NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA Efficacy Supplement
Application Number(s)	050779/S-027
Priority or Standard	Standard
Submit Date(s)	January 20, 2020
Received Date(s)	January 20, 2020
PDUFA Goal Date	November 20, 2020
Division/Office	Division of Anti-Infectives (DAI)/Office of Infectious Diseases (OID)
Review Completion Date	November 6, 2020
Established/Proper Name	Cefazolin sodium and dextrose solution
Trade Name	Cefazolin for Injection USP and Dextrose Injection USP in the Duplex® Container
Pharmacologic Class	Cephalosporin antibacterial
Applicant	B. Braun Medical Inc.
Dosage form	Injection, powder, lyophilized, for solution
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Perioperative Prophylaxis in Pediatric Patients (10-17 years of age)
Recommended Dosing Regimen	Pediatric Patients (10-17 years old): Less than 50 kg body weight: 1 gram IV (single dose) Greater than or equal to 50 kg body weight: 2 gram IV (single dose)

Table of Contents

Table of Tables

Table of Figures

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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

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
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
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
USPI	US prescribing information

1. Executive Summary

The proposed product is a single strength of Cefazolin for Injection USP and Dextrose Injection USP in the Duplex® Container (a dual-chamber, single-use container supplied in two concentrations: 1 g Cefazolin for Injection USP and 50 mL 4% Dextrose Injection USP and 2 g Cefazolin for Injection USP and 50 mL 3% Dextrose Injection USP) for the proposed indication of perioperative prophylaxis in pediatric patients 10 to 17 years of age. The listed drug is Ancef® (cefazolin injection), NDA 050461, owned by GlaxoSmithKline, and originally approved in 1973 for several indications including perioperative prophylaxis in adults.

Pertinent to this supplemental NDA (sNDA), on January 13, 2012, NDA 050779/S-018 was approved for perioperative prophylaxis in adults and provided an additional strength of 2 g for Cefazolin for Injection USP and Dextrose Injection USP in the Duplex Container. The 2 g dose was considered a new dosing regimen and based on the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the Applicant was required to assess the safety and effectiveness of the product for the indication in pediatric patients. The Agency waived the pediatric study requirement for ages birth to 9 years because the product did not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and was not likely to be used in a substantial number of pediatric patients in this group. The Agency deferred submission of pediatric studies for ages 10 to 17 years because this product was ready for approval for use in adults and the pediatric studies had not yet been completed. The deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act were required postmarketing studies and are listed below:

- For PMR 1869-1, Study HC-G-H-1202 was conducted. It was a pharmacokinetic (PK) study of a single dose administration of cefazolin in 12 pediatric patients, ages 10 to 12 years, to determine the cefazolin dose required to match exposures achieved in adults administered a single 2 gram dose of cefazolin (Please see DARRTS for the Clinical review of PMR 1869-1, dated 05/06/2015). This PMR was considered fulfilled on 9/18/14.
- For PMR 1869-2, Study HC-G-H-1601 was conducted. It was a safety study in 61 pediatric patients, ages 10-17 years, of a single dose of cefazolin for preoperative prophylaxis using the dose equivalent to a 2 gram adult exposure.

Based on the data submitted in this sNDA, namely, the clinical study report for Study HC-G-H-1601 used to fulfill PMR 1869-2 and information previously submitted to fulfill PMR 1869-1, the Applicant has provided sufficient data to support labeling Cefazolin for Injection and Dextrose Injection for the indication of perioperative prophylaxis for pediatric patients aged 10 to 17 years. Additionally, it is recommended that PMR 1869-2 be considered fulfilled.

1.1 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 050779/S-027, the Applicant seeks approval of Cefazolin for Injection USP and Dextrose Injection USP in the Duplex® Container (1 g/vial and 2 g/vial) for the proposed indication of perioperative prophylaxis in pediatric patients 10 to 17 years of age. The Applicant conducted two pediatric studies: Study HC-G-H-1601, a non-comparative safety study in 61 pediatric patients, ages 10 to 17 years, using a single dose of cefazolin equivalent to a 2-gram adult exposure for perioperative prophylaxis; and Study HC-G-H-1202, a non-comparative study that examined the pharmacokinetics and safety of cefazolin in 12 pediatric subjects aged 10 to 12 years following administration of a single IV dose of cefazolin for perioperative prophylaxis. The clinical study report for Study HC-G-H-1601 was submitted in the current sNDA and is the primary subject of this review.

The most common adverse reactions associated with cefazolin are: gastrointestinal (nausea, vomiting, diarrhea), and allergic reactions (anaphylaxis, urticaria, skin rash). The most frequently reported adverse reactions observed in Study HC-G-H-1601 (pediatric patients 10-17 years old) were nausea, reported by 9 subjects (14.8%), infusion site pain, reported by 4 subjects (6.6%), and headache, reported by 3 subjects (4.9%). The safety findings observed in Study HC-G-H-1601 were similar to those observed in Study HC-G-H-1202 as well as those observed in the clinical trials of the listed drug (Ancef) in adult patients.

Based on the data submitted in this sNDA from Study HC-G-H-1601 used to fulfill PMR 1869-2 and information previously submitted to fulfill PMR 1869-1, the Applicant has provided sufficient data to support labeling Cefazolin for Injection USP and Dextrose Injection USP for the indication of perioperative prophylaxis for pediatric patients aged 10 to 17 years. Additionally, it is recommended that PMR 1869-2 be considered fulfilled.

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 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	prophylaxis are site specific, but most commonly target Gram-positive cocci such as *Staphylococcus* spp. • Broader coverage and longer durations of therapy than are recommended have not been shown to reduce the incidence of SSI.	• The current IDSA guidelines recommend narrow-spectrum antibacterial drug therapy selected according to the surgery performed. • The administration of cefazolin for perioperative prophylaxis is limited to one dose or continued for less than 24 hours post-surgery.
Current Treatment Options	• There are other approved antibacterial drugs for perioperative prophylaxis including cefoxitin, cefuroxime, cefotetan, ceftriaxone, and ertapenem. However, only cefoxitin and cefotaxime have perioperative prophylaxis dosing regimens for pediatric patients (infants and children, and neonates, infants, and children, respectively).	• Cefazolin is a commonly used antibacterial drug for perioperative prophylaxis in the U.S.
Benefit	• Efficacy in pediatric patients was extrapolated from the Agency's prior finding of efficacy in adults for the indication of perioperative prophylaxis based on the demonstration of comparable exposures between pediatric patients aged 10 to 17 years (weight-based dosing) and healthy adults receiving 2 grams of Cefazolin for Injection and Dextrose Injection.	• Cephalosporins (such as cefazolin) are appropriate first line agents for most surgical procedures, targeting the most likely organisms while avoiding broad spectrum antibacterial drug therapy that may lead to the development of antibacterial resistance.
Risk and Risk Management	• The most common adverse reactions observed in pediatric patients receiving Cefazolin for Injection and Dextrose Injection for perioperative prophylaxis in Study HC-G-H-1601 included: nausea, infusion site reactions, and headache.	• The safety profile of cefazolin in pediatric patients is adequately described in labeling and is similar to those in adults.

2. Therapeutic Context

2.1 Analysis of Condition

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

The administration of Cefazolin for Injection and Dextrose Injection is to be limited to one dose or continued for less than 24 hours post-surgery.

2.2 Analysis of Current Treatment Options

The following table provides a summary of antibacterial drugs approved for perioperative prophylaxis or for similar indications. Of note, there are only two cephalosporins approved for perioperative prophylaxis in pediatric patients: cefoxitin (infants and children) and cefotaxime (neonates, infants, and children).

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

Product Name(s)	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 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.	The most common adverse reactions have been local reactions (thrombophlebitis) following intravenous injection.	Use in adults and pediatric patients (3 months and older).
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).

Product Name(s)	Relevant Indication	Year of Approval	Dosing/Administration	Important Safety and Tolerability Issues	Other Comments
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 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 (e.g., during coronary artery bypass surgery).	1984	Single 1 gram 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.

Product Name(s)	Relevant Indication	Year of Approval	Dosing/Administration	Important Safety and Tolerability Issues	Other Comments
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 IV, 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.

Source: Medical Officer's Table. Reference: Drugs@FDA
Abbreviations: AE, adverse event; IM, intramuscular; IV, intravenous

Reviewer's Comment: *Clindamycin and vancomycin are used off-label under certain circumstances, such as prophylaxis for patients with beta-lactam allergy.*

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

On January 13, 2012, NDA 050779/S-018 which provided an additional strength of 2 g for Cefazolin for Injection USP and Dextrose Injection USP in the Duplex Container was approved for perioperative prophylaxis in adults. The 2 g dose provided for a new dosing regimen and based on the requirements of PREA, the Applicant was required to assess the safety and effectiveness of the product for the claimed indication in pediatric patients. The Agency waived the pediatric study requirement for ages birth to 9 years because the product did not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and was not likely to be used in a substantial number of pediatric patients in this group. The Agency deferred submission of pediatric studies for ages 10 to 17 years of age because this product was ready for approval for use in adults and the pediatric studies had not yet been completed. The required postmarketing studies listed in the approval letter were as follows. Note that the original PMR numbers 1458-1 and 1458-2 were updated to 1869-1 and 1869-2, respectively, on May 1, 2012, due to changes in the FDA postmarketing tracking database:

- PMR 1869-1: A pharmacokinetic (PK) study of single dose administration of cefazolin in pediatric patients, ages 10 to 17 years, to determine the cefazolin dose required to match exposures achieved in adults administered a single 2 gram dose of cefazolin.
- PMR 1869-2: A safety study in 100 pediatric patients, ages 10-17 years, of a single dose of cefazolin for preoperative prophylaxis using the dose equivalent to a 2 gram adult exposure (as determined in the PK study) in pediatric patients.

3.2 Summary of Presubmission/Submission Regulatory Activity

- January 13, 2012: The addition of a 2 g strength was approved for perioperative prophylaxis under Supplement 018 (NDA 050779/S-018).

- August 14, 2012: The Division agreed to the Applicant's proposal to use modeling to establish doses in pediatric patients 13-17 years to match exposures achieved in adults. The model and simulations would be updated after obtaining PK data in children aged 10 to 12 years in Study HC-G-H-1202 to establish doses in Study HC-G-H-1601.

- March 19, 2014: The Applicant requested that an extension to the timelines for the second study since the dosing for PMR 1869-2 was to be determined based on the

findings from the PK study PMR 1869-1. The Sponsor proposed the following revisions to the timelines going forward:

- Final Protocol Submission: March 2015
- Study/trial Completion: March 2017
- Final Report Submission: September 2017

- March 20, 2014: The Applicant submitted the clinical study report for Study HC-G-H-1202 of single dose administration of cefazolin in pediatric patients, ages 10 to 12 years, and a revised pharmacokinetic model for dosing pediatric patients by weight as an sNDA 050779/S-023. This was the study associated with PMR 1869-1. This PMR was considered fulfilled on September 18, 2014.

- March 27, 2015: The Applicant submitted a Partial PREA Waiver Request to NDA 050779 for Cefazolin for Injection USP and Dextrose Injection USP in the Duplex Container, 2g strength, in lieu of the Pediatric Safety Study Protocol. The Partial PREA Waiver was intended to satisfy PMR 1869-2. The Agency denied the Partial PREA Waiver on August 10, 2015, as PeRC recommended that Study PMR 1869-2 be conducted in pediatric patients 10-17 years of age, using the 1 g dose in those weighing 25 to <60 kg and the 2 g dose in those weighing ≥60 kg.

- May 5, 2016: The Agency issued a Postmarketing Requirement-Notification of Missed Milestone letter informing the Applicant that because the final protocol had not been submitted, the PMR was considered delayed, thus requiring the Applicant to provide a revised PMR timetable. The Sponsor provided the updated timeline on May 19, 2016.

- October 20, 2017: The Agency issued a Notification of PREA Non-Compliance Letter. The Agency determined that the Applicant failed to meet the PMR because the pediatric assessment for PMR 1869-2, which was deferred until September 30, 2017, had not been submitted.

- November 2, 2017: The Applicant responded to the PREA Non-Compliance Letter and requested the following dates for deferral extension for PMR 1869-2:

  - Final Protocol Submission: September 2016 (already completed)
  - Study Completion: September 2018
  - Final Report Submission: March 2019

- December 6, 2017: The Applicant received a Deferral Extension Granted Letter from the Agency.

