, plan to conduct additional QSAR evaluation(s) and revised comprehensive toxicological assessment(s) as needed.

3. The 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.
4. The drug product specifications in the 09/14/2018 amendment, with the unspecified impurities above the identification and qualification thresholds, are considered inadequate. The in-use stability data will be evaluated during the next review cycle after the drug product specification deficiency is addressed.
5. The proposed drug product specifications are not considered acceptable because three of the impurities (RRT (b) (4)) are above the identification and qualification thresholds. We do not agree that the referenced ANDA Guidance is applicable to this NDA product. Qualification data should be submitted for all impurities above the qualification threshold.
6. No characterization data or descriptions 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.
7. 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. This is not adequate. The analytical methods should be validated for the measurement of the specified impurities in the drug product specifications.
8. ***Additional nonclinical studies may be needed to qualify any impurities that exceed the safety qualification threshold described in ICH Guidance Q3B(R2) 'Impurities in New Drug Products'.¹***

¹ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf>

Background:

The Applicant, HQ Specialty Pharma Corp., submitted a 505(b)(2) NDA requesting marketing approval to license Cefazolin for Injection USP, 2g/vial. The proposed drug product is intended to be a copy of the reference listed drug [RLD] Cefazolin for Injection USP (B. Braun Medical, Inc; NDA#: 050779); with identical active ingredients, excipients, concentration, dosage form, and route of administration. For this product, HQ Specialty Pharma is seeking only the indication of perioperative prophylaxis (1 to 2 g IV prior to surgery, 500 mg to 1 g IV during surgery, 500 mg to 1 g IV every 6-8 hours for 24 hours postoperatively, and continued prophylactic administration up to 3-5 days following completion of surgery as needed). The Applicant is not seeking any of the treatment indications approved for the RLD, B.Braun, Cefazolin for Injection product.

Cefazolin for Injection, USP 2 g/vial container closure system consists of a (b) (4) clear glass vial (MF# (b) (4)) and a rubber stopper (MF# (b) (4)). An aluminum/plastic flip off overseal is placed on top of the rubber stopper.

The Applicant provided Letters of Authorization (LOA) (b) (4) (b) (4) (b) (4) for specific information on their rubber stopper (b) (4) (b) (4).

The Applicant did not submit any new relevant pharmacology / toxicology information for review in their original 505(b)(2) NDA. No pharmacology/toxicology information was reviewed in full to support this 505(b)(2) NDA. The labeling for the relevant pharmacology/toxicology sections submitted in the original NDA were modified to be compliant with Physician Labeling Rule (PLR), including Pregnancy Lactation Labeling Rule (PLLR). In addition, the reviewer updated Section 13.1 **Carcinogenesis, Mutagenesis, Impairment of Fertility** with fertility study data from the published literature.

In my conversation with the CMC reviewer, Dr. Englund informed me of at least 3 unidentified drug product impurities (and specified limits), RRT (b) (4) (b) (4) in their Cefazolin for Injection in-use solution. Dr. Englund determined these impurities exceeded identification and qualification thresholds described in ICH Guidance Q3B(R2) and likely were novel to this product, stating also that the Applicant's justification for the limits of the unspecified impurities "are not adequate". Dr. Englund provided her comments regarding these unidentified and unqualified impurities in the list of comments above. The presence of unidentified and unqualified impurities in the drug product is similarly unacceptable from a

pharmacology/toxicology perspective. As mentioned in the comments to the Applicant above, the Applicant may need to submit qualification data for any new impurities not in the RLD, or for all impurities above the qualification threshold. Note that the qualification threshold for cefazolin is 0.15%, since the dose exceeds 2 grams a day.

(Reviewer Comment: A comment will be sent to inform the Applicant that additional nonclinical studies may be needed to qualify any impurities that exceed the safety qualification threshold described in ICH Guidance Q3B(R2) 'Impurities in New Drug Products'.)

At the Pre-NDA meeting (8/26/2017) with HQ Pharma, the Applicant was recommended to include a leachable/extractable study with their drug product in their NDA submission. Additional information requests (IR) from the review team were later sent to the Applicant requesting completion and providing guidance on the recommended leachable/extractable study, including after the initial NDA submission (3/12/2018), after receipt of the draft leachable study protocol (4/30/3028), and after receipt of the final leachable study protocol (5/11/2018). On July 3, 2018, the Applicant submitted the final report for the leachable study, containing the table of detected leachables below (Table 14 2-4 from their briefing document).

