Ceftriaxone Sodium CTD

Janki Patel

Edson College of Nursing and Health Innovation, Arizona State University - Online

HCR577 – Global Regulatory Affairs

Professor: Clare Elser

April 15, 2025

Table of Contents

Module 1 Administrative Information

1.1 Forms

1.2 Cover Letters

Roche Pharmaceuticals
1234 N Main St.
San Francisco, CA 12345

Date (Month DD, YYYY)

Food & Drug Administration
Center for Drug Evaluation & Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Sir/Madam,

Roche Pharmaceutical is seeking approval for a new drug application (NDA) for Ceftriaxone Sodium, which they plan to introduce as a third-generation antibiotic. Clinical trials have been conducted on adults and children, and the results showed positive outcomes in effectively treating infections.
Indications:

- Respiratory
- Skin
- Soft Tissue
- Urinary Tract Infection (UTI)
- Uncomplicated Gonorrhea
- Pelvic Inflammatory Diseases

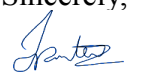
The dosage forms are:

- Pediatric: The total daily dose is 50 to 75mg given a day and should not exceed 2 grams.
- Adult: The daily dose is 1 to 2 grams once a day and should not exceed 4 grams.

Please find attached the completed application for your review.

Thank you for considering my request. If you have any questions or need further information, please don't hesitate to contact me.

Sincerely,



Janki Patel
Director Regulatory Affairs

1.3 Administrative Information

1.3.1 Contact/Sponsor/Applicant Information

1.3.1.1 Change of Address or Corporate Name

1.3.1.2 Change in Contact/agent

1.3.1.3 Change in Sponsor

1.3.1.4 Transfer of Obligation

1.3.1.5 Change in Ownership of an Application or Reissuance of License

1.3.2 Field Copy Certification

1.3.3 Debarment Certification

On the FDA website, I verifies that my name is not on the debarment list. The link I used is this one.

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/fda-debarment-list-drug-product-applications

1.3.4 Financial Certification and Disclosure

1.3.5 Patent and Exclusivity

1.3.5.1 Patient Information

1.3.5.2 Patient Certification

1.3.5.2 Exclusivity Claim

1.3.6 Tropical Disease Priority Review Voucher

1.4 References

1.4.1 Letter of Authorization

1.4.2 Statement of right of reference

1.4.3 List of Authorized Persons To Incorporate by Reference

1.4.4 Cross Reference to Previously Submitted Information

1.5 Application Status

1.5.1 Withdrawal of an IND

1.5.2 Inactivation Request

1.5.3 Reactivation Request

1.5.4 Reinstatement Request

1.5.5 Withdrawal of an Unapproved BLA, NDA, ANDA, or Supplement

1.5.6 Withdrawal of Listed Drug

1.5.7 Withdrawal of Approval of an Application or Revocation

1.6 Meetings

1.6.1 Meeting Request

Requesting TYPE C meeting MONTH, DD, YYYY in order to discuss labeling and warning.

1.12.3 Request to Charge Expanded Access

1.12.4 Request for Comments and Advise

1.12.5 Request for a Waiver

1.12.6 Exception from Informed Consent for Emergency Work

1.12.7 Public Disclosure Statement for Exception from Informed Consent for Emergency Work Research

1.12.8 Correspondence Regarding Exception from Informed Consent for Emergency Work Research

1.12.9 Notification of Discontinuation of Clinical Trial

1.12.10 Generic Drug Enforcement Act Statement

1.12.11 ANDA Basis for Submission Statement

1.12.12 Comparison of Generic Drug and Reference Listed Drug

1.12.13 Request for Waiver for in vivo Studies

1.12.14 Environmental Analysis

1.12.15 Request for in vivo Bioavailability Studies

1.12.16 Field Alert Reports

At this moment, there are no filed Field Alert Reports for Ceftriaxone Sodium. The FAR regulations in 21 CFR 314.81(b)(1) require NDA and ANDA applicants to quickly report specific issues to the FDA to protect patient health (Research, 2024). They must submit a FAR within three working days if they learn about (i) incidents where drugs or their labels are confused with something else and (ii) bacterial contamination or significant changes in the drug product. This rule applies to all products approved under an NDA or ANDA, including drug-device combinations, PET drugs, and medical gases (Research, 2024).

Reference

Research, C. F. D. E. A. (2024, November 5). *Field Alert Report Submission: Questions and Answers Guidance for industry*. U.S. Food And Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/field-alert-report-submission-questions-and-answers-guidance-industry