- September 10, 2018: The Applicant submitted a new Deferral Extension Request to continue to enroll subjects in the pediatric safety study. The Applicant requested the following revised dates for PMR 1869-2:

  - Final Protocol Submission: September 2016 (already completed)
  - Study Completion: July 2019
  - Final Report Submission: January 2020

- April 3, 2019: In email communication, the Applicant provided the study status with FDA and requested the FDA consider the data acquired up to that point adequate to justify study termination.

- April 4, 2019: In email communication, the FDA advised the Applicant to continue enrollment until July 31, 2019, at which time the study could be terminated.

- January 28, 2020: The Sponsor submitted the clinical study report for PMR 1869-2 as an efficacy supplement, assigned S-027.

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

4.1 Office of Scientific Investigations (OSI)

No OSI inspections were performed for this pediatric efficacy supplement.

4.2 Product Quality

The Office of Pharmaceutical Quality (Office of Lifecycle Drug Products, Division of Post-Marketing Activities I) reviewed the information contained in this sNDA and found the submitted CMC information to be adequate. There were no CMC-related changes to the USPI. This sNDA is recommended for approval from the CMC perspective. Please refer to the OPQ review in Panorama for additional details.

5. Clinical Pharmacology

5.1 Executive Summary

The Office of Clinical Pharmacology (Division of Infectious Disease Pharmacology and Division of Pharmacometrics) reviewed the information contained in this sNDA. The clinical pharmacology information submitted in the sNDA supports the approval of Cefazolin for Injection USP and Dextrose Injection USP in the Duplex® Container for perioperative prophylaxis in pediatric patients ages 10 to 17 years, administered by an intravenous (IV) infusion route.

5.2 Summary of Clinical Pharmacology Assessment

The Applicant proposed the dosing regimen shown below for perioperative prophylaxis in pediatric patients ages 10 to 17 years based on the results of Studies HC-G-H-1202 and HC-G-H-1601, population PK analyses, and simulation results.

- Patients <50 kg body weight: 1 gram IV administered 1/2 hour to 1 hour prior to the start of surgery.
- Patients ≥50 kg body weight: 2 gram IV administered 1/2 hour to 1 hour prior to the start of surgery.

The clinical study report for HC-G-H-1202 was originally reviewed by Dr. Yang He (see details in review dated 9/14/2014 in DARRTS). Please refer to the following section for a summary of Study HC-G-H-1601 and Appendix 17.4 for the pharmacometrics review.

5.2.1. Study HC-G-H-1601

Study HC-G-H-1601, entitled, "A Phase 4, Open-label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects with a Weight of at Least 25 kg but Less Than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects With a Weight of at Least 60 kg Scheduled for Surgery," enrolled 61 subjects, and 58 (95.1%) completed the study. Thirty-three subjects were in the ≥25 kg-<60 kg group and received a single dose of 1 g cefazolin. Twenty eight subjects were in the ≥60 kg group and received a single dose of 2 g cefazolin.

In a PK subset of 26 subjects (13 subjects in each treatment group), pharmacokinetic (PK) samples were obtained at 0.5 to 1 hour, 2 hours (±15 minutes), 3 hours (±15 minutes), and 4 hours (±15 minutes) after the start of the study drug infusion. Among these 26 subjects, 8 subjects (30.8%) were in the 10- to 13-year-old age bracket, and 18 (69.2%) subjects were in the greater than 13- to 17-year-old age bracket. Cefazolin plasma concentrations were used to refine the population PK model.

Plasma samples were analyzed by [redacted] (b) (4). The performance of the bioanalytical assay was reported in the report titled, "Quantitation of Cefazolin in Human Plasma via HPLC with MS/MS Detection, Project AKBY," and is acceptable.

5.2.2. General Dosing and Therapeutic Individualization

Based on the population PK analysis, body weight was the only covariate on CL and Vc, Vp, and Q, with fixed allometric exponents of 0.75 and 1, respectively. To identify the weight cut-off for 1 g dosing in pediatric patients for perioperative prophylaxis, the Applicant performed Monte Carlo simulations with age and weight ranges of 10-17 years and 25-85 kg, respectively, with normal renal function. The simulation results indicated that a cut-off of 50 kg resulted in median exposures that were comparable to adult geometric mean exposures after receiving the labelled dose.

The pharmacometrics reviewer conducted an independent analysis to identify the weight cut-off for the 1 g dose by creating a virtual population with a weight distribution between 10-17 years according to the CDC growth chart. The simulation results support the Applicant's finding that 50 kg is an appropriate cut-off below and above which patients should receive the 1 g and 2 g dose, respectively.

6. Sources of Clinical Data and Review Strategy

From a clinical perspective, one study (Study HC-G-H-1601) was reviewed for safety. The study enrolled 61 patients, ages 10-17 years, who received a single dose of cefazolin equivalent to a 2 gram adult exposure for perioperative prophylaxis. (Please see the Clinical Protocol Synopsis in the Clinical Appendices.)

6.1 Review Strategy

The clinical reviewer utilized JReview for the analysis of the safety datasets. The PK assessment was performed by the clinical pharmacology reviewers.

7. Statistical and Clinical and Evaluation

This study was conducted to evaluate the safety of a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery. No efficacy evaluation was performed.

Table 2: Subject Disposition

Disposition	Single Dose of 1 g Cefazolin N=33 n (%)	Single Dose of 2 g Cefazolin N=28 n (%)	Totals N=61 n (%)
Completed	30 (90.9)	28 (100.0)	58 (95.1)
Discontinued	3 (9.1)	0 (0.0)	3 (4.9)
Reason for discontinuation from study[a]			
Lost to follow-up	2 (6.1)	0 (0.0)	2 (3.3)
Investigator decision	1 (3.0)	0 (0.0)	1 (1.6)
Safety population[b]	33 (100.0)	28 (100.0)	61 (100.0)
PK population[c]	13 (39.4)	13 (46.4)	26 (42.6)

Source: CSR (Study HC-G-H-1601) Table 10-1 Summary of Subject Disposition (All Subjects) page 43.
[a] Percentages for primary reason for discontinuation are based on the number of subjects discontinued. All other percentages are based on the number of subjects enrolled.
[b] The safety analysis set included all subjects who received any drug.
[c] The pharmacokinetic analysis set included all subjects from whom at least 1 measurable concentration pharmacokinetic sample was obtained.
Abbreviations: PK, pharmacokinetics

A total of 61 subjects were enrolled and 58 subjects (95.1%) completed the study; 30 of 33 subjects (90.9%) who received 1 g of cefazolin, and 28 of 28 subjects (100.0%) who received 2 g of cefazolin.

Three subjects (4.9%) discontinued the study early (all were enrolled in the 1 gram treatment arm):

- Subject (b) (6) and Subject (b) (6) were lost to follow-up
- Subject (b) (6) was discontinued per investigator decision. The treating physician requested the 30-minute infusion of study drug be stopped before the full dose was administered and to instead use a nonstudy antibacterial drug.

All 61 enrolled subjects (100%) were included in the safety analysis set, and the 26 subjects (42.6%) who consented to participate in the PK portion of the study were included in the PK analysis set. Twenty-one subjects in the PK analysis set were considered PK completers.

7.1 Review of Safety

Since the approval of Ancef (cefazolin injection) in 1973, significant safety experience has been gained in the U.S. and worldwide. Cefazolin is a well-tolerated cephalosporin antibacterial drug and its range of adverse reactions is similar to the other approved cephalosporins. The most common adverse reactions listed in the USPI for cefazolin are gastrointestinal (nausea, vomiting, diarrhea), and allergic reactions (anaphylaxis, urticaria, skin rash).

7.1.1. Review of the Safety Database

Overall Exposure

Sixty-one pediatric subjects received a single dose of 1 g or 2 g cefazolin.

Demographics and Baseline Characteristics

Demographic and baseline characteristics for subjects in the safety analysis set are summarized in the following table.

Table 3: Summary of Subject Demographics and Baseline Characteristics

Demographics and Baseline Characteristics	Treatment A N=33	Treatment B N=28	Overall N=61
Age (years)			
Mean (SD)	13.5 (2.03)	14.9 (1.96)	14.1 (2.10)
Minimum, maximum	10, 17	11, 17	10, 17
Age categories			
≥10 to ≤13 years	18 (54.5)	9 (32.1)	27 (44.3)
>13 to ≤17 years	15 (45.5)	19 (67.9)	34 (55.7)
Sex, n (%)			
Male	17 (51.5)	12 (42. 9)	29 (47.5)
Female	16 (48.5)	16 (57.1)	32 (52.5)

Demographics and Baseline Characteristics	Treatment A N=33	Treatment B N=28	Overall N=61
Race, n (%)			
White	26 (78.8)	20 (71.4)	46 (75.4)
Black or African American	4 (12.1)	6 (21.4)	10 (16.4)
Asian	2 (6.1)	0	2 (3.3)
Other	0	1 (3.6)	1 (1.6)
Multi-racial	1 (3.0)	1 (3.6)	2 (3.3)
Ethnicity, n (%)			
Hispanic or Latino	2 (6.1)	4 (14.3)	6 (9.8)
Not Hispanic or Latino	31 (93.9)	24 (85.7)	55 (90.2)
Height (cm)			
Mean (SD)	158.61 (12.701)	169.33 (8.899)	163.43 (12.301)
Minimum, maximum	132.5, 183.7	156.8, 190.0	132.5, 190.0
Weight (kg)			
Mean (SD)	49.68 (8.322)	81.49 (17.694)	64.29 (20.815)
Minimum, maximum	25.9, 59.3	60.9, 122.7	25.9, 122.7

Source: CSR- Table 14.1.2.1 Demographic and Baseline Characteristics Safety Analysis Set
Note: Percentages are based on the number of subjects in the safety analysis set. Treatment A: 1 g cefazolin for pediatric surgical subjects weighing ≥25 kg but <60 kg. Treatment B: 2 g cefazolin for pediatric surgical subjects weighing ≥60 kg.
Abbreviations: SD, standard deviation

For the safety analysis set, subjects ranged in age from 10 to 17 years of age, with an overall mean age of 14.1 years. The majority of subjects were white (46 subjects, 75.4%). There was a similar number of male subjects (29 subjects, 47.5%) and female subjects (32 subjects, 52.5%). Twenty-seven subjects (44.3%) were in the ≥10 to ≤13 year age group, and 34 subjects (55.7%) were in the >13 to ≤17 year age group.

7.2 Relevant Characteristics of the Safety Population

All the subjects underwent outpatient surgical procedures; 62% of which were orthopedic procedures.

Adequacy of the Safety Database

The overall number of pediatric subjects exposed to a single dose of 1 gm cefazolin and 2 gm cefazolin (n=61) appears adequate to perform a safety evaluation.

7.2.1. Safety Results

Deaths

No deaths were reported during the study.

Serious Adverse Events

Only 1 SAE was reported: post-operative pain. The subject had received a single dose of cefazolin 1 g. The investigator considered the SAE unrelated to study drug and reported it as mild in severity. (Note: The subject narrative is described in the Clinical Appendicies.)

Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations due to adverse reactions in the study.

Significant Adverse Events

No significant AEs were observed in the study.