*Table 14.2-4
Semi-Volatile organic leachables: PH-18-010454 (Reverse storage)*

			Test A	Test B	Test C
Id. level	Semi-volatile compounds	CAS	µg/vial	µg/vial	µg/vial
(b) (4)					

Considering the proposed maximum recommended human dose for Cefazolin for Injection for perioperative prophylaxis is 2 vials, up to 4 g/day (1 g, 4x daily), two of the leachables (b) (4)

(b) (4) detected in their product were found to exceed the safety concern threshold (SCT) of 5 mcg/day originally established by PQRI (Product Quality Research Institute) and adopted by the OND review divisions for leachables detected in parenteral products.²

² Paskiet D., Janke D., Ball D., et. al. Extractables Working Group Initiatives for Parenteral and The Product Quality Research Institute (PQRI) Leachables and Ophthalmic Drug Product (PODP). *PDA J Pharm Sci and Tech* 2013, 67 430-447

(Reviewer's Comment: The CDER/OND "best practices" approach to leachables and extractables were extrapolated from the PQRI recommendations for parenteral products. PQRI Leachables and Extractables Working Groups is a collaboration of chemists and toxicologists from the US FDA, industry, and academia).

It was concluded that additional safety qualification assessment would likely be needed to support the safety of the two identified leachables from the container closure system. An IR was sent to the Applicant on 7/24/2018 requesting additional toxicological safety assessments for these two leachables exceeding the SCT of 5 mcg/day. In response to our IR, the Applicant responded that only one leachable exceeded a SCT of (b) (4) mcg/day, (b) (4)

(b) (4) In the follow-up T-con with the Applicant (8/3/2018), the CMC/PharmTox reviewers discussed with the Applicant the noted deficiencies in impurities and leachable study. *(In the telephone conversation, it was noted that all but two of the regulatory and scientific personnel were absent from the meeting, citing a 6 week vacation as the reason).* The Division later provided a follow-up IR to the Applicant after the T-Con to reinforce the discussion on the need for a comprehensive toxicological risk assessment for these two leachables detected in their product, and provided the relevant ICH guidances and PQRI publication previously referenced.

The Applicant provided a limited computational toxicology QSAR assessment for genetic toxicology data on two leachables (with identified CAS numbers) on 8/8/2018 and the Applicant was immediately informed a more comprehensive risk assessment including local and systemic toxicity, mutagenicity, and reproductive toxicity of the leachables would be needed. Also, the Applicant was asked to confirm the CAS#s for the leachables as the CAS#s could not be located by CMC and pharm/tox reviewers in the literature or databases. In response to our IR the Applicant later replied "HQSP confirms that there was an error in the CAS # provided by the software used by (b) (4) for the leachables studies. There is no CAS for the two leachables proposed." The Applicant submitted the final report for the requested toxicology risk assessment for the two leachables on 09/14/2018 (5 weeks before the PDUFA action date of 10/21/2018). Unable to find the structures and CAS#s identified by their software package (b) (4) 2018), the Applicant used the following appropriate risk assessment approaches:

- 1) Prediction methods applied for genotoxic assessment according the ICH M7 Guidance (2017) for impurities in pharmaceutical, including a computational QSAR analysis (Derek™ and Case Ultra™ software);

- 2) A “read-across” approach involving a search of the published toxicological literature including public toxicology databases on compounds with similar chemical structures and potential hydrolysis products of the proposed structure.

The Applicant determined the following conclusions on the genotoxic potential and systemic toxicity profile of these two leachables in their toxicological assessments:

1.  (b) (4)
2. 