1.12.17 Orphan Drug Designation

1.13 Annual Report

1.13.1 Summary of Nonclinical Studies

1.13.2 Summary of Clinical Pharmacology Information

1.13.3 Summary of Safety Information

1.13.4 Summary of Labeling Changes

1.13.5 Summary of Manufacturing Changes

1.13.6 Summary of Microbiological Changes

1.13.7 Summary of Other Significant New Information

1.13.8 Individual Study Information

1.13.9 General Investigational Plan

1.13.10 Foreign Marketing

1.13.11 Distribution Data

1.13.12 Status of Postmarketing Study Commitments and Requirements

1.13.13 Status of Other of Postmarketing Studies and Requirements

1.13.14 Log of Outstanding Regulatory Business

1.13.15 Development Safety Update Report (DSUR)

1.14 Labeling

1.14.1 Draft Labeling

1.14.1.1 Draft Carton and Container Label

1.14.1.2 Annotated Draft Labeling Text

1.14.1.3 Draft Labeling Text

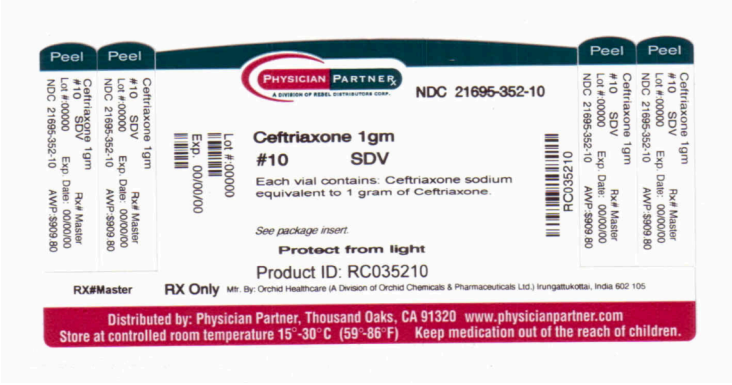
1.14.1.4 Labeling History

1.14.2 Final Labeling

1.14.2.1 Final Carton or Container Labels

Mfg. by: Hospira Healthcare India Pvt. Ltd.

Ceftriaxone 1 gm



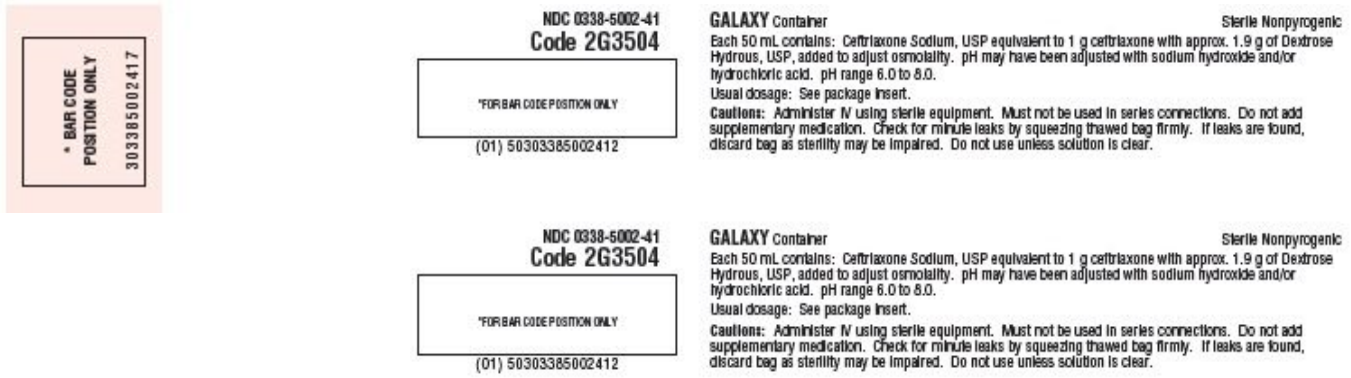
DailyMed - CEFTRIAXONE SODIUM injection, powder, for solution. (n.d.).

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=473ab78d-5015-4a4a-8a2c-8f594b8de41d#i4i_clinical_studies_id_12a633f3-a385-4948-9e10-19c30895eba4

Baxter Ceftriaxone Injection 1 g

Carton Label - 1g - Panel 1

Carton Label - 1g - Panel 2



DailyMed - CEFTRIAXONE-

ceftriaxone sodium injection, solution. (n.d.).

https://www.dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4c5c2d3f-5038-41a1-a2fe-4dcd048dbac1

Baxter Ceftriaxone Injection 2 g

Carton Label - 2g - Panel 1

Carton Label - 2g - Panel 1

Carton Label - 2g - Panel 2

Carton Label - 2g - Panel 2

DailyMed - CEFTRIAXONE-

ceftriaxone sodium injection, solution. (n.d.).

https://www.dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4c5c2d3f-5038-41a1-a2fe-4dcd048dbac1

1.16 Risk Management Plan

1.16.1 Risk Management (Non-REMS)

1.16.2 Risk Evaluation and Mitigation Strategy (REMS)

1.16.2.1 Final REMS

1.16.2.2 Draft REMS

1.16.2.3 REMS Assessment

1.16.2.4 REMS Assessment Methodology

1.16.2.5 REMS Correspondence

1.16.2.6 REMS Modification History

1.17 Postmarketing Studies

1.17.1 Correspondence Regarding Postmarketing Commitments

1.17.2 Correspondence Regarding Postmarketing Requirements

1.18 Proprietary Names

1.19 Pre-EUA and EUA

1.20 General Investigation Plan for Initial IND

Module 2 Product Summary

2.2 Introduction to Summary

The FDA approved ceftriaxone, a third-generation cephalosporin antibiotic. It mainly treats community-acquired pneumonia and mild to severe sickness patients. It is also a recommended drug for the treatment of gonorrhea and bacterial meningitis (Li et al., 2012). This CTD Module 2 presents the Quality Overall Summary (QOS), which includes information on the drug substance, drug product, stability, and control measures. The nonclinical section focuses on key data from animal studies related to pharmacology, pharmacokinetics, and toxicology.