Treatment Emergent Adverse Reactions

Treatment emergent adverse reactions (TEAEs) by System Organ Class (SOC) and Preferred Terms reported in the study are summarized in Table 4 below:

Table 4: Summary of Treatment-Emergent Adverse Reactions by SOC and Preferred Terms

System Organ Class Preferred Term	Single Dose of 1 g Cefazolin N=33 n (%)	Single Dose of 2 g Cefazolin N=28 n (%)	Totals N=61 n (%)
Subjects with at least 1 TEAE[a]	13 (39.4)	14 (50.0)	27 (44.3)
Gastrointestinal disorders	4 (12.1)	6 (21.4)	10 (16.4)
Nausea	3 (9.1)	6 (21.4)	9 (14.8)
Constipation	0 (0.0)	1 (3.6)	1 (1.6)
Vomiting	2 (6.1)	0 (0.0)	2 (3.3)

System Organ Class Preferred Term	Single Dose of 1 g Cefazolin N=33 n (%)	Single Dose of 2 g Cefazolin N=28 n (%)	Totals N=61 n (%)
General disorders and administration site conditions	4 (12.1)	6 (21.4)	10 (16.4)
Infusion site pain	2 (6.1)	2 (7.1)	4 (6.6)
Infusion site erythema	0 (0.0)	2 (7.1)	2 (3.3)
Chills	1 (3.0)	1 (3.6)	2 (3.3)
Infusion site warmth	1 (3.0)	1 (3.6)	2 (3.3)
Pyrexia	0 (0.0)	1 (3.6)	1 (1.6)
Injection site bruising	0 (0.0)	1 (3.6)	1 (1.6)
Catheter site bruise	1 (3.0)	0 (0.0)	1 (1.6)
Infusion site bruising	1 (3.0)	0 (0.0)	1 (1.6)
Skin and subcutaneous tissue disorders	2 (6.1)	3 (10.7)	5 (8.2)
Rash	0 (0.0)	2 (7.1)	2 (3.3)
Pruritus	1 (3.0)	1 (3.6)	2 (3.3)
Erythema	1 (3.0)	0 (0.0)	1 (1.6)
Rash macular	1 (3.0)	0 (0.0)	1 (1.6)
Vascular disorders	0 (0.0)	2 (7.1)	2 (3.3)
Hypotension	0 (0.0)	1 (3.6)	1 (1.6)
Hot flush	0 (0.0)	1 (3.6)	1 (1.6)
Nervous system disorders	3 (9.1)	2 (7.1)	5 (8.2)
Migraine	0 (0.0)	1 (3.6)	1 (1.6)
Clumsiness	0 (0.0)	1 (3.6)	1 (1.6)
Headache	3 (9.1)	0 (0.0)	3 (4.9)
Dizziness	1 (3.0)	0 (0.0)	1 (1.6)
Injury, poisoning and procedural complications	3 (9.1)	1 (3.6)	4 (6.6)
Incision site pruritus	0 (0.0)	1 (3.6)	1 (1.6)
Contusion	0 (0.0)	1 (3.6)	1 (1.)
Procedural pain	2 (6.1)	0 (0.0)	2 (3.3)
Anaesthetic complication neurological	1 (3.0)	0 (0.0)	1 (1.6)
Vascular access site pain	1 (3.0)	0 (0.0)	1 (1.6)
Respiratory, thoracic and mediastinal disorders	3 (9.1)	1 (3.6)	4 (6.6)
Sneezing	0 (0.0)	1 (3.6)	1 (1.6)
Nasal pruritus	2 (6.1)	0 (0.0)	2 (3.3)
Painful respiration	1 (3.0)	0 (0.0)	1 (1.6)
Eye disorders	1 (3.0)	1 (3.6)	2 (3.3)
Ocular hyperaemia	0 (0.0)	1 (3.6)	1 (1.6)
Eye pain	0 (0.0)	1 (3.6)	1 (1.6)
Conjunctival hyperaemia	1 (3.0)	0 (0.0)	1 (1.6)
Blood and lymphatic system disorders	0 (0.0)	1 (3.6)	1 (1.6)
Anaemia	0 (0.0)	1 (3.6)	1 (1.6)
Musculoskeletal and connective tissue disorders	1 (3.0)	1 (3.6)	2 (3.3)
Muscle spasms	0 (0.0)	1 (3.6)	1 (1.6)
Pain in extremity	1 (3.0)	0 (0.0)	1 (1.6)
Infections and infestations	1 (3.0)	0 (0.0)	1 (1.6)
Nasopharyngitis	1 (3.0)	0 (0.0)	1 (1.6)
Investigations	1 (3.0)	0 (0.0)	1 (1.6)
Blood creatine phosphokinase increased	1 (3.0)	0 (0.0)	1 (1.6)
Ear and labyrinth disorders	1 (3.0)	0 (0.0)	1 (1.6)
Vertigo	1 (3.0)	0 (0.0)	1 (1.6)

Source:Medical Officer's analysis using JReview.
[a] Count subjects and % with data
Abbrevviations: SOC, system organ class; TEAE, treatment-emergent adverse event

Reviewer's Comment: *The most commonly reported TEAEs by SOC were from the Gastrointestinal disorders and General disorders and Administration Site conditions. No surgical site infections were reported as TEAEs in this study.*

Overall, 27 subjects (44.3%) reported a total of 61 TEAEs during the study; 13 of 33 subjects (39.4%) reported TEAEs after the 1 g dose, and 14 of 28 subjects (50.0%) reported TEAEs after the 2 g dose. The most frequently reported TEAEs overall were nausea, reported by 9 subjects (14.8%), infusion site pain, reported by 4 subjects (6.6%), and headache, reported by 3 subjects (4.9%).

The majority of subjects experienced TEAEs considered unrelated to study drug (24 subjects [39.3%]) overall; only 3 subjects (4.9%) experienced TEAEs considered possibly related to study drug (nasal pruritus [in the 1 g arm] and pruritus and hypotension [both in the 2 g arm]). All TEAEs were considered mild in severity.

Infusion-Related Reactions

The site of study drug infusion was evaluated for signs of infusion-related reactions including pain, erythema/redness, induration/swelling, localized warmth, and bruising at the infusion site. Infusion site assessments were performed at 15 minutes, 0.5 to 1 hour, and 3 hours after the start of the study drug infusion, postsurgery, and at the safety follow-up visit.

The following table summarizes the infusion site reactions experienced during the study.

Table 5: List of Adverse Event Coding for Infusion-Site Reactions

Patient	Reported Term of Adverse Event	AE Preferred Term	System Organ Class Term	High-Level Group Term	High-Level Term
(b) (6)	Slight bruising of right hand	Contusion	Injury, poisoning and procedural complications	Injuries NEC	Skin injuries NEC
	Bruising at infusion site	Injection site bruising	General disorders and administration site conditions	Administration site reactions	Injection site reactions
	Tenderness at infusion site	Infusion site pain	General disorders and administration site conditions	Administration site reactions	Infusion site reactions
	Erythema, study drug infusion site	Infusion site erythema	General disorders and administration site conditions	Administration site reactions	Infusion site reactions
	Warmth, study drug infusion site	Infusion site warmth	General disorders and administration site conditions	Administration site reactions	Infusion site reactions
	Pain, study drug infusion site	Infusion site pain	General disorders and administration site conditions	Administration site reactions	Infusion site reactions
	Warmth, study drug infusion site	Infusion site warmth	General disorders and administration site conditions	Administration site reactions	Infusion site reactions
	Subject reported pain at infusion site at the 0.5-1hr time point for the infusion site assessment	Infusion site pain	General disorders and administration site conditions	Administration site reactions	Infusion site reactions
	Patient reported soreness in arm when IV was placed, not when medication was administered.	Vascular access site pain	Injury, poisoning and procedural complications	Procedural related injuries and complications NEC	Cardiac and vascular procedural complications
	Slight bruising from IV removal	Catheter site bruise	General disorders and administration site conditions	Administration site reactions	Implant and catheter site reactions
	Slight redness around IV site	Infusion site erythema	General disorders and administration site conditions	Administration site reactions	Infusion site reactions
	Pain at IV site	Infusion site pain	General disorders and administration site conditions	Administration site reactions	Infusion site reactions
	Slight bruising at IV site	Infusion site bruising	General disorders and administration site conditions	Administration site reactions	Infusion site reactions

Source: Applicant's Table 1: List of Adverse Event Coding- Cumulative Data (HC-G-H-1601)-May 4, 2020-Information Request Page 3.
Abbreviations: AE, adverse event; IV, intravenous; NEC, not elsewhere classified

Reviewer's Comment: *Subject (b) (6) reported two AEs (injection site bruising and infusion site pain), Subject (b) (6) reported two AEs (infusion site erythema, and infusion site warmth), Subject (b) (6) reported two AEs (infusion site pain, and infusion site warmth), and Subject (b) (6) reported two AEs (infusion site pain, and infusion site bruising).*

Vital Signs

Subject (b) (6) had a blood pressure of 74 mm Hg systolic and 35 mm Hg diastolic on 24 May 2018 at 12:32 that was reported as a TEAE of transient hypotension. The study drug infusion (2 gram dose) occurred from 12:01 to 12:31. The decreased blood pressure occurred 1 minute after the end of study drug infusion, at the start of the surgical procedure (hardware removal right knee; time of surgery 12:32 to 13:32). The event did not require treatment and resolved without sequelae. A subsequent blood pressure measured later the same day at 15:01 was 105 mm Hg systolic and 59 mm Hg diastolic.

Electrocardiograms (ECGs)

The majority of subjects had ECGs that were considered normal. There were no TEAEs reported based on ECG results. Mean ECG parameters observed after study drug administration were similar to those observed at baseline.

Laboratory Findings

Hematology

There were no significant hematology findings. As would be expected, the mean hematocrit and hemoglobin were lower at the postsurgery visit as compared with baseline, and mean leukocytes and neutrophils were higher at the postsurgery visit as compared with baseline.

Clinical Chemistry

The mean values for clinical chemistry were generally similar after study drug administration as compared with baseline values. As would be expected, mean CPK values increased post-surgery, but reverted to baseline levels or lower by the safety follow-up visit.

7.3 Conclusions and Recommendations

In conclusion, a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age administered for perioperative prophylaxis was generally safe and tolerated by the subjects in this study. The clinical reviewer recommends approval of this sNDA.

According to the clinical pharmacology assessment, the PK information submitted in the application supports the approval of Cefazolin for Injection USP and Dextrose Injection USP in the Duplex Container for perioperative prophylaxis in pediatric patients ages 10 to 17 years, administered by an intravenous (IV) infusion route.

8. Advisory Committee Meeting and Other External Consultations

There were no issues in the application that needed input from an advisory committee or external experts.

9. Pediatrics

The Applicant conducted Study HC-G-H-1601, a safety study of a single dose of cefazolin for preoperative prophylaxis using the dose equivalent to a 2-gram adult exposure in 100 pediatric patients, ages 10-17 years to fulfill PMR 1869-2.

The Division presented the findings of Study HC-G-H-1601 to the Pediatric Review Committee (PeRC) on 5/12/2020. PeRC agreed that the submission fulfilled PMR 1869-2.

10. Labeling Recommendations

10.1 Prescription Drug Labeling

The following table provides a high-level summary of the review team's labeling recommendations.

Reviewer's Comment: *Please note that the reviewer's proposed significant labeling changes (below) are high level changes and not necessarily direct quotations from the PI. Additional high level labeling changes were made to subsection 12.3 Pharmacokinetics of the USPI (please see the Clinical Pharmacology section of this Unireview for additional details).*

Table 6: Summary of Significant Prescribing Information Labeling Changes

Labeling Section	Applicant-Proposed Labeling	FDA-Revised Indication
1 INDICATIONS AND USAGE	(b) (4)	Specified that the indications for treatment of infections were for adults and pediatric patients for whom appropriate dosing with this formulation can be achieved. Specified that the perioperative prophylaxis indication was for adults and pediatric patients,10-17 years of age. For pediatric patients, (b) (4) were provided as an example.
Reviewer's Comment: *The treatment indication statements were updated to include that Cefazolin for Injection and Dextrose Injection is indicated in adults and pediatric patients for whom appropriate dosing with this formulation can be achieved. The indication statement for perioperative prophylaxis in pediatric patients was revised to reflect the population studied, namely pediatric patients 10 to 17 years of age.The majority of the surgeries were* (b) (4)*.*		
1.INDICATIONS AND USAGE		Added the following phrase to the treatment indications (subections 1.1 to 1.8 of the PI): "in adults and pediatric patients for whom appropriate dosing with this formulation can be achieved"
2. DOSAGE AND ADMINISTRATION		
Important Administration Instructions	Applicant proposed Cefazolin for Injection and Dextrose Injection (b) (4)	FDA revised to read as: "If a dose of Cefazolin for Injection and Dextrose Injection is required that does not equal 1 gram or 2 grams, this product is not recommended and an alternative formulation of cefazolin should be considered."
Dosage for Treatment of Indicated Infections in Pediatric Patients	Dosing instructions for pediatric treatment indications (b) (4)	Table added to improve readability.
Dosage for Perioperative Prophylaxis in Pediatric Patients Aged 10 to 17 years	(b) (4)	Table added to improve readability.
Dosage in Pediatric Patients with Renal Impairment	No dosage recommendations for pediatric patients with renal impairment.	Dosing recommendations for pediatric patients with renal impairment added in the form of a table to improve readability.
Reviewer's Comment: *The Applicant's dosing regimen for perioperative prophylaxis in pediatric patients 10 to 17 years old is based on population PK analysis using pooled data from healthy adults (n=24), pediatric patients aged 10 to 17 years (n=26), and pediatric patients aged 10 to 12 years (n=12).*		