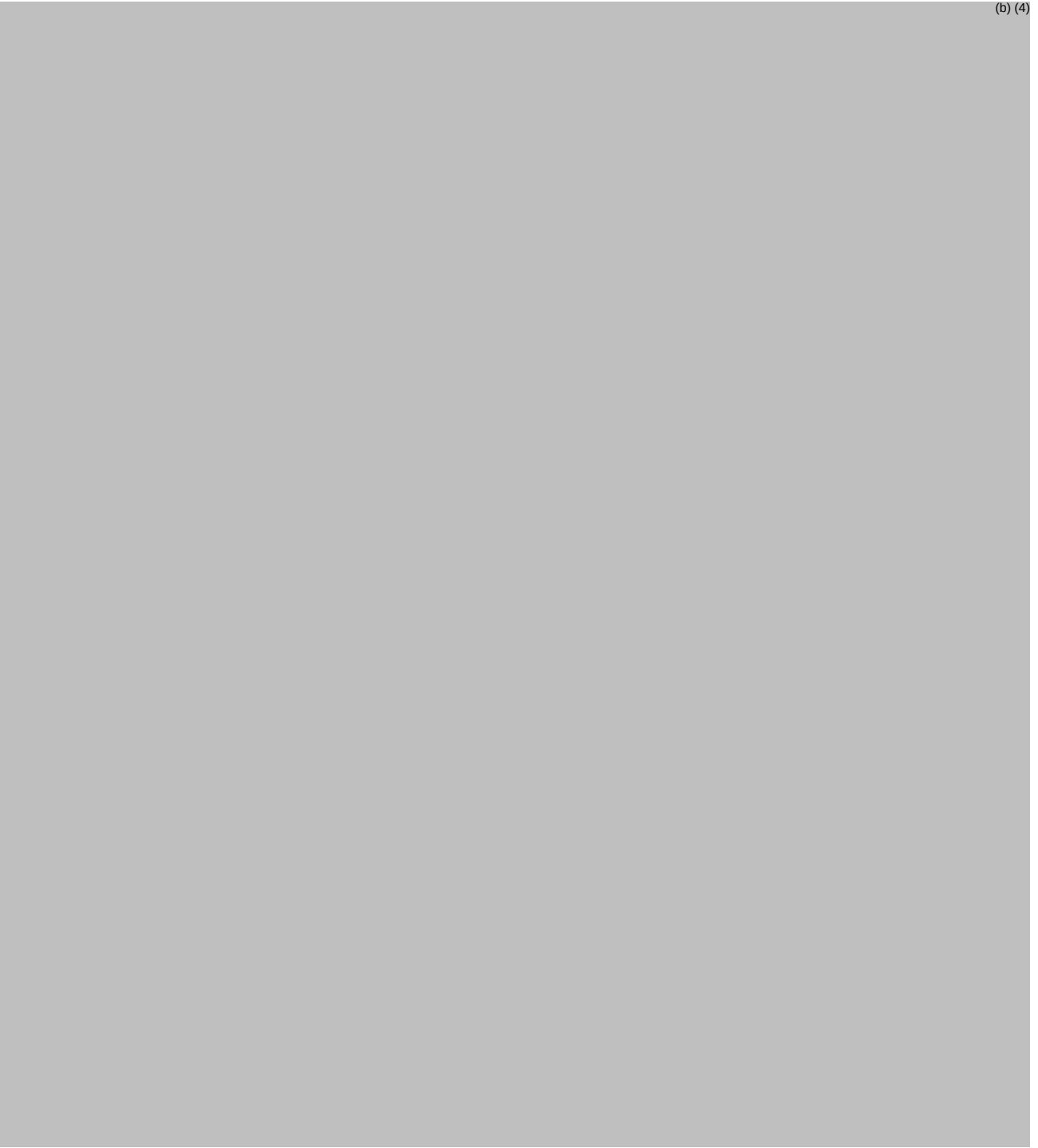
Overall Conclusion: While the Applicant’s approach to determine the genotoxic potential and systemic toxicity profile for the above leachables appears appropriate, there is any underlying concern for the validity of the original structures of both leachables identified by the  (b) (4) Software used by the Applicant. The software determined both the structure and associated CAS# for the leachables, however because the CAS# was later identified to be incorrect, there is uncertainty that the associated structures were correctly identified by the Applicant. Since the QSAR and read-across approaches in toxicology risk assessment is based entirely on the similarities to the proposed structure of the leachable, the lack of certainty of the structure would diminish the interpretability and utility of the risk assessment findings.

(Reviewer’s comment: A comment will be sent to the Applicant noting the uncertainty on the accuracy of the structures proposed for the two leachables, and the tentative value and utility of the results obtained using the QSAR and read-across approaches that are based entirely on the original structures in question. CMC requested the Applicant provide additional characterization data to support the proposed structures of the leachables, and once the Applicant has confirmed the structures, or have proposed structures with greater certainty, then additional QSAR evaluation(s) and revised comprehensive toxicological assessment(s) should be conducted as needed.)

The Applicant submitted the revised package insert to the NDA on 8/8/2018. The combined DMPH and pharm/tox reviewer's recommended labeling changes in the pharmacology/toxicology relevant sections of the labeling (Indications and Usage, Subsections 8.1, 8.2, and 13.1) can be found in red and strikethrough below.

Labeling:

(b) (4)



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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERRY J MILLER
10/15/2018

Clinical Review of NDA

NDA(505)b(2)	211413
Applicant	HQ Specialty Pharma Corporation
Date of Submission	12/21/2017
PDUFA Goal Date	10/21/2018
Proprietary Name	Cefazolin for Injection USP, 2 gm/vial
Established or Proper Name	Cefazolin for Injection USP
Referenced Listed Drugs	2 g Cefazolin for Injection USP and Dextrose Injection USP in Duplex [®] Container (NDA 50779); Ancef [®] (NDA 50461)
Dosage Form(s)/Strength	Powder in 2 gram vials
Route of Administration	Intravenous
Applicant Proposed Indication	Perioperative prophylaxis
Applicant Proposed Dosing Regimen(s)	• 1 to 2 grams IV administered ½ hour to 1 hour prior to the start of surgery. • For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram IV during surgery (administration modified depending on the duration of the operative procedure). • 500 mg to 1 gram IV every 6 to 8 hours for 24 hours postoperatively.
Recommended Population(s)	Adults
Clinical Reviewer	Alma Davidson, M.D.
Clinical Team Leader	Peter Kim, M.D., M.S.
Recommendation	Complete Response