The Clinical Overview highlights findings from the Clinical Summary and individual investigations, summarizing critical clinical data from the CTD (U.S. Department of Health and Human Services et al., 2017). Regulatory organizations use the clinical overview to analyze the advantages and disadvantages of marketing applications, determine the risks and benefits, and help with prescription information. The CTD format satisfies FDA regulations to ensure regulatory fulfillment. Its pharmacokinetics, toxicology, and biopharmaceutical characteristics are investigated to ensure ceftriaxone satisfies safety and efficacy requirements derived from earlier studies.

2.3 Quality Overall Summary

The Quality Overall Summary reviews a product's ingredients, manufacturing process, and chemical properties to ensure it meets quality standards. Ceftriaxone for injection is a powerful antibiotic belonging to the cephalosporin class. It is intended to be administered intramuscular or intravenous. This medication meets the standards set by the United States Pharmacopeia (USP) (*Ceftriaxone: Package Insert / Prescribing Information*, n.d.).

In its powdered form, ceftriaxone sodium appears white to yellowish-orange, dissolving quickly in water. It has limited solubility in methanol and very low solubility in ethanol (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.). Ceftriaxone stays effective for up to two years when stored at the right temperature and kept sterile. This ensures it remains safe and beneficial for patients. Injectable ceftriaxone, which comes in a bulk box from SmartPak® pharmacies, is only meant for individuals who require a whole 1-gram dosage. Patients who need less than a 1-gram quantity shouldn't receive it.

2.4 Nonclinical Overview

The non-clinical overview of Ceftriaxone includes pharmacology, pharmacokinetics, and toxicology data obtained from preclinical studies. In pharmacology, Ceftriaxone works in the body, including its mechanism of action and effectiveness in fighting infections. Pharmacokinetics explains that medication is absorbed, distributed, broken down, and eliminated from the body after it has entered (Dp_Admin, 2024). Toxicology displays Ceftriaxone's possible adverse effects based on preclinical research. Ceftriaxone establishes its safety and efficacy across various animal models.

Ceftriaxone can cause calcium salt concretions to form in the gallbladder bile of dogs and rats (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.). Toxicity data in rats and dogs showed that a lethal dose (LD50) was over 5000 mg/kg, indicating low toxicity. Toxicity studies show overdose, hemodialysis, or peritoneal dialysis won't reduce drug levels, and there is no antidote available (PubChem, n.d.). Ceftriaxone is safe for nursing mothers and is unlikely to harm breastfeeding infants. It may cause minor issues like diarrhea or thrush, but these are not well studied.

2.5 Clinical Overview

Clinical research supports the effectiveness of ceftriaxone in addressing serious bacterial infections such as meningitis, pelvic inflammatory disease, bacterial septicemia, lower respiratory tract infections, urinary tract infections, bone and joint infections, intra-abdominal infections, and surgical prophylaxis (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.). Clinical studies show that ceftriaxone is an effective antibiotic that successfully targets and eliminates harmful bacteria in the body. When used correctly, it also helps lower the chances of bacteria developing resistance to the treatment.

Ceftriaxone is usually safe and well-accepted by most people. The most frequent side effects are shortness of breath, chills, cough, fever, chest pain, sore throat, swollen glands, unusual tiredness or weakness, allergic reactions, diarrhea, and pain at the injection site (*Ceftriaxone Side Effects: Common, Severe, Long Term*, n.d.). These symptoms are generally mild and not severe. Clinical trials have shown that the drug has a good balance between its benefits and potential risks. This positive outcome confirms its continued suggested worldwide treatments.

2.6 Nonclinical Written and Tabulated Summaries

2.6.1 Introduction

Ceftriaxone has been thoroughly studied in nonclinical research to get comprehensive data about its components and impacts. These studies concentrate on the drug's safety processing, absorption, metabolism, mechanism of action, and distribution inside the body. The toxicology aspect is crucial since it helps ensure Ceftriaxone is safe and works well to treat infections (PubChem, n.d.). The body processes the medicine, and it doesn't change significantly for people with liver or kidney conditions or older people. An intramuscular injection of Ceftriaxone causes complete absorption, with maximum plasma levels occurring two to three hours later (*Ceftriaxone Dosing, Indications, Interactions, Adverse Effects, and More*, n.d.).

2.6.2 Pharmacology Written Summary

Ceftriaxone treats infections (respiratory, skin, soft tissue, UTI, ENT) caused by susceptible organisms. Organisms that are generally susceptible to ceftriaxone include S. pneumoniae, S. pyogenes (group A beta-hemolytic streptococci), coagulase-negative staphylococci, Some Enterobacter spp, H. influenzae, N. gonorrhoeae, P. mirabilis, E. coli, Klebsiella spp, M. catarrhalis, B. burgdorferi, and some oral anaerobes. Ceftriaxone is a cephalosporin/cephamycin beta-lactam antibiotic used to treat bacterial infections caused by susceptible, usually gram-positive, organisms. Ceftriaxone has *in vitro* activity against gram-positive aerobic, gram-negative aerobic, and anaerobic bacteria. The bactericidal activity of ceftriaxone results from the inhibition of cell wall synthesis and is mediated through ceftriaxone binding to penicillin-binding proteins (PBPs). Ceftriaxone is stable against hydrolysis by various beta-lactamases, including penicillinases, cephalosporinases, and

extended-spectrum beta-lactamases. However, resistance to ceftriaxone usually occurs through beta-lactamase hydrolysis, altered PBPs, or reduced bacterial cell permeability. Ceftriaxone should not be mixed with or given in the same IV line as diluents/products containing calcium, as they may cause ceftriaxone to precipitate. Ceftriaxone use may also cause biliary sludge or gallbladder pseudolithiasis (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.).