Labeling Section	Applicant-Proposed Labeling	FDA-Revised Indication
6.1. ADVERSE REACTIONS in Pediatric Patients for Perioperative Prophylaxis	No adverse reactions for Study 1 were included in the PI by the Applicant.	Included the following: In Study 1 (Study HC-G-H-1601), a single dose of Cefazolin for Injection and Dextrose Injection 1 g or 2 g (weight-based dosing) for perioperative prophylaxis, the most frequently reported adverse reactions were nausea (14.8%), infusion site pain (6.6%), and headache (4.9%). There were no adverse reactions leading to study discontinuation or deaths reported during the study. In Study 2 (Study HC-G-H-1202), 12 pediatric patients 10 to 12 years of age administered a single dose of Cefazolin for Injection and Dextrose Injection 1 g or 2 g (weight-based dosing) for perioperative prophylaxis, the safety findings were similar to those observed in adult patients and the pediatric patients in Study 1.
Reviewer's Comment: *The adverse reactions reported in Study 1 and Study 2 are consistent with the adverse reactions already found in the Ancef USPI.*		
6.2. Postmarketing Experience	No Postmarketing Experience subsection was proposed by the Applicant.	Added Immune system disorders: Serum sickness-like reaction and Renal and urinary disorders: Acute tubulointerstitial nephritis (ATIN)
Reviewer's Comment: *Based on a safety review of recent literature publications for cefazolin, the clinical reviewer found two serious adverse reactions (i.e., serum sickness-like reaction and acute tubulointerstitial nephritis) that warrant mentioning under the newly created subsection 6.2 Postmarketing Experience.*		

Labeling Section	Applicant-Proposed Labeling	FDA-Revised Indication
8. USE IN SPECIFIC POPULATIONS		
8.1 Pregnancy	(b) (4)	Available published clinical data do not demonstrate an association of major birth defects or miscarriage with cephalosporin antibacterial drug use in pregnancy. Animal reproduction study data were moved from 8.3 to 8.1 and did not demonstrate an increased risk of malformations. Included standard language on estimated background risk of birth defect, loss, or other adverse outcomes during pregnancy in the U.S. population.
8.2 Lactation	(b) (4)	Cefazolin is present in human milk, but is not expected to accumulate in the breastfed infant. No data on effects of cefazolin on breastfed child or on milk production. The benefits/risk of breastfeeding while a mother is on cefazolin should be considered along with the mother's clinical need for cefazolin.
8.3 Females and Males of Reproductive Potential	No evidence of impaired fertility in nonclinical studies. No human data available.	This section was deleted because no data were located regarding effects of cefazolin on human infertility or hormonal contraception. In addition, there is no indication of fetal harm that would require pregnancy testing or contraceptive use during treatment with cefazolin.
8.4 Pediatric Use	Included information regarding the pediatric perioperative prophylaxis Studies 1 and 2.	Provided additional information related to the pediatric perioperative Studies 1 and 2. Updated the language regarding the limitations of the available dose strengths and recommendation to use an alternative formulation of cefazolin in patients who cannot receive the full 1 or 2 gram doses. Noted that the safety and effectiveness of Cefazolin for Injection and Dextrose Injection for perioperative prophylaxis have not been established in pediatric patients younger than 10 years old.
10. OVERDOSAGE	None	Accidental overdosage resulting in seizures may occur in patients with renal impairment who receive doses greater than the recommended dosage of Cefazolin for Injection and Dextrose Injection *[see Warnings and Precautions (5.2)].* If seizures associated with accidental overdosage occur, discontinue Cefazolin for Inhjection and Dextrose Injection and give supportive treatment.

Reviewer's Comment: *Added wording to section 10 based on warning (in subsection 5.2 of the PI) regarding seizures that may occur with accidental overdosage in patients with renal impairment.*

Labeling Section	Applicant-Proposed Labeling	FDA-Revised Indication
	(b) (4)	

Abbreviations: USP, United States Pharmacopeia; PI, Prescribing information; AEs, adverse events

11. Postmarketing Requirements and Commitment

Data from the postmarketing pediatric study used to satisfy PMR 1869-2 were included in this sNDA to evaluate Cefazolin for Injection and Dextrose Injection for perioperative prophylaxis in pediatric patients 10 to 17 years of age.

PMR 1869-2 will be considered fulfilled.

No additional postmarketing studies are needed at this time.

12. Division Director (Clinical) Comments

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

13. Appendices

13.1 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.

UpToDate® Surgical Prophylaxis

Ancef® (cefazolin for injection) [package insert], 06/02/2004

13.2 Financial Disclosure

A financial disclosure report was submitted.

Covered Clinical Study (Name and/or Number): HC-G-H-1601

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of principal investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor: 0		

Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant)

Table 7: List of Principal Investigators

Investigator	Site Number	Site Address
Michael Schmitz, MD	100	Arkansas Children's Hospital 1 Children's Way Little Rock, AR 72202
Shawn Safford, MD	102	102 Highland Avenue, SE Suite 404 Roanoke, VA 24013
Peter Szmuk, MD	105	Children's Health, Dallas 1935 Medical District Drive Dallas, TX 75235
Sumit Gupta, MD	106	204 North Keane Street Suite 102 Columbia, MO 65201
Maria Matuszczak, MD	107	McGovern Medical School 6431 Fannin Street, MSB 5.020 Houston, TX 77030

13.3 OCP Appendices (Technical documents supporting OCP recommendations)

13.3.1. Population PK Analysis

13.3.1.1. Review Summary

The Applicant's population PK analysis is acceptable for determination of the appropriate weight cutoff below and above which patients should receive the cefazolin 1 g and 2 g dose, respectively. Both goodness-of-fit plots and prediction corrected visual predictive checks indicate that the final population PK model is adequate in characterizing the PK profile of Cefazolin for Injection and Dextrose Injection in adult subjects and pediatric surgical patients. The inter-individual variability (IIV) for CL (27.1%) and Vc (36.3%) were small. IIV for Vp and Q were fixed to 0%. Eta Shrinkages for CL (1.2%) and Vc (23.8%) are reasonable and support evaluation of covariates of CL and Vc. Renal excretion is a major route for cefazolin elimination, although creatinine clearance (CLCR) was tested as a covariate for renal clearance (Clr), it was not a significant covariate because most subjects had normal renal function. Body weight was the only covariate on CL and Vc, Vp, and Q, with fixed allometric exponents of 0.75 and

1, respectively. The estimated PK parameters, such as CL and Vc appear reasonable. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

The developed model was used to support labeling of Cefazolin for Injection and Dextrose Injection as outlined in Table 8.

Table 8: Reveiwer's Specific Comments on Applicant's Final Population PK model

Utility of the Final Model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Pediatric dosing is dependent on body weight. Body weight is a significant covariate on CL and Vc	Through Monte-Carlo simulations the Applicant's analysis shows that pediatric subjects weighting <50 kg should receive 1 g IV, while those ≥50 kg should receive 2 g to match pediatric exposures to those observed in adults
	Extrinsic factor	Extrinsic factors were not evaluated for effect on PK parameters	Monte-Carlo simulation for exposure matching is acceptable since the model predictive performance was reasonable as indicated by prediction corrected visual predictive checks (PcVPC) and shrinkage for CL is reasonable (1.2%)
Derive exposure metrics for exposure-response analyses	Predicted exposures from the PK model were not used for exposure vs. response analyses		
Predict exposures at alternative dosing regimen	The model was not used to assess predicted exposures at other doses than 1 g and 2 g		Cefazolin and dextrose formulations are available at the 1 g and 2 g dose of cefazolin

Source: Reviewer's Table
Abbreviations: CL, apparent clearance; IV, intravenous; PK, pharmacokinetics; Vc, central compartment volume

13.3.1.2. Introduction

The primary objectives of this analysis were to:

- Refine a previously developed cefazolin population PK model (based on adult and pediatric 10-12 years) by incorporating data from pediatric subjects 10-17 years old (Study HC-C-H-1601).
- Utilize a final model for updating cefazolin dose recommendations in pediatric surgery patients 10-17 years old.

13.3.1.3. Model development

Data

The analyses were based on PK data from 3 studies. The study design, study population, and timing of blood samples varied among the 3 clinical studies. Brief descriptions of the studies are presented in Table 9.

The final NONMEM data file for analysis contained 721 PK observations from 62 subjects. Table 10 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 9: Summary of Studies with PK Sampling Included in Population PK Analysis

Study Number	Patient Population	Study Design	Dosing Regimen	PK Sample Collection
HC-G-H-0906	Healthy adults	Phase 1, open label, randomized, multiple dose PK study	1.5 g or 2 g infused over 15 min. Single dose on Day 1, followed by TID dosing Days 2-10, finally single dose on Day 11	Days 1 and 11: predose and 0.13, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dose administration. Morning predose samples on Days 2 through 10
HC-G-H-1202	Pediatric surgical patients 10-12 yrs old	Open label, non-randomized, single dose study for surgical prophylaxis, PK and safety evaluation	1 g for patients <50 kg and 2 g for patients ≥50 kg, infused over 30 min	Blood samples were drawn at: end of infusion, 0.25, 0.5, 1, 2, 3, 6, and 8 hours after the end of infusion.
HC-G-H-1601	Pediatric surgical patients 10-17 yrs old	Phase 4, Open label, non-randomized, parallel group, single dose study for surgical prophylaxis, PK and safety evaluation	1 g for patients <60 kg and 2 g for patients ≥60 kg, infused over 30 min	Blood samples were drawn at: between 0.5-1 hr, and at 2, 3, and 4 (+- 0.25 hr) after start of infusion

Source: Reviewer's independent analysis
Abbreviations: PK, pharmacokinetics; TID, three times a day; hr, hour

Table 10: Summary of Baseline Demographics in the Population PK Dataset

Demographic Characteristic Parameter	Pediatrics		Adults	
	1 g Dose N=21	2 g Dose N=17	1.5 g Dose N=12	2 g Dose N=12
Race, n (%)				
American Indian/Alaska Native	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)
Caucasian	15 (71.4)	12 (70.6)	6 (50.0)	3 (25.0)
Black/African American	4 (19.0)	3 (17.6)	6 (50.0)	9 (75.0)
Asian	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Other/Unspecified	1 (4.8)	1 (5.9)	0 (0.0)	0 (0.0)
Sex, n (%)				
Male	13 (61.9)	9 (52.9)	11 (91.7)	10 (83.3)
Female	8 (38.1)	8 (47.1)	1 (8.3)	2 (16.7)
Age (years), mean (SD)	12.90 (2.39)	14.12 (2.60)	44.08 (7.96)	33.92 (8.17)
Height (cm), mean (SD)	155.67 (14.41)	167.47 (10.44)	176.83 (9.60)	176.00 (9.33)
Weight (kg), mean (SD)	47.65 (9.97)	75.19 (17.94)	83.52 (10.20)	79.28 (11.23)
BSA (kg/m^2), mean (SD)	1.44 (0.21)	1.87 (0.26)	2.01 (0.17)	1.96 (0.18)
CLCRN (mL/min/1.73 m^2), mean (SD)	128.62 (39.83)	116.10 (37.41)	88.72 (20.59)	96.50 (17.54)

Source: Reviewer's independent analysis
Abbreviations: BSA, body surface area; CLCRN, normalized creatinine clearance; PK, pharmacokinetics; SD, standard deviation

Base Model

The base model was a population PK model developed using cefazolin PK data from healthy adults and pediatric surgical patients in Studies HC-G-H-0906 and HC-G-H-1202. The base model was a two-compartment structural model with zero-order input through IV administration and linear elimination kinetics. The model was parameterized in non-renal clearance (CLnr), renal clearance (CLr), central compartment volume (Vc), inter-compartment clearance (Q), and peripheral volume (Vp). Creatinine clearance (CLCR) was a covariate on CLr and body weight (WT) were covariates for total clearance (CLt). Body weight was also a covariate for Vc, Vp, and Q. Covariate coefficient for CLCR was estimated while coefficients for WT were fixed to literature values of 0.75 for CL and Q, and 1 for Vc and Vp. Estimated model parameters and parameterization of covariate effects are given in Table 11 below. Body weight based allometric scaling of the PK parameters aimed at enabling prediction of cefazolin exposure in children (10-17 yrs). However, after inclusion of data from Study HC-G-1601 and re-estimation of parameters, the base model was no longer able to describe PK in adults (HC-G-H-0906) and in pediatric surgical patients (HC-G-H-1202). The model failed internal validation, prediction corrected visual predictive check indicated under-prediction of PK data from Studies HC-G-H-0906 and HC-G-H-1202 (See Figure 1).