1. Introduction

The applicant has submitted this 505(b)(2) New Drug Application (NDA), Cefazolin 2 gm to the FDA on December 21, 2017. The reference listed drugs (RLD) are BBraun NDA 050779 and Ancef[®] (NDA 50461) (see Table 1 for comparison). There are no clinical trials conducted by the applicant to support this 505(b)(2) NDA for Cefazolin 2 gm/vial. The applicant intends to rely solely on the Agency's previous findings of safety and efficacy data for the reference listed drug (RLD) which is BBraun's NDA 050779 for the perioperative prophylaxis indication and not for the other approved indications of the listed drug. Additionally, the applicant seeks dosing administration based on the Ancef[®]'s label, (b) (4)

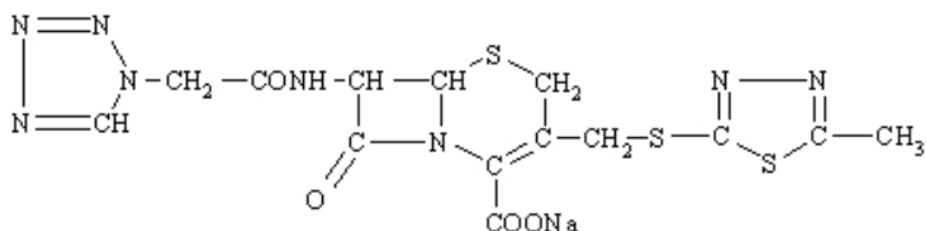
(b) (4)

2. Background

Cefazolin is a semi-synthetic, first generation cephalosporin antibacterial agent with *in vitro* activity against Gram-positive and a limited number of Gram-negative bacteria. It shares the same mechanism of action as other beta-lactam antibacterials, namely inhibition of cell wall biosynthesis mediated by binding to penicillin-binding proteins. Cefazolin was originally approved for use in the United States in 1973 under NDA 050461 (ANCEF[®], GlaxoSmithKline).

Cefazolin for Injection USP is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-methyl}-8-oxo-7-[2-(1*H*-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid.

Structural formula:



C₁₄H₁₃N₈NaO₄S₃ M.W. 476.5

Table 1: Formulation Comparison between Approved Products (RLDs) and Proposed Product

Parameter	BBraun- Cefazolin for Injection & Dextrose	GSK – Cefazolin (Ancef [®]) (Discontinued)	HQ's Cefazolin injection, powder	Applicant's Comments
Active Ingredient	Cefazolin Sodium	Cefazolin Sodium	Cefazolin Sodium	No change
Inactive Ingredient	Dextrose	N/A	N/A	Proposed product could be diluted with various diluents
Strength	500 mg 1 g 2 g	250 mg 500 mg 1 g 5 g 10 g	2 g	Strength same as BBraun RLD

NDA 211413
Cefazolin for Injection USP, 2 gm/vial

In-active Ingredient	Dextrose	Various diluents (see below)	Various diluents (see below)	Proposed product is powder filled vial to be reconstituted
Container	BBraun Duplex Bag	Glass Vial	Glass Vial	Different container closure system from RLD
Formulation	Duplex Bag with powder and diluent in separate chambers	Powder	Powder	Products must be reconstituted prior to use
Diluents	Dextrose	-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% (b) (4) Dextrose Injection, USP (b) (4)	Possible diluents will be based on the previously approved Ancef diluents; not only Dextrose as used by BBraun.

NDA 211413
Cefazolin for Injection USP, 2 gm/vial

Parameter	BBraun- Cefazolin for Injection & Dextrose	GSK – Cefazolin (Ancef®) (Discontinued)	HQ's Cefazolin injection, powder	Applicant's Comments
			(b) (4)	
Directions for Preparation	Must be reconstituted prior to use	Must be reconstituted prior to use	Must be reconstituted prior to use	No change
Directions for Administration	For IV additive Use Only	For Direct Slow IV or IV additive Use Only	For (b) (4) IV additive Use Only	No change
Indication	Respiratory Tract Infections Urinary Tract Infections Skin and Skin Structure Infections Biliary Tract Infections Bone and Joint Infections Genital Infections Septicemia Endocarditis Perioperative prophylaxis	Respiratory Tract Infections Urinary Tract Infections Skin and Skin Structure Infections Biliary Tract Infections Bone and Joint Infections Genital Infections Septicemia Endocarditis Perioperative Prophylaxis	- - - - - - - - - - Perioperative prophylaxis Prophylaxis	Proposed product only for one indication perioperative prophylaxis

Reviewer Comment: As noted in the table above, the applicant is proposing (b) (4) intermittent or continuous IV infusion administration.