Animal Pharmacology: Concretions consisting of the precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs and baboons treated with ceftriaxone. These appeared as gritty sediment in dogs that received 100 mg/kg/day for 4 weeks. A similar phenomenon has been observed in baboons but only after a protracted dosing period (6 months) at higher dose levels (335 mg/kg/day or more). The likelihood of this occurrence in humans is considered to be low since ceftriaxone has a greater plasma half-life in humans, the calcium salt of ceftriaxone is more soluble in human gallbladder bile, and the calcium content of human gallbladder bile is relatively low.

2.6.3 Pharmacology Tabulated Summary

This part was not included in the PIL.

2.6.4 Pharmacokinetic Written Summary

Pharmacokinetics in the Middle Ear Fluid: In one study, total ceftriaxone concentrations (bound and unbound) were measured in middle ear fluid obtained during the insertion of tympanostomy tubes in 42 pediatric patients with otitis media. Sampling times were from 1 to 50 hours after a single intramuscular injection of 50 mg/kg of ceftriaxone. Mean (± SD) ceftriaxone levels in the middle ear reached a peak of 35 (± 12) μg/mL at 24 hours and remained at 19 (± 7)

μg/mL at 48 hours. Based on middle ear fluid ceftriaxone concentrations in the 23 to 25 hour and the 46 to 50 hour sampling time intervals, a half-life of 25 hours was calculated. Ceftriaxone is highly bound to plasma proteins. The extent of binding to proteins in the middle ear fluid is unknown (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.).

2.6.5 Pharmacokinetic Tabulated Summary

This part was not included in the PIL.

2.6.6 Toxicology Written Summary

Ceftriaxone overdose may increase the risk of urolithiasis and subsequent post-renal acute renal failure (PARF). Other symptoms of overdose are unavailable in the literature. However, they are likely similar to the adverse effects of the medication. If an overdose of ceftriaxone occurs, treat with symptomatic and supportive treatment, as ceftriaxone levels will not be reduced by dialysis (FDA, n.d.).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Mutagenesis

Genetic toxicology tests included the Ames test, a micronucleus test, and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for genotoxic activity in these studies.

Impairment of Fertility

Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 2.8 times (mg/m^2 comparison) the recommended clinical dose of 2 grams/day.

13.2 Animal Toxicology and/or Animal Pharmacology

Concretions consisting of the precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs and baboons treated with ceftriaxone. These appeared as a gritty sediment in dogs that received 100 mg/kg/day for 4 weeks.

A similar phenomenon has been observed in baboons but only after a protracted dosing period (6 months) at higher dose levels (335 mg/kg/day or more).

(*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.)

2.6.7 Toxicology Tabulated Summary

This part was not included in the PIL.

2.7 Clinical Written and Tabulated Summaries

2.7.1 Introduction

Ceftriaxone is a medication widely studied in clinical research, particularly its biopharmaceutical properties and associated analytical methods, clinical pharmacology, and clinical efficacy used to analyze it. These studies also explore how Ceftriaxone works in different groups of people, such as children, pregnant women, those who are breastfeeding, and older adults (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.). A critical aspect of Ceftriaxone is how bacteria can develop resistance to it. Ceftriaxone works against some enzymes that bacteria produce to resist antibiotics, including both Gram-negative and Gram-positive types (*Ceftriaxone: Package Insert / Prescribing Information*, n.d.). Dosing strategies in biopharmaceutical studies to keep the right amount of medicine in the body. They help ensure the medication works effectively and safely for the patient.

2.7.2 Summary of Biopharmaceutical Studies and Associated Analytical Methods

This part was not included in the PIL.

2.7.3 Summary of Clinical Pharmacology Studies

12.1 Mechanism of Action

Ceftriaxone is an antibacterial drug.

12.3 Pharmacokinetics

Average plasma concentrations of ceftriaxone following a single 30-minute intravenous (I.V.) infusion of a 0.5, 1, or 2 g dose in healthy subjects are presented in Table 3. Multiple

intravenous doses ranging from 0.5 to 2 g at 12- to 24-hour intervals resulted in 15% to 36% accumulation of ceftriaxone above single-dose values.

Over a 0.15 to 3 g dose range in healthy adult subjects, the mean elimination half-life ranged from 5.8 to 8.7 hours, plasma clearance ranged from 0.58 to 1.45 L/hour, and renal clearance ranged from 0.32 to 0.73 L/hour.