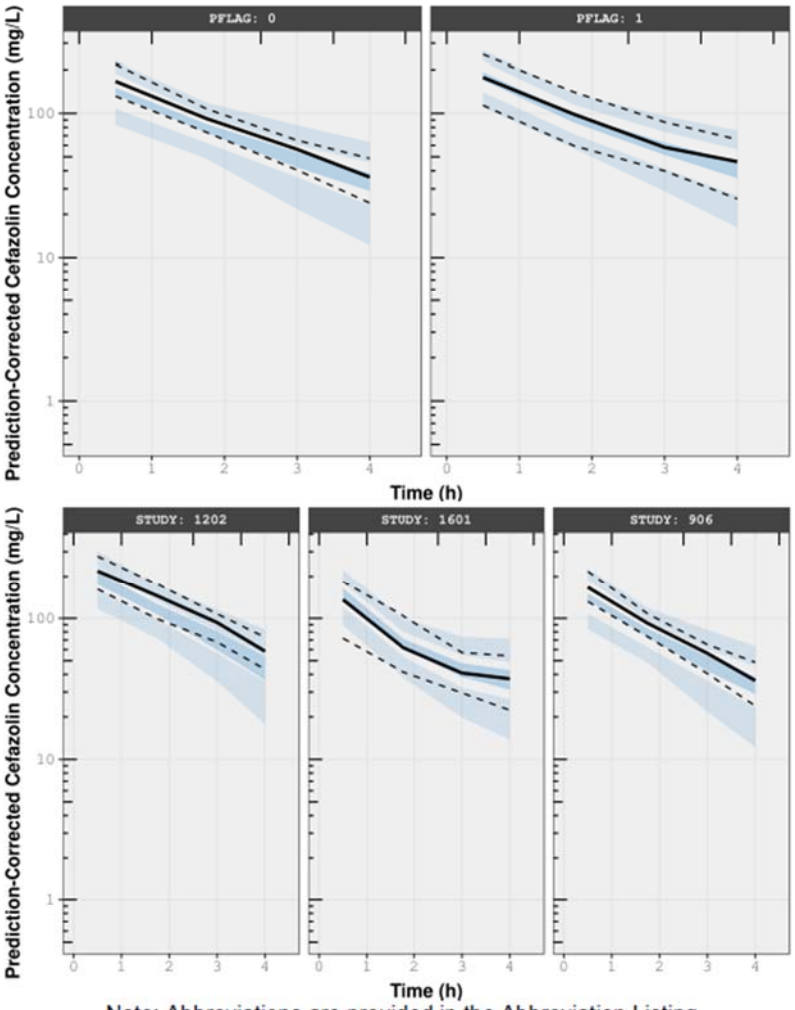
Table 11: Estimated Model Parameters and Parameterization of the Covariate Effects for the Base Model

Parameter	Population mean		Magnitude of interindividual variability (%CV)	
	Final estimate	Bootstrap %SEM	Final estimate	Bootstrap %SEM
CLr (L/hr) coefficient	3.63	3.15		
PEDS shift (Proportional shift in CL if pediatric subject)	-0.335	22.9	0.0122 (11.0% CV)	33.3
CLcr power	0.337	51.3		
IOV	1.0	—	0.0115 (11.0% CV)	20.2
Vc (L) coefficient	4.72	4.84	0.0351 (18.7% CV)	30.4
CLd (L/hr) coefficient	7.89	11.0		
Residual variability model				
Constant CV component	0.0112 (10.6% CV)	10.5		
Additive component	0.845	48.5		
Minimum value of the objective function = 4359.982				

Source: Applicant's Clinical Study Report (Sponsor study number HC-G-H-1202 , page 63 of 1001)
Abbreviations: CL, apparent clearance: CV, coefficient of variation; SEM, structural equation modeling; Vc, central compartment volume ; IOV, inter occasion variability; CLr, renal clearance; CLcr, creatinine clearance

Inter-individual variability (IIV) was modeled assuming a log-normal distribution for patient level random effects. Residual variability was modelled as a combined additive plus proportional residual error on cefazolin concentration. Model evaluations and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Figure 1: Prediction Corrected Visual Predictive Checks Using the Base Model Developed With Studies HC-G-H-0906 and HC-G-H-1202



Note: Abbreviations are provided in the Abbreviation Listing.
PFLAG represents flag variable for denoting whether the population is adult or pediatric.
Black lines represent 50th (solid) and 5th/95th percentiles (dashed) of the observed data; Dark blue shaded region represents the 95% confidence interval around the 50th percentile of predictions; light blue shaded regions represent 95% confidence intervals around the 5th (lower) and 95th (upper) percentiles of predictions.

Source: Applicant's report number ICPD 00477-1 (page 33 of 143)

Covariate Analysis

To improve the ability of the population PK model to characterize cefazolin PK across population, the following changes were made:

- Day 2 - 11 concentrations were excluded from analysis for 3 reasons: subjects receiving 1.5 g had paradoxically higher cefazolin concentrations on Days 2-10 compared to those receiving the 2 g dose; despite 33% dose difference no dose proportionality was observed with Day 11 PK data; and the analysis was intended for Day 1 single dose administration, therefore Day 11 PK is irrelevant.

- Due to exclusion of Day 2 - 11 data, inter-occasional variability parameter was removed from the model.
- Limiting PK analysis to Day 1 data resulted in removal of proportional shift in CL for pediatric subjects.
- Exploration of covariance indicated correlation between CL and Vc, therefore covariance was introduced.
- Since most subjects had CLCRN in the normal range of renal function, the CLr-CLCRN covariate relationship was removed. This resulted in a non-significant increase in OFV ($\Delta OFV = 3.9$) and decrease in model conditional number (124.7 - 78.6) justifying removing the relationship.
- Body weight based allometric scaling of clearance and volume parameters were maintained. Exponents were fixed to literature values.

13.3.1.4. Final Model

The parameter estimates for the final covariate model are listed in Table 12. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 2. The Visual Predictive Check (VPC) plot for the final covariate model with adult and pediatric data are given in Figure 3.

Table 12: Parameter Estimates and Objective Function Values of Applicant's Final Model

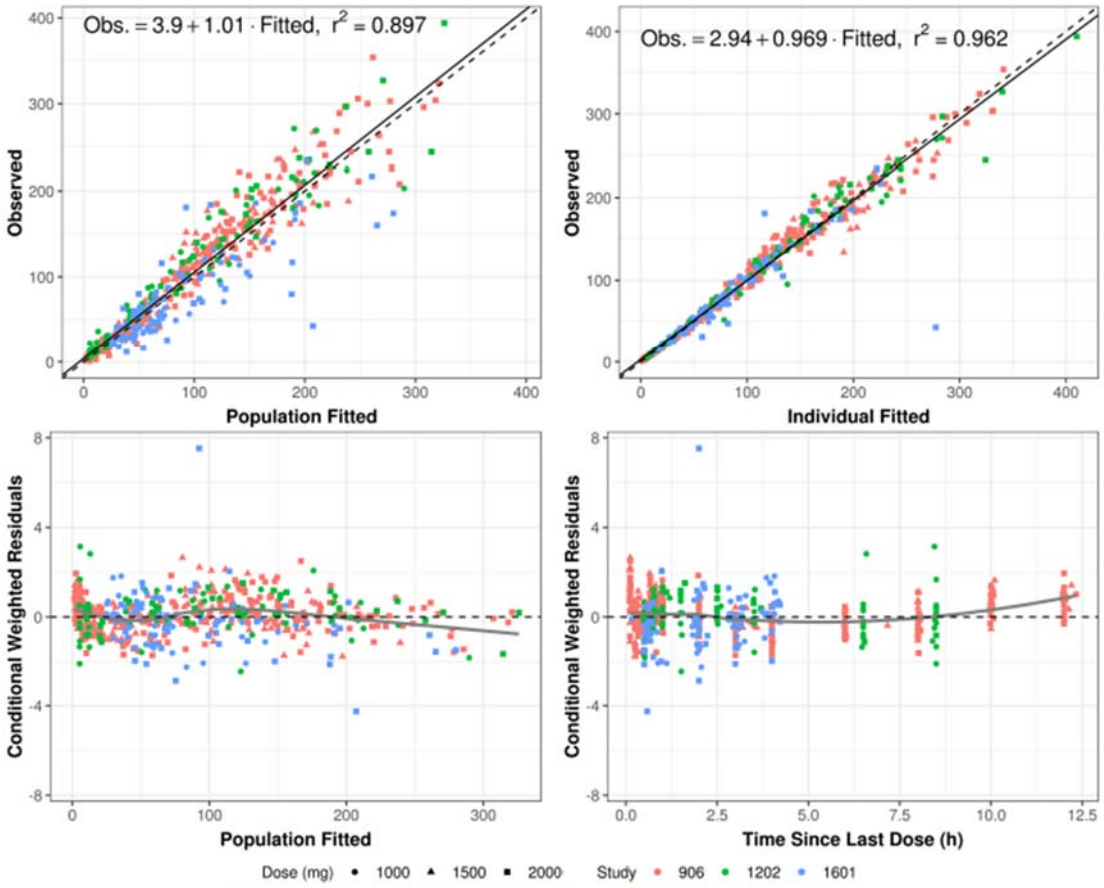
Parameter[a, b, c]	Population Mean		Magnitude of IIV (CV%)		
	Estimate	%RSE	Estimate	%RSE	%Shrinkage
CL_R (L/h)	3.43	3.7	27.1[d,e]	27.9	1.2
CL_{NR} (L/h)	0.153	FIXED			
V_C (L)	5.38	6.0	36.3	21.0	5.4
CL_D (L/h)	8.04	9.6	---	---	---
V_P (L)	3.84	3.2	---	---	---
Proportional RV (CV%)	11.1	32.0	---	---	11.8
Additive RV (mg/L)	0.5	FIXED	---	---	11.8
Condition number: 78.6					

Note: Abbreviations are provided in the Abbreviation Listing.

a. Cefazolin total clearance is calculated as
$CL = [0.153 + 3.43] \cdot \left(\frac{WTKG}{70}\right)^{0.75} \times \exp(IIV)$
b. Cefazolin V_C and V_P coefficients are multiplied by $(WTKG/70)^1$
c. Cefazolin CL_D coefficient is multiplied by $(WTKG/70)^{0.75}$
d. IIV of systemic CL as noted in a.
e. CL-V_C correlation (%RSE): 75.2% (30.0%)

Source: Applicant's report number ICPD 00477-1 (page 44 of 143)
Abbreviations: CL_D, distribution clearance;CL_{NR}, non-renal clearance; CL_R, renal clearance; CV, coefficient of variation; IIV, inter-individual variability; RV, residual variability;Vc, central compartment volume; Vp, peripheral compartment volume