3. Product Quality:

According to the Office of Product Quality (OPQ) reviewer, the applicant has submitted leachable and extractables data and was determined that two leachables detected in the proposed cefazolin product exceed the proposed safety concern threshold and therefore may require a comprehensive toxicological risk assessment that evaluates both the genotoxicity and general toxicology of the leachables. The Federal Food, Drug, and Cosmetic Act (21 CFR 210 and 211) states that packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug products. (Please see the OPQ review for details.)

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology studies were conducted by the applicant. However, according to the pharmacology/toxicology reviewer, in accordance with current FDA best practices and recommendations by the Product Quality Research Institute workgroup on

parenteral products, the applicant will need to submit a comprehensive toxicological risk assessment (i.e., local toxicity, systemic toxicity, mutagenicity, carcinogenicity, reproductive toxicity, etc.) for any leachable that exceeds a daily total intake limit of 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for an indication of < 1 month for most potentially genotoxic impurities, or be adequately qualified for mutagenicity and carcinogenicity as described in ICH Guidance M7(R1). The overall risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Leachable testing should be conducted on at least one drug product registration stability batch and be continued until the planned expiration date is reached. (Please see the pharmacology/toxicology review for details.)

Reviewer's Comment: The OPQ and pharmacology/toxicology reviewers' information request (IR) as based on their findings were sent to the applicant on August 9, 2018. As of today's date (September 6, 2018), the applicant has not responded to the IR. An addendum clinical review will be provided after review of the applicant's response to the IR.

5. Clinical Pharmacology

No new clinical pharmacology studies were conducted by the applicant.

6. Clinical Microbiology

Cefazolin is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Predominant mechanisms of bacterial resistance to cephalosporins include the presence of extended-spectrum beta-lactamases and enzymatic hydrolysis.

Cefazolin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections including Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*), and Gram-negative bacteria (*Escherichia coli*, and *Proteus mirabilis*).

7. Clinical

Efficacy: No clinical trials were conducted by the applicant to support this 505(b)(2) NDA for Cefazolin 2 gm/vial. The applicant intends to rely solely on the Agency's previous findings of safety and efficacy data for the reference listed drug (RLD), that is, BBraun's NDA 050779 for the indication of perioperative prophylaxis.

Reviewer's Comment: Since the applicant is proposing (b) (4) continuous or intermittent (b) (4) infusion administration, the M.O. reviewed the safety of both forms of administration.

Safety Review Update

The applicant provided a safety review of the literature for cefazolin. According to the applicant, they contracted (b) (4) a global research firm for companies to perform the safety review of literature. (b) (4) has identified 30 papers in total in which eleven were considered by the applicant's evaluator to be of highest relevance (summarized below).

Review of Literature for the cefazolin (not administered via 2 g IV bolus injection)

1. Valerie Zeller, Frederick Durand, Marie-Dominique Kitzis, Luc Lhotellier, Jean- Marc Ziza, Patrick Mamoudy, and Nicole Desplaces. "Continuous Cefazolin Infusion to Treat Bone and Joint Infections: Clinical Efficacy, Feasibility, Safety, and Serum and Bone Concentrations." *Antimicrob. Agents Chemother.* March 2009 vol. 53 no. 3 883-887.

In this article, two moderate grade AEs were observed. Two patients experienced cefazolin-related AEs. The first patient developed *C. difficile* colitis, and the second patient became confused.

2. Schmitz, ML., Blumer, JL., Cetnarowski, W., Rubinod, CM. "Determination of Appropriate Weight-Based Cutoffs for Empiric Cefazolin Dosing Using Data from a Phase 1 Pharmacokinetics and Safety Study of Cefazolin Administered for Surgical Prophylaxis in Pediatric Patients Aged 10 to 12 Years." *Antimicrob Agents Chemother.* 2015 Jul; 59(7): 4173-80.

In this study, post-dose pharmacokinetic and safety assessments were conducted following drug administration.

Safety assessment. During the study period, 6 of the 12 patients reported a total of nine AEs. The majority of the AEs were mild or moderate. One patient experienced nausea, and five others experienced vomiting. The remaining three AEs were two cases of hypotension and one of hypertension. One of the cases of hypotension was considered by the investigator to be severe, life threatening, and possibly related to treatment. The patient, who weighed 52.7 kg, underwent inhalation induction with oral intubation, receiving propofol and morphine for the surgical excision of a left branchial cleft cyst. Eight minutes after anesthetic induction, i.v. infusion of a 2-g dose of cefazolin as antibiotic prophylaxis commenced. Cefazolin was infused over a period of 30 min. Eighteen minutes after the start of cefazolin administration, the patient intraoperatively experienced moderate hypotension. None of the other AEs were assessed as related to cefazolin and there were no discontinuations from the study because of AEs.