Distribution

Ceftriaxone is reversibly bound to human plasma proteins and the binding of ceftriaxone decreases with increasing concentration from a value of 95% at plasma concentrations less than 25 mcg/mL to 85% at a plasma concentration of 300 mcg/mL. Over a 0.15 to 3 g dose range in healthy adult subjects, the apparent volume of distribution ranged from 5.8 to 13.5 L.

Ceftriaxone crosses the blood-placenta barrier.

Ceftriaxone penetrates the inflamed meninges of infants and pediatric patients. The average values of maximum plasma concentration, cerebrospinal fluid (CSF) concentrations, elimination half-life, plasma clearance, and volume of distribution after a 50 mg/kg intravenous dose and after a 75 mg/kg intravenous dose in pediatric patients suffering from bacterial meningitis.

After a 1-gram intravenous dose, average concentrations of ceftriaxone, determined from 1 to 3 hours after dosing, were 581 mcg/mL in the gallbladder bile, 788 mcg/mL in the common duct bile, 898 mcg/mL in the cystic duct bile, and 78.2 mcg/gram in the gallbladder wall compared to a corresponding concentration of 62.1 mcg/mL in plasma.

Excretion

Ceftriaxone concentrations in urine.

Thirty-three percent to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug, and the remainder was secreted in the bile and ultimately found in the feces as microbiologically inactive compounds.

The elimination of ceftriaxone is not altered by probenecid.

Special Populations

Average pharmacokinetic parameters of ceftriaxone in healthy subjects, elderly subjects, subjects with renal impairment, and subjects with liver disease are summarized in Table 6. Compared to healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with renal or hepatic impairment; therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2 grams per day. Ceftriaxone was not removed to any significant extent from the plasma by hemodialysis. In 6 of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced, suggesting that plasma concentrations of ceftriaxone should be monitored in these patients to determine if dosage adjustments are necessary.

Drug Interactions

Interaction with Calcium: Two *in vitro* studies, one using adult plasma and the other neonatal plasma from umbilical cord blood, have been carried out to assess the interaction of ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved *in vivo* following administration of 2 grams of ceftriaxone infused over 30 minutes) were combined with calcium concentrations up to 12 mM (48 mg/dL). Recovery of ceftriaxone from plasma was reduced with calcium concentrations of 6 mM (24 mg/dL) or higher in adult

plasma or 4 mM (16 mg/dL) or higher in neonatal plasma. This may be reflective of ceftriaxone-calcium precipitation.

12.4 Microbiology

Mechanism of Action

Ceftriaxone is a bactericidal agent that acts by inhibiting bacterial cell wall synthesis. Ceftriaxone has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Mechanism of Resistance

Resistance to ceftriaxone is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by the FDA. (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.)

2.7.4 Summary of Clinical Efficacy (Indication)

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftriaxone for Injection and other antibacterial drugs, Ceftriaxone for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be

considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Ceftriaxone for Injection is indicated for the treatment of the following infections when caused by susceptible bacteria:

1.1 Lower Respiratory Tract Infections

Lower respiratory tract infections caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis,* or *Serratia marcescens*.

1.2 Skin and Skin Structure Infections

Skin and skin structure infections caused by *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes,* Viridans group streptococci, *Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii*[1], *Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis,* or *Peptostreptococcus* species.

1. Indication and Usage

The efficacy of these organisms in this organ system was studied in fewer than ten infections.

1.3 Complicated and Uncomplicated Urinary Tract Infections

Complicated and uncomplicated urinary tract infections caused by *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii,* or *Klebsiella pneumoniae*.

1.4 Pelvic Inflammatory Disease

Pelvic inflammatory disease caused by *Neisseria gonorrhoeae*. Ceftriaxone sodium, like other cephalosporins, has no activity against *Chlamydia trachomatis*. Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *Chlamydia trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

1.5 Bacterial Septicemia

Bacterial septicemia is caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae,* or *Klebsiella pneumoniae*.

1.6 Bone and Joint Infections

Bone and joint infections caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae,* or *Enterobacter* species.

1.7 Intra-abdominal Infections

Intra-abdominal infections caused by *Escherichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium* species, or *Peptostreptococcus* species.

1.8 Meningitis

Meningitis is caused by *Haemophilus influenzae, Neisseria meningitidis,* or *Streptococcus pneumoniae*. Ceftriaxone sodium has also been used successfully in a limited number of cases of meningitis and shunt infection caused by *Staphylococcus epidermidis* and *Escherichia coli*; however, the efficacy for these organisms in this organ system was studied in fewer than ten infections.

1.9 Surgical Prophylaxis

The preoperative administration of a single 1-gram dose of ceftriaxone may reduce the incidence of postoperative infections in 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). Although ceftriaxone sodium has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibacterial in the prevention of infection following coronary artery bypass surgery.

2 DOSAGE AND ADMINISTRATION

Ceftriaxone for Injection USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1-gram dose and not any fraction thereof.
Ceftriaxone for Injection USP, Pharmacy Bulk Package bag SmartPak® should not be used in patients requiring less than 1 gram of Ceftriaxone.

2.1 Adult Population

Ceftriaxone for Injection, USP, Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1-gram dose and not any fraction thereof. Ceftriaxone for Injection USP Pharmacy Bulk Package bag SmartPak® should not be used in patients who require less than the 1 gram dose of Ceftriaxone. Ceftriaxone for Injection should be reconstituted with

Sterile Water for Injection, USP, to a concentration of 100 mg per mL and further diluted in 50 mL of a compatible solution.