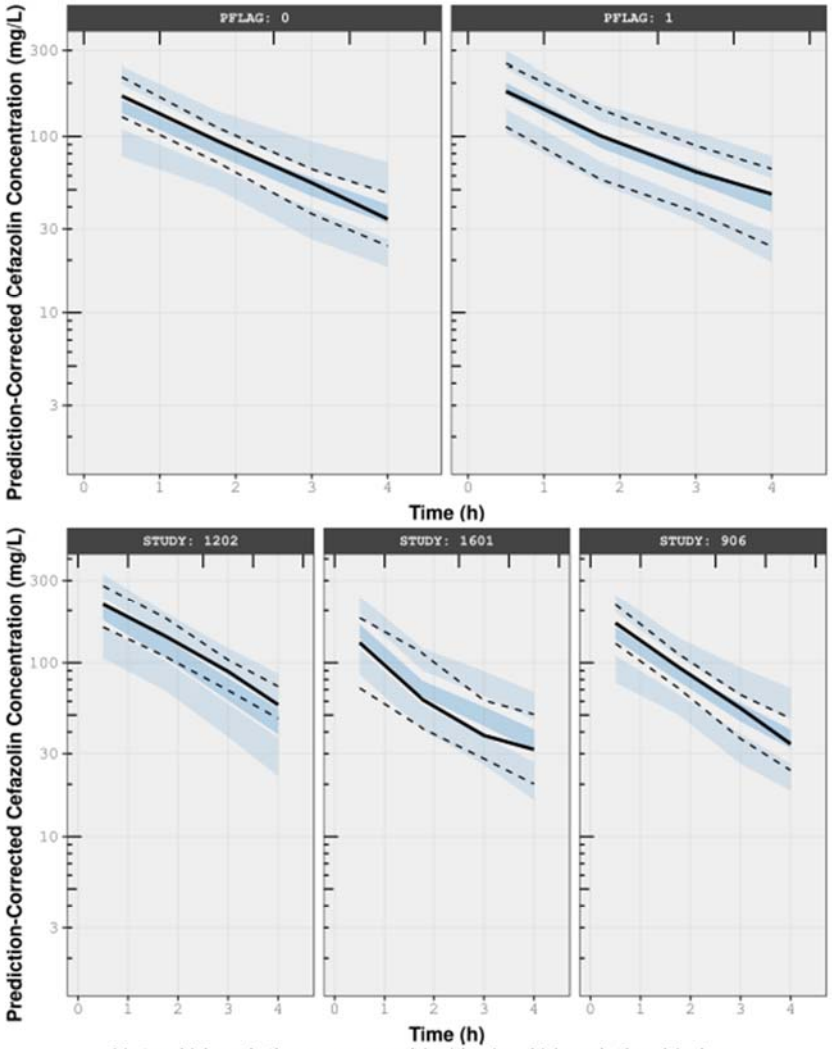
Figure 2: Goodness-of-Fit Plot for the Cefazolin Population PK Model in Pediatric Surgical Patients and Healthy Adults (Final Model)



Note: Abbreviations are provided in the Abbreviation Listing.
Note: Two CWRES values eclipsed the threshold value of ±4 but were ultimately retained secondary to their inability to influence either population- or individual-level fitting.
Dashed lines represent reference lines (line of identity, top; zero-residual line, bottom); solid lines represent lines of best fit (top) or loess smoothers through the data (bottom).

Source: Applicant's report number ICPD 00477-1 (page 42 of 143)
Abbreviations: Obs, observed

Figure 3: Prediction Corrected Visual Predictive Check of the Final Model



Note: Abbreviations are provided in the Abbreviation Listing.
PFLAG represents flag variable for denoting whether the population is adult or pediatric.
Black lines represent 50th (solid) and 5th/95th percentiles (dashed) of the observed data; Dark blue shaded region represents the 95% confidence interval around the 50th percentile of predictions; light blue shaded regions represent 95% confidence intervals around the 5th (lower) and 95th (upper) percentiles of predictions.

Source: Applicant's report number ICPD 00477-1 (page 46 of 143)

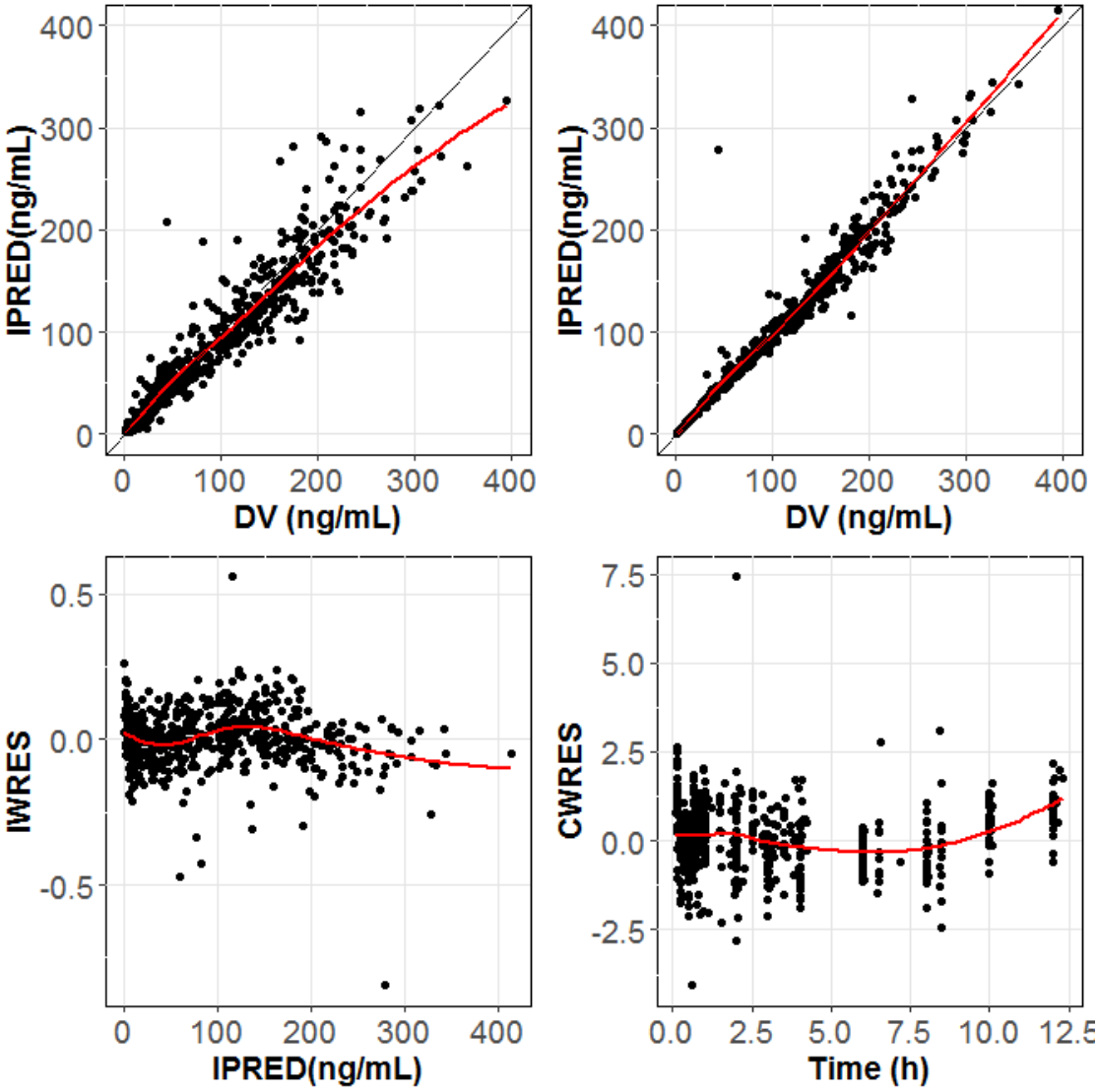
The reviewer finds the Applicant's model development steps and identification of covariate effects to be acceptable. Therefore, the reviewer did not perform independent exploration of covariate effects. However, the Applicant fixed the additive residual to half of the limit of quantification value (0.5 mg/L). The reviewer repeated the Applicant's analysis, unfixing the additive residual and refixing to the estimated parameter. Results from the reviewer's analysis are given in Table 13 and goodness of fit plots in Figure 4. Parameter estimates from the reviewer's final model were consistent with those reported by the Applicant.

Table 13: Parameter Estimates and Objective Function Values From Reviewer's Repeat Analysis of Applicant's Final Model

Parameters	Estimates (RSE)
OFV	2853.978
CLr (L/h)	3.417(4%)
Vc (L)	5.413(6%)
Q (L/h)	7.552(9%)
Vp (L)	3.89(3%)
CLnr (L/h)	0.153(NA%)
BSV CL (%CV)	0.2706(14%)
variance correlation between CL and Vc	0.7585(11%)
BSV Vc (%CV)	0.3591(11%)
Proportional residuals (%CV)	0.1146(14%)
Additive residuals (mg/L)	0.1328(NA%)

Source: Reviewer's analysis
BSV for CL and V were the same as those reported by the applicant. Shrinkage was also similar.
Abbreviations: BSV, between-subject variability; CL, apparent clearance; CV, coefficient of variation; OFV, objective function value; Q, intercompartmental clearance; RSE, relative standard error; Vc, central compartment volume; Vp, apparent peripheral volume of distribution; CLr, renal clearance; CLnr, non-renal clearance;

Figure 4: Goodness-of-Fit Plots for Final Applicant's Model Reanalyzed by the Reviewer



Source: reviewer's independent analysis
Abbreviations: CWRES, conditional weighted residuals; DV, dependent values observed; IPRED, individual predictions; IWRES, individual weighted residuals;

Reviewer's conclusion: *The Applicant's final population PK model adequately describes the observed data and is therefore acceptable for simulation of exposures in pediatric subjects at different doses based on practical weight cut-offs.*

13.3.1.5. Identification of Weight Cut-Off for 1 g Dosing in Pediatric Surgical Patients

The Applicant performed Monte Carlo simulations to identify a weight cut-off below which pediatric dosing would be a 1 g single dose infused over 30 min for perioperative prophylaxis

instead of the 2 g for heavier patients. In these simulations, the Applicant created a virtual pediatric population with age and weight ranges of 10-17 years and 25-85 kg, respectively. The virtual patients were assumed to have normal renal function. Specifically, the virtual patients were created as follows.

- Six thousand virtual patients were created (3000 for ages 10-12 years, and 3000 for 13-17 years) by assuming uniform age distribution between 10-17 years. Approximately 50% of the subjects were female.

- For each subject, two Z-scores were simulated. Both Z-scores were sampled from a normal distribution with mean = 0. The standard deviations were 0.75 and 0.5 for the first and second normal distributions, respectively. The Z-score from the first distribution (first z-score) was used to calculate the individual's height using equation (1). The first z-score was also multiplied with probability of second Z-score in the second normal-distribution to obtain a third Z-score ($Third\ Z-score\ =\ first\ Z-score\times probability\ of\ first\ Z-score$). The third Z-score was used to calculate the individual's weight using equation (1).

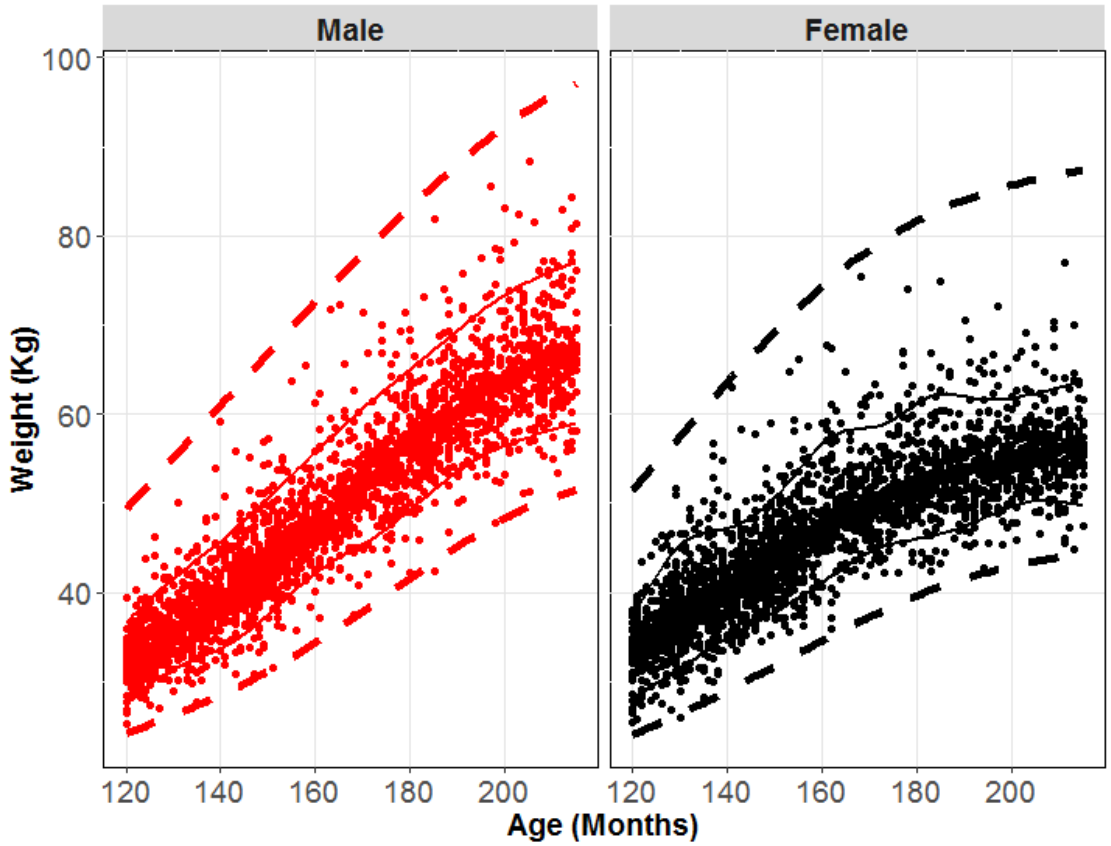
- CLCR was assigned to each individual using a standard equation that assumes normal renal function, adjusted for age and BSA.

$$\begin{aligned} X\ &=\ M\times[(1+LSZ)^{1/L}], \qquad L\ \neq\ 0 \\ X\ &=\ M\times e^{(SZ)}, \qquad\qquad L\ =\ 0 \end{aligned}$$

$$\begin{aligned} Whereby: \\ X\ &=\ Weight\ or\ height\ variable \\ M\ &=\ Median\ of\ X\ for\ age\ as\ given\ in\ CDC\ growth\ chart \\ L\ &=\ Box-cox\ transformation\ parameteras\ given\ in\ CDC\ growth\ chart \\ S\ &=\ generalized\ coefficientofvariationas\ given\ in\ CDC\ growth\ chart \\ Z\ &=\ simulated\ Z-score \end{aligned} \qquad (1)$$

Weight versus age profiles of the virtual patients are as given in Figure 5. It can be seen from the figure that the 3rd and 97th percentiles of weight of the virtual patients are much higher and smaller compared to respective parameters of the CDC growth chart indicating that the range of weight distribution per age for the simulated patients is much smaller than the range for the true population distribution.