3. Cox VC., Zed PJ. "Once-daily cefazolin and probenecid for skin and soft infections". *Ann Pharmacother.* 2004 Mar; 38(3):458-63. Epub 2004 Jan 23.

Three pharmacokinetic studies and 2 clinical trials evaluating the use of cefazolin with probenecid for the treatment of SSTI were included in this review.

Adverse events in the once-daily cefazolin group included fatigue (n = 3), nausea (n = 2), headache (n = 2), sore gums (n = 1), and rash (n = 1).

4. Tosukhowong T1, Eiam-Ong S, Thamutok K, Wittayalertpanya S, Na Ayudhya DP. "Pharmacokinetics of intraperitoneal cefazolin and gentamicin in empiric therapy of peritonitis in continuous ambulatory peritoneal dialysis patients." *Perit. Dial. Int.* 2001 Nov-Dec; 21(6): 587-94

No adverse events are reported in this article.

5. Stitely M, Sweet M, Slain D, Alons L, Holls W, Hochberg C, Briggs F. "Plasma and tissue cefazolin concentrations in obese patients undergoing cesarean delivery and receiving differing pre-operative doses of drug." *Surg. Infect. (Larchmt)*. 2013 Oct; 14(5): 455-9.

This article reports that no maternal or neonatal adverse reactions were attributed to cefazolin beyond the one subject who developed an allergic reaction and thus was excluded from the study.

6. Stone PA, AbuRahma AF, Campbell JR, Hass SM, Mousa AY, Nanjundappa A, Srivastava M, Modak A, Emmett M. "Prospective randomized double-blinded trial comparing 2 anti-MRSA agents with supplemental coverage of cefazolin before lower extremity revascularization." *Ann Surg.* 2015 Sep; 262(3): 495-501.

Patients were randomized to either the cefazolin plus vancomycin arm or the cefazolin plus daptomycin arm. Thirteen (13) of the 93 patients (14%) in the Cefazolin plus Daptomycin and 8 of the 85 patients (9%) in the Cefazolin plus Vancomycin arm developed an infection including both early and late infections.

7. Brucculeri, M., Charlton, M., Serur, D. "Serum sickness-like reaction associated with Cefazolin." *BMC Clin Pharmacol.* 2006; 6: 3.

This article reports a probable case of serum sickness-like reaction (SSLR) following a single dose of Cefazolin. Postoperative day ten was marked by the emergence of fevers as high as 38.4 C, generalized weakness, and arthralgias involving bilateral knees, wrists, ankles, and metacarpophalangeal (MCP) joints. Simultaneously, a cutaneous eruption appeared which was initially limited to bilateral upper extremities but soon involved his trunk, back, face and lower extremities. Furthermore, additional MCP joints become swollen and tender in sequential order from medial to lateral. Upon questioning, the patient denied the presence of any gastrointestinal disturbance such as nausea, emesis, or diarrhea. Based on the aforementioned clinical findings, the absence of systemic vasculitis, and a history of a cephalosporin antibiotic exposure approximately two weeks earlier, a diagnosis of a SSLR was made.

8. Flynt LK, Kenney RM, Zervos MJ, Davis SL. "The Safety and Economic Impact of Cefazolin versus Nafcillin for the Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections." *Infect Dis Ther*. 2017 Jun;6 (2): 225-231.

The authors conducted a retrospective cohort study to compare adverse effects and clinical outcomes among patients with MSSA bacteremia treated with cefazolin or nafcillin. Risk of nephrotoxicity is increased with nafcillin compared with cefazolin. The primary endpoint, incidence of acute kidney injury, AKI, was 26/81 (32%) versus 9/68 (13%) ($p = 0.007$), in the nafcillin and cefazolin arms, respectively. The incidence of additional adverse events for cefazolin versus nafcillin were: *Clostridium difficile* 0% versus 6.3% ($p = 0.036$), neutropenia 2.5% versus 2.9% ($p = 0.869$), increased liver function tests to greater than 3 times the upper limit of normal 2% versus 9.9% ($p = 0.032$) and drug rash 4.4% versus 4.9% ($p = 0.88$). Cefazolin should be considered as a safer alternative to nafcillin for select patients with MSSA bacteremia.

9. Winans, SA., Luce, AM, Hasbun R. "Outpatient parenteral antimicrobial therapy for the treatment of methicillin-susceptible *Staphylococcus aureus*: a comparison of cefazolin and ceftriaxone." *Infection*. 2013 Aug;41 (4): 769-74.