2.2 Pediatric Patients

To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the adult 1-gram dose of ceftriaxone.

2.3 Preparation for Use of Ceftriaxone for Injection, USP, Pharmacy Bulk Package bags, SmartPak®

Ceftriaxone for Injection, USP Pharmacy Bulk Package bag SmartPak® should be used only in patients who require a 1 gram dose and not any fraction thereof. (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.)

2.7.5 References

This part was not included in the PIL

2.7.6 Synopses of Individual Studies

Clinical Trials in Pediatric Patients With Acute Bacterial Otitis Media

In two adequate and well-controlled U.S. clinical trials, a single IM dose of ceftriaxone was compared with a 10-day course of oral antibiotics in pediatric patients between the ages of 3 months and 6 years.

Table 5 Clinical Efficacy in Pediatric Patients with Acute Bacterial Otitis Media				
Clinical Efficacy in Evaluable Population				
Study Day	Ceftriaxone Single Dose	Comparator – 10 Days of Oral Therapy	95% Confidence Interval	Statistical Outcome
Study 1 – U.S.		amoxicillin/clavulanate		
14	74% (220/296)	82% (247/302)	(-14.4%, -0.5%)	Ceftriaxone is lower than control at study day 14 and 28.
28	58% (167/288)	67% (200/297)	(-17.5%, -1.2%)	
Study 2 – U.S.[1]		TMP-SMZ		
14	54% (113/210)	60% (124/206)	(-16.4%, 3.6%)	Ceftriaxone is equivalent to control at study day 14 and 28.
28	35% (73/206)	45% (93/205)	(-19.9%, 0.0%)	

An open-label bacteriologic study of ceftriaxone without a comparator enrolled 108 pediatric patients, 79 of whom had positive baseline cultures for one or more of the common pathogens.

Weeks 2 and 4 Bacteriologic Eradication Rates in the Per Protocol Analysis in the Roche Bacteriologic Study by Pathogen. (*Ceftriaxone: Package Insert / Prescribing Information*, n.d.)

Table 6 Bacteriologic Eradication Rates by Pathogen

	Study Day 13-15		Study Day 30+2	
Organism	No. Analyzed	No. Erad. (%)	No. Analyzed	No. Erad. (%)
Streptococcus pneumoniae	38	32 (84)	35	25 (71)
Haemophilus influenzae	33	28 (85)	31	22 (71)
Moraxella catarrhalis	15	12 (80)	15	9 (60)

2.8 Literature References

Ceftriaxone dosing, indications, interactions, adverse effects, and more. (n.d.). https://reference.medscape.com/drug/ceftriaxone-342510#0

Ceftriaxone: package insert / prescribing information. (n.d.). Drugs.com. https://www.drugs.com/pro/ceftriaxone.html#s-34092-7

Ceftriaxone: Uses, interactions, mechanism of action | DrugBank Online. (n.d.). DrugBank. https://go.drugbank.com/drugs/DB01212

Ceftriaxone side effects: common, severe, long term. (n.d.). Drugs.com. https://www.drugs.com/sfx/ceftriaxone-side-effects.html

DailyMed - CEFTRIAXONE- ceftriaxone sodium injection, powder, for solution. (n.d.). https://www.dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5cd2d96f-83e5-4326-ae87-d0ede4ba493a#section-13

DailyMed - CEFTRIAXONE SODIUM injection, powder, for solution. (n.d.). https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=473ab78d-5015-4a4a-8a2c-8f594b8de41d

Dp_Admin. (2024, March 4). *Non-clinical development: Basic principles - EUPATI Toolbox*. EUPATI Toolbox. https://toolbox.eupati.eu/resources/non-clinical-development-basic-principles/

FDA. (n.d.). *ROCEPHIN* [Report]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050585s064lbl.pdf

Li, X., Li, H., Li, S., Zhu, F., Kim, D. J., Xie, H., Li, Y., Nadas, J., Oi, N., Zykova, T. A., Yu, D. H., Lee, M., Kim, M. O., Wang, L., Ma, W., Lubet, R. A., Bode, A. M., Dong, Z., & Dong, Z. (2012). Ceftriaxone, an FDA-approved cephalosporin antibiotic, suppresses

lung cancer growth by targeting Aurora B. *Carcinogenesis*, *33*(12), 2548–2557. https://doi.org/10.1093/carcin/bgs283

PubChem. (n.d.). *Ceftriaxone*. PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/Biotrakson#section=Effects-During-Pregnancy-and-Lactation

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), & Center for Biologics Evaluation and Research (CBER). (2017). M4E(R2): The CTD — Efficacy. In *M4E(R2): The CTD — Efficacy* [Guidance]. https://www.fda.gov/media/93569/download

Module 3 Quality

3.2 Body of Data

3.2.S.1 Drug Substance

Brand Name: Rocephin

Generic Name: Ceftriaxone

Manufacturer: Hospira Healthcare India Pvt. Ltd. and SAMSON MEDICAL TECHNOLOGIES LLC.