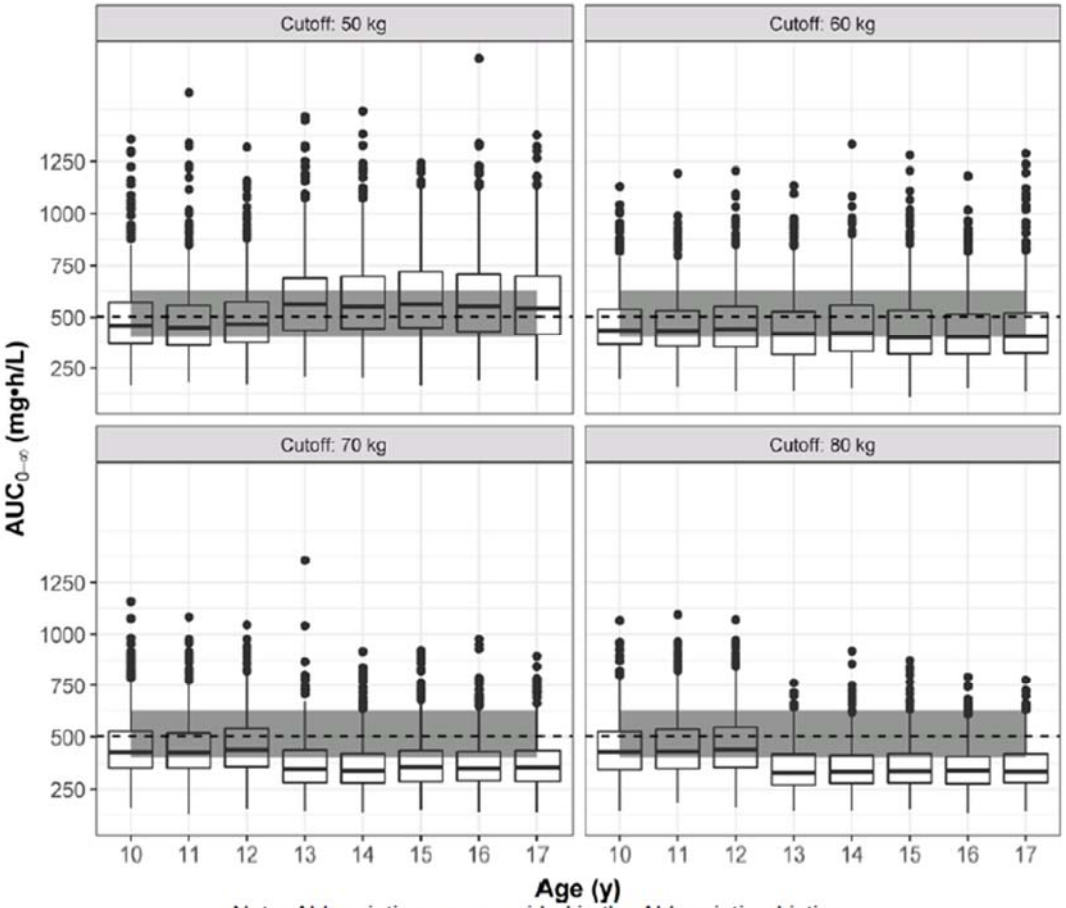
Figure 5: Weight vs. Age Profiles for Virtual Patients Created by the Applicant



Source: reviewer's analysis based on applicant's description on creation of virtual population
Thick dashed line represent 3rd and 97th percentiles of the CDC growth chart while solid lines represent 3rd and 97th percentiles of the virtual population

For each virtual patient, the final population PK model was used to simulate individual clearance (CLi) and concentration-time profiles which were used to calculate $AUC_{0-\infty}$ and $C_{max,}$ respectively. The considered cut-offs for 1 g dosing were 50 kg, 60 kg, 70 kg, and 80 kg. Figure 6 shows the $AUC_{0-\infty}$ distribution at different ages after 1 g or 2 g single IV dose given depending on cut-offs of 50, 60, 70, or 80 kg. A cut-off of 50 kg results in median exposures that are comparable to adult geometric mean exposure. At higher cutoffs, the median exposures are consistently below the geometric mean exposure in adults. Therefore, 50 kg is an appropriate cutoff for 1 g dosing in pediatric subjects.

Figure 6: Box and Whisker Plots of the Simulated $AUC_{0\text{-infty}}$ in Pediatric Surgical Patients by Age and Stratified by Weight Cutoff



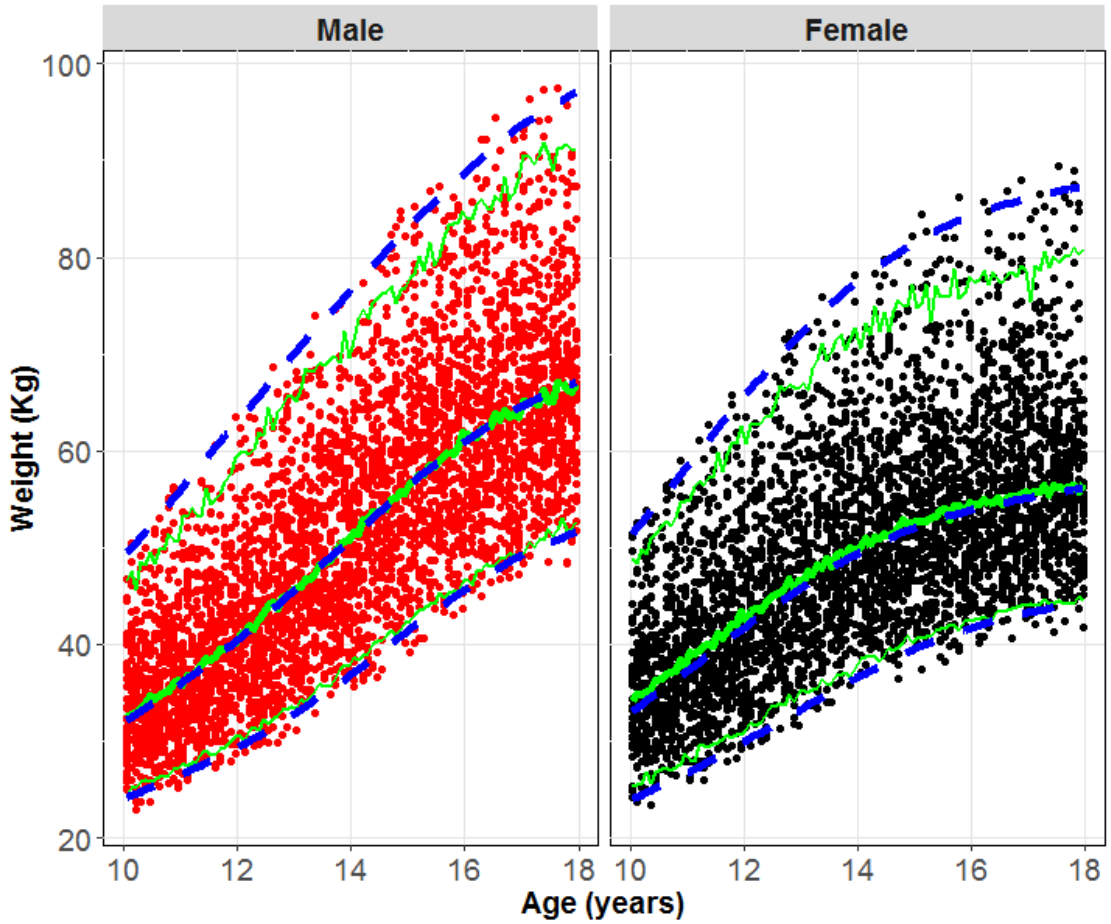
Note: Abbreviations are provided in the Abbreviation Listing.
Dashed horizontal line is geometric mean for adults; band represents 80-125% of geometric mean. Line in middle of box is the median, upper and lower limits of the box represent the 75th and 25th percentiles, respectively.

Source: Applicant's report number ICPD 00477-1 (page 49 of 143)
Abbreviaitons: AUC, area under the curve over the total time

13.3.1.6. Reviewer's Independent Analysis for Identification of Weight Cut-Off for 1 g Dose

The reviewer created a virtual population with a weight distribution at each age that reflects the CDC growth chart (See Figure 7). For creation of virtual population, mean and standard deviation of Box-Cox or log transformed weight and height were back-calculated using M, L and S parameters from the CDC growth chart. The calculated mean and standard deviation were used to obtain Z-scores which were subsequently used to calculate weight and height at each age in the CDC growth chart using equation (1).

Figure 7: Weight vs. Age Profiles for Virtual Patients Created by the Reviewer



Source: reviewer's independent analysis.
Thick dashed lines represent 3rd, 50th and 97th percentiles of the CDC growth chart while solid lines represent 3rd, 50 and 97th percentiles of the virtual population.

Summary demographics of the virtual population are a given in Table 14.