Adverse events were similar between each group, with 5.1% in the cefazolin group compared to 2.3 % in the ceftriaxone group ($p = 0.65$). The most common adverse event reported was nausea/vomiting/diarrhea (2.6 versus 0%), followed by elevated blood urea nitrogen and serum creatinine (1.9 versus 0%), anemia (1.9 versus 0%), and rash (0 versus 2.3%). Cefazolin also induced the following adverse event: renal insufficiency.

10. Rao, SN., Rhodes, NJ., Lee, BJ., Scheetz, MH., Hanson, AP., Segreti, J., Crank, CW., Wang SK. "Treatment outcomes with cefazolin versus oxacillin for deepseated methicillin-susceptible *Staphylococcus aureus* bloodstream infections." *Antimicrob. Agents Chemother*. 2015 Sep; 59(9): 5232-8.

In this article, nephrotoxicity was reported as an adverse event for cefazolin in one patient.

11. Tacconelli E1, Cataldo MA, Albanese A, Tumbarello M, Arduini E, Spanu T, Fadda G, Anile C, Maira G, Federico G, Cauda R. "Vancomycin versus cefazolin prophylaxis for cerebrospinal shunt placement in a hospital with a high prevalence of methicillin-resistant *Staphylococcus aureus*." *J. Hosp. Infect*. 2008 Aug; 69(4): 337-44.

This prospective randomized trial undertaken to compare the efficacy of vancomycin and cefazolin in preventing bacterial infections following CSF insertion and to record any adverse effects. Fifteen patients in the vancomycin group (17%) and 21 patients (24%) in the cefazolin group suffered from post-surgical bacterial infections. Four patients developed shunt infections in the vancomycin group compared with 12 patients in the

cefazolin group. The article noted that no antibiotic-related adverse effects were observed in either of the two treatment groups and no cases of drug intolerance were recorded.

Reviewer's Comment: The reported adverse events in the above articles are listed in the cefazolin label except serum-sickness-like reaction (SSLR) associated with cefazolin. It is notable that serum sickness reaction is mentioned in other cephalosporins package inserts including ceftriaxone, cefuroxime axetil, and cefdinir. I suggest that the SSLR should be mentioned under a newly-created Postmarketing section of this Cefazolin for Injection, 2 gm/vial PI.

(b) (4)

8. Pediatrics

PREA does not apply to this application.

9. Labeling

Review of Cefazolin prescribing information in PLR and PLLR will be performed after approval of this NDA.

10. Recommendation

From the clinical perspective, since there is sufficient safety data for the 2-gram dose via intermittent or continuous IV infusion given approximately over 30 minutes (b) (4)

(b) (4)

(b) (4) dosing of 500 mg to 1- 2 gm IV (b) (4) is noted in the label of one of the RLDs for perioperative prophylaxis (Cefazolin for Injection USP and Dextrose Injection USP in Duplex® Container, NDA 50779), (b) (4)

(b) (4) dosing (b) (4) (b) (4) may be acceptable for the proposed drug product.

If there were no other safety concerns associated with this NDA, such as resolving the leachables issue, the NDA could be approved only for the 2-gram dose administered via intermittent or continuous IV infusion given approximately over 30 minutes. However, because the applicant has not provided a comprehensive toxicological risk assessment (i.e., local toxicity, systemic toxicity, mutagenicity, carcinogenicity, reproductive toxicity, etc.) for any leachable that exceeds a daily total intake limit of 5 mcg/day, at this time, the M.O. recommends a complete response. Should the applicant resolve the above mentioned toxicology issues, the M.O. would reconsider the approvability of this NDA.

References

1. FDA Adverse Events Reporting System (FAERS)
2. Cefazolin for Injection USP and Dextrose Injection USP prescribing information- Revised 10/2015.
3. Ancef® (cefazolin for injection) prescribing information- dated 06/02/2004.

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/s/

ALMA C DAVIDSON
09/06/2018

PETER W KIM
09/06/2018

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	211413
Submission Date	12/21/17
Drug	Cefazolin
OCP Reviewer	Cristina Miglis, Pharm.D, MSc, BCPS
OCP Team Leader	Zhixia (Grace) Yan, Ph.D.
OCP Division	DCP4
OND Division	DAIP
Sponsor	HQ Specialty Pharma
Submission Type	505(b)(2)
Formulation	Injection [2 g/vial]
Indication	Perioperative prophylaxis
Dosage and Administration	1 to 2 grams IV administered 1/2 hour to 1 hour prior to the start of Surgery - For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram IV during surgery (administration modified depending on the duration of the operative procedure) 500 mg to 1 gram IV every 6 to 8 hours for 24 hours postoperatively

Background

HQ Specialty Pharmaceuticals has developed Cefazolin for Injection, 2 g/vial with the intent of obtaining FDA approval via the 505(b)(2) New Drug Application (NDA) pathway. The Listed Drug (RLD) that forms the basis for the NDA is intravenous Cefazolin (NDA 50779; BBraun). The proposed HQ Cefazolin for Injection is similar to the RLD in terms of the strength, indication, dosing but contains a different formulation matrix. The current RLD is diluted in dextrose while the proposed product can be diluted in various diluents based on patient needs. A comparison of the proposed product and reference listed drug is presented in **Table 1**.