3.2.S.1.1 General Information

Ceftriaxone sodium is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone for Injection, USP, is available in the following SmartPak® Pharmacy Bulk Package bags of 100 grams. Each 100-gram Pharmacy Bulk Package bag contains sterile ceftriaxone sodium equivalent to 100 grams of ceftriaxone (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.).

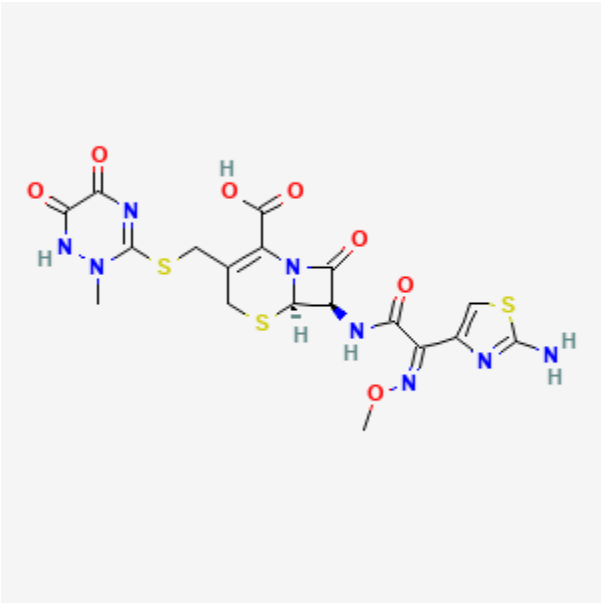
3.2.S.1.2 Nomenclature

Chemical Name:

(6*R*,7*R*)-7-[[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-[(2-methyl-5,6-dioxo-1*H*-1,2,4-triazin-3-yl)sulfanylmethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

(PubChem, n.d.)

3.2.S.1.3 Structure



(PubChem, n.d.)

3.2.S.1.4 General Properties

Molecular Formula : C18 H18N8O7S3

Molecular Weight: 554.58 g/mol (PubChem, n.d.)

Ceftriaxone sodium is a white to yellowish-orange crystalline powder, which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The *p*H of a 1% aqueous solution is approximately 6.7 (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.).

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Hospira Healthcare India Pvt. Ltd.

Irungattukottai - 602 105, India

Mfg. for:

Apotex Corp.

Weston, FL 33326

DATE OF REVISION: JUNE 2010

SmartPak is a registered trademark of Samson Medical Technologies, L.L.C.

C6100d

SAMSON

MEDICAL TECHNOLOGIES L.L.C.

Cherry Hill, NJ 08003, USA

by

ACS Dobfar S.p.A.

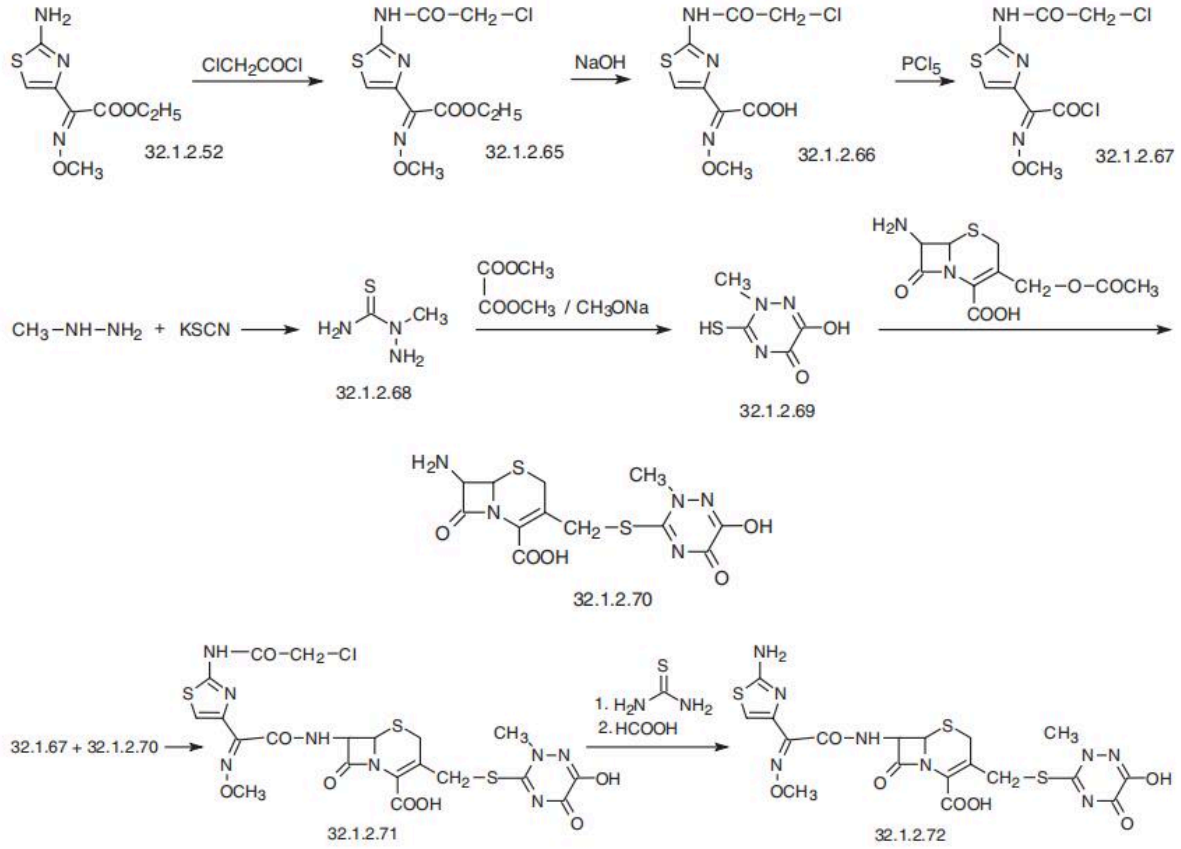
20067 Tribiano (Milano) Italy

Manufactured for

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Ceftriaxone Sodium is a semi-synthetic broad-spectrum cephalosporin antibiotic, sterilized and synthesized through a multi-step organic chemical process, followed by salt formation. The process begins with the synthesis of the cephalosporin nucleus with a 7-aminocephalosporanic acid (7-ACA) core, which undergoes a side-chain upsurge, followed by chemical modifications to yield the active ceftriaxone intermediate. Additionally, an active ingredient is reacted with sodium hydroxide under carefully regulated pH and temperature settings to increase water solubility, which permits its usage in parenteral formulations which produce sodium salt.

The following image contains the flow map for the synthesis of Ceftriaxone Sodium:



(CEFTRIAXONE synthesis)

(*CEFTRIAXONE | 73384-59-5*, n.d.)

The final steps in manufacturing involve high-level environmental and contamination controls due to its sterile injectable dosage form. After this purification process, Ceftriaxone Sodium is dissolved in sterile water for injection, sterile filtered, and filled into vials under aseptic conditions. The guidelines outlined by the FDA and ISO Class 5 cleanroom requirements are closely followed during every stage of this sterile manufacturing process ("Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice," 2004).

While manufacturing Ceftriaxone Sodium on a large scale, process validation studies for validating key synthesis steps, crystallization, sterilization, and lyophilization processes are integral. Process control techniques such as monitoring reaction kinetics, sodium ion concentration, and solvent use methods are applied to ensure consistent batch-to-batch production. To understand the impact of variability in raw materials and environmental conditions on the critical qualities of the drug, a Quality by Design (QbD) approach is often applied. Such robust and validated manufacturing processes ensure a reliable supply of highly pure Ceftriaxone Sodium that satisfies pharmacopeial specifications and regulatory expectations.

3.2.S.2.3 Controls of Methods

Control of materials is an essential factor in ensuring the safety, consistency, and efficacy of the quality of Ceftriaxone Sodium during the manufacturing process. It also includes a strict selection, testing, and documentation process of all raw materials, components, solvents, and mediators used during synthesis and purification. In the case of Ceftriaxone Sodium, the flow map in Section 3.2.S.2.2 shows where each material is used during the manufacturing process. A

healthy material monitoring system ensures high-quality, compliant materials that satisfy regulatory and compendial standards, lowering the risk of variability and ensuring patient safety.

3.2.S.2.4 Control of Critical Steps and Intermediates

Process control is important, especially during the critical steps of the manufacturing process of Ceftriaxone Sodium. Such critical steps include a 7-aminocephalosporanic acid (7-ACA) core, formation of the thiotriazinedione side chain, and final sodium salt conversion under sterile conditions. Each of these steps requires thorough monitoring of temperature, pH, reaction time, filtration, and inert conditions. Manufacturing is carried out in classified and clean environments following proper manufacturing practices (Chong et al., 2022).

3.2.S.2.5 Process Validation and/or Evaluation

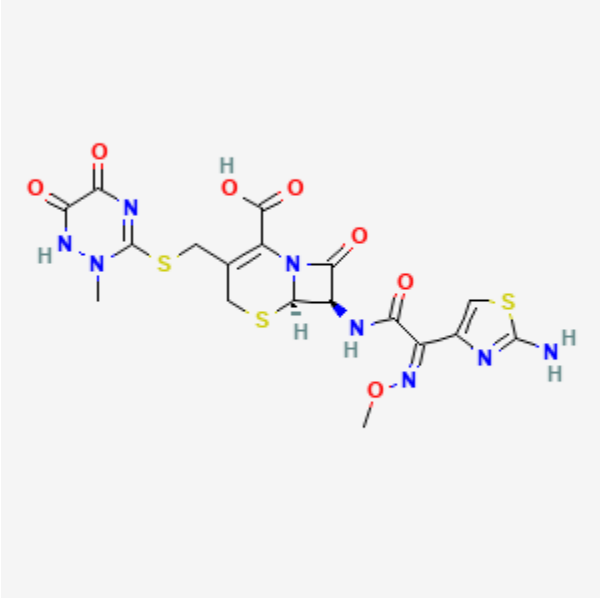
All critical steps in manufacturing Ceftriaxone Sodium, such as sterilization, crystallization, and disinfectant packaging, require careful validation. To ensure sterility safety, these procedures are verified by conducting purity tests, chromatographic behavior, and chemical reactivity (European Medicines Agency, 1995). All these steps are summarized under protocols and validation reports, while specific acceptance criteria for