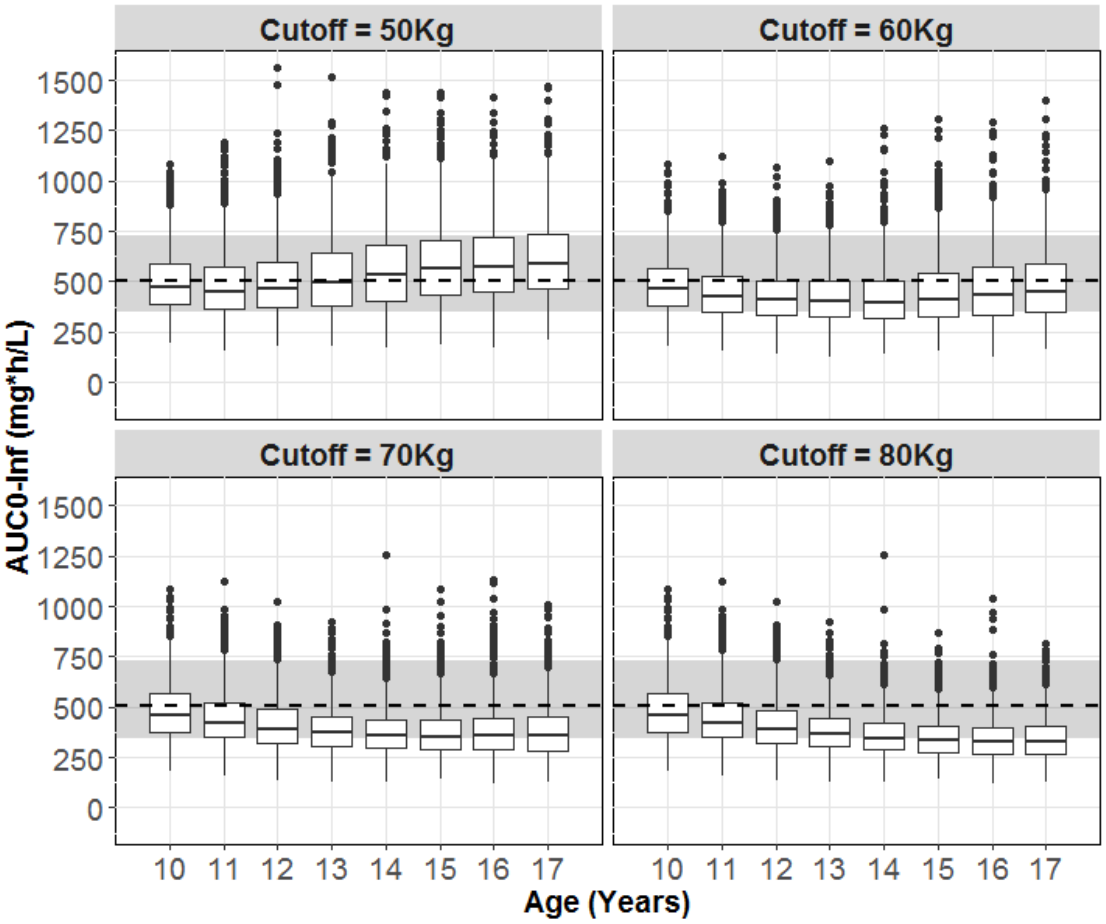
Table 14: Summary Demographics of the Virtual Population

Demographic Characteristic Parameter	Adolescents (13-17 Years) N=5000	Children (10-12 Years) N=3000
Age (years), mean (SD)	15.50 (1.44)	11.50 (0.86)
Weight (kg), mean (SD)	56.92 (10.96)	40.50 (8.47)
Height (Cm), mean (SD)	165.72 (9.21)	146.82 (8.89)
CLCRN (mL/min/1.73 m^2), mean (SD)	129.75 (24.11)	121.14 (21.17)
GFR (mL/min/1.73 m^2), mean (SD)	123.49 (25.34)	132.85 (26.44)
Sex, n (%)		
Male	2584 (51.7)	1581 (52.7)
Female	2416 (48.3)	1419 (47.3)
Age (years), n (%)		
10		1000 (33.3)
11		1000 (33.3)
12		1000 (33.3)
13	1000 (20.0)	
14	1000 (20.0)	
15	1000 (20.0)	
16	1000 (20.0)	
17	1000 (20.0)	

Source: reviewer's independent analysis
Abbreviatios: CLCRN, normalized creatinine clearance; GFR, glomerular filtration rate; SD, standard deviation

Using this virtual population and model parameters estimated by the reviewer, the reviewer performed Monte-Carlo simulations to determine the weight cutoff for the 1 g dosing in pediatric patients. The results of the reviewer's analysis are given in Figure 8. The figure shows boxplots overlaid on a band of 90% confidence interval of the geometric mean (geomean = 502, 90% CI = 347 - 730 mg*h/L). Using the cutoff of 50 kg, all boxplots are contained within this band. At higher cutoffs, the median exposures are consistently below the reference geometric mean exposure in adults and the boxplots are not entirely contained within the 90% CI band indicating underexposure for some individuals compared to adult patients receiving 2 g dosing. These results support the Applicant's finding that 50 kg is an appropriate cutoff below and above which patients should receive the 1 g and 2 g dose, respectively.

Figure 8: Box and Whisker Plots of the Simulated $AUC_{0\text{-}inf}$ in Pediatric Surgical Patients by Age and Stratified by Weight Cutoff: Results From Reviewer's Analysis



Source: reviewer's independent analysis
Abbreviations: $AUC_{0\text{-}inf}$, area under the curve over the total time

13.4 Clinical Appendices

The following postmarketing requirement studies were conducted by the Applicant as required by PREA:

PMR 1869-1: Brief Summary

Study Title: Single dose study to evaluate the pharmacokinetics of Cefazolin for Injection USP and Dextrose Injection USP in the DUPLEX® Drug Delivery System in Pediatric Subjects of 10–12 years (inclusive) scheduled for surgery.

This was a multiple-center, non-comparative (open-label) study that examined the PK of cefazolin in children aged 10 years to 12 years (inclusive) (N=12) following administration of a

single IV dose of cefazolin (1 g or 2 g) for surgical prophylaxis. Children aged 10 years to 12 years (inclusive) who had scheduled surgical procedures requiring administration of cefazolin as a prophylactic antibacterial were eligible for enrollment. The data obtained in the study were compared to data from a previous study conducted in normal, healthy adults as well as simulated adolescent data. Given that the Cefazolin Duplex® product is only available in fixed doses of 1 g or 2 g, the following weight-based dosage regimen was employed for the surgical prophylaxis study in children aged 10 years to 12 years: 1 g cefazolin for subjects weighing ≥25 kg to <50 kg, and 2 g cefazolin for subjects weighing ≥50 kg to ≤85 kg.

Based on the PK results of cefazolin in 12 pediatric surgical subjects aged 10 to 12 years in this first PMR study and the revised population PK model for cefazolin, the upper weight limit of 59 kg was set for the 1 g dose. Subjects weighing greater than or equal to 60 kg received the 2 g dose.

Safety results: Nine (9) adverse reactions were reported by six (6) subjects. The majority of adverse reactions were mild or moderate and due to gastrointestinal disorders (one case of nausea and five cases of vomiting. The remaining three adverse reactions were related to vascular disorders (two cases of hypotension and one case of hypertension). One serious adverse reaction was reported in a subject who developed hypotension during the 30-minute 2 g cefazolin infusion period. There were no discontinuations from the study due to AEs. No deaths. It is notable that all adverse reactions reported in the study are labeled in the cefazolin PI.

PMR 1869-2 :Clinical Protocol Synopsis

STUDY TITLE: A Phase 4, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects with a Weight of at Least 25 kg but Less Than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects With a Weight of at Least 60 kg Scheduled for Surgery

STUDY PERIOD: 20 November 2017 (First Subject First Visit) 26 July 2019 (Last Subject Last Visit)

OBJECTIVES:

Primary objective:
The primary objective was to evaluate the safety of a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

Secondary objective:
The secondary objective was to determine the cefazolin plasma concentrations following a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

METHODOLOGY:
This was a Phase 4, open-label, single-dose, parallel-group, multicenter, safety study of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

Approximately 110 subjects were originally planned to be enrolled and assigned to 1 of the 2 dose groups in a 1:1 ratio (55 subjects in each group). Subjects with a weight of at least 25 kg but less than 60 kg received a single dose of 1 g cefazolin (Treatment A). Subjects with a weight of at least 60 kg received a single dose of 2 g cefazolin (Treatment B). Dose groups were not balanced by age or gender.

The study consisted of a screening period of up to 30 days, a treatment period on Day 1 (day of surgery), and a follow-up period including a visit on Day 8 (±1 day). The maximal study duration for an individual subject was 39 days.

During the screening period (up to 30 days before the study drug administration), all subjects had screening and baseline examinations performed to ensure their eligibility for the study. The screening visit could have occurred on Day 1 (day of surgery) as long as all screening visit assessments were properly completed. Study drug was administrated on Day 1 (day of surgery) over 30 minutes as an infusion starting 0.5 to 1 hour before surgery began and followed institutional guidelines. Planned surgical procedures may have been performed in an outpatient or inpatient setting and were expected to last no longer than 3 hours. If the surgery was unexpectedly extended beyond the 3-hour limit, additional doses of study drug were permitted according to institutional guidelines. Safety was assessed by monitoring adverse events (AEs), physical examinations, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory tests. During the follow-up period, a follow-up visit was performed on Day 8 (±1 day) for safety assessments.

In a subset planned for 40 subjects, 4 pharmacokinetic (PK) samples were to be obtained to determine the cefazolin plasma concentrations in this population. Pharmacokinetic samples were obtained at 0.5 to 1 hour, 2 hours (±15 minutes), 3 hours (±15 minutes), and 4 hours (±15 minutes) after the start of the study drug infusion. A minimum of 10 of the 40 subjects were planned to be 10 to 13 years old. If the surgery was unexpectedly extended beyond the 3-hour limit and an additional dose of study drug was administered, best efforts were made to obtain the 3-hour and possibly the 4-hour PK samples prior to administration of the additional dose of study drug. Pharmacokinetic sample collection did not continue after the administration of an additional dose of study drug.

Subject completion was defined as completion of the follow-up visit or the time of the subject's last data collection. In the cases of an additional dose of study drug, subjects from whom a 3-hour PK sample was obtained prior to administration of the additional dose were considered PK completers.

Duration of treatment: After reconstitution, the study drug solution was administered IV over 30 minutes through an infusion line by using an infusion pump on Day 1 (day of surgery) for surgery prophylaxis. The study drug administration began 0.5 to 1 hour prior to the start of surgery and followed institution guidelines. If the surgery was unexpectedly extended beyond the 3-hour limit, additional doses of study drug were permitted according to institutional guidelines.

CRITERIA FOR EVALUATION:
Safety: Safety was determined by monitoring AEs, physical examination findings, vital sign measurements, ECGs, and clinical laboratory test results.

Pharmacokinetics: Cefazolin plasma concentrations were presented in data listings and summarized using descriptive statistics. Cefazolin plasma concentrations were used to refine the population PK model.

Statistical Methods: All safety analyses were based on the safety analysis set, and all PK analyses were based on the PK analysis set.

Results: (Note: The study results are discussed under respective clinical safety and pharmacokinetic sections in this unireview.)

Narrative for Subject (b) (6) who reported an SAE (post-operative pain)- PMR 1869-2

The subject was a 17-year-old white female who underwent a left knee arthroscopic-assisted reconstruction with bone-patellar tendon-bone autograft on (b) (6). The subject weighed 58.7 kg at screening.

The subject's medical history included tympanostomy tube placement (2001), obstructive sleep apnea (2006), tonsillectomy and adenoidectomy (2006), and acne (2014, ongoing). A left knee anterior cruciate ligament rupture occurred on (b) (6) and was the event that precipitated the surgical intervention. No prior medications were reported.

Study drug (cefazolin 1 g) was administered over 28 minutes on (b) (6) prior to the surgical procedure. Peri-operative medications included fentanyl 50 µg, propofol 200 mg, dexamethasone 6 mg, lactated ringers (dose unknown), lidocaine hydrochloride 60 mg, fentanyl 25 µg as needed, epinephrine (dose unknown), acetaminophen 750 mg, ondansetron 4 mg, ropivacaine 20 mL, clonidine 50 µg, hydromorphone 0.2 mg, hydromorphone 0.04 mg as needed, Toradol® 30 mg, and oxycodone 5 mg. Diazepam 5 mg and dexmedetomidine 8 µg were administered as needed to treat a concomitant TEAE of emergence delirium (an anesthetic complication).

On (b) (6), the subject was hospitalized for intermittent post-operative pain, mild in intensity. The event was considered serious due to hospitalization. The subject was admitted to the hospital overnight for pain control. Oral acetaminophen 650 mg and oxycodone 5 mg were administered to treat the SAE of post-operative pain. Other medications administered during the overnight hospitalization included sodium chloride 20 mL/hour and cefazolin 1470 mg for infection prophylaxis (non-study drug). Medications continuing at hospital discharge (to be taken as needed) included acetaminophen 325 mg, ibuprofen 200 mg, ondansetron 4 mg, and oxycodone 5 mg. The subject was discharged from the hospital on (b) (6) at which time the event was considered resolved. The investigator reported the causal relationship to study drug as unrelated, and likely related to complications from the surgery itself.

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/s/

JOSEPH C DAVI
11/17/2020 03:47:22 PM

MAUREEN P DILLON PARKER
11/17/2020 08:39:28 PM

SEONG H JANG
11/17/2020 11:08:08 PM

KUNYI WU
11/18/2020 09:27:45 AM

ELIFORD N KITABI
11/18/2020 10:06:48 AM

JUSTIN C EARP
11/18/2020 02:28:34 PM

ALMA C DAVIDSON
11/18/2020 02:40:20 PM

PETER W KIM
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ABIMBOLA O ADEBOWALE
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SUMATHI NAMBIAR
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