Table 1. Formulation Comparison Between the Approved Product and the Proposed Product

Parameter	BBraun- Cefazolin for Injection & Dextrose	GSK – Cefazolin (Discontinued)	HQ's Cefazolin injection, powder	Comments
Active Ingredient	Cefazolin Sodium	Cefazolin Sodium	Cefazolin Sodium	No change
Inactive Ingredient	Dextrose	N/A	N/A	Proposed product could be diluted with various diluents
Strength,	500 mg 1 g 2 g	250 mg, 500 mg, 1 g, 5 g, 10 g	2 g	Strength same as BBraun RLD

No new clinical pharmacology information was submitted. A waiver of in vivo bioavailability studies has been requested for the proposed Cefazolin product, supported by the following:

1. The proposed drug product Cefazolin for Injection [2 g/vial] is intended solely for administration by injection.

2. The product contains the same active and inactive ingredients in the same concentration as the RLD, but contains a different formulation matrix. The current RLD is diluted in dextrose while the proposed product can be diluted in various diluents.

The Biopharmaceutics team has reviewed the Sponsor's biowaiver request and agrees that a waiver is appropriate. A waiver of studies in pediatric patients has also been requested for the proposed Cefazolin product. The Sponsor includes neonates to patients less than 17 years of age in their waiver request based on the reason that the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric age groups. The Sponsor references PIND 131420 written response from the Agency dated August 26, 2018 which states exception is appropriate for this age group.

In addition, the Sponsor has submitted a literature review identifying several new risks in the use of Cefazolin that should be documented in the package/product insert, for the reporting period of July 27, 2000 to the present. These include: 1) serum sickness-like reaction 2) arthralgias involving bilateral knees, wrists, ankles, and metacarpophalangeal joints 3) anemia *and others that potentially fall outside of the known Renal and Hepatic adverse reactions*: 4) acute kidney injury 5) increased liver function tests to greater than 3 times the upper limit of normal 6) nephrotoxicity.

Labeling Comments/Recommendations

Several formatting changes are proposed to Section 12.3 Pharmacokinetics of the proposed labeling. This section also includes one comment to the Applicant regarding the recommended deletion of information regarding cefazolin concentrations in cord blood and milk of nursing mothers as highlighted below.

(b) (4)

Recommendation

The Office of Clinical Pharmacology, Division of Clinical Pharmacology⁴ has reviewed the application. No new clinical pharmacology information was submitted. The Clinical Pharmacology review team recommends approval of this NDA.

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/s/

CRISTINA M MIGLIS
08/29/2018

ZHIXIA YAN
08/29/2018

STATISTICAL REVIEW AND EVALUATION

NDA#:	211413
NDA Type:	505b(2)
Drug Name:	Cefazolin 2gm powder for injection
Applicant:	HQ Specialty Pharma
Date(s):	Stamp date: 12/21/17 Goal date: 12/21/18
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Karen Higgins, Sc.D.
Concurring Reviewers:	Daphne Lin, Ph.D.
Medical Division:	Division of Anti-Infective Products
Clinical Reviewer:	Alma Davidson, MD, Medical Officer
Project Manager:	Jacquelyn Rosenberg, RPh, PharmD

Summary

This NDA is for Cefazolin 2gm powder for injection submitted by HQ Specialty Pharma (the Applicant). The Applicant is relying on the previous findings of safety and efficacy demonstrated for the approval of the reference listed drug (NDA 50779) BBraun Cefazolin for Injection USP. The Applicant did not conduct any new clinical studies.

The sponsor states the following:

No new studies have been conducted by HQ. HQ intends to rely solely on the Agency's previous findings of safety and efficacy data contained as described in the Summary Basis of Approval for the Ancef NDA 050461 and the BBraun NDA 050779 as the sole source of data to support its 505(b)(2) submission. The route of administration and dosing regimen (dose, frequency, and duration) for HQ's Cefazolin for Injection product will be same as the Ancef or BBraun product when diluted with appropriate diluents.

The proposed label is consistent with BBraun cefazolin IV prescribing information in that it does not contain a clinical studies section. There is no statistical review needed for this NDA submission.

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/s/

KAREN M HIGGINS
02/08/2018

TSAE YUN D LIN
02/08/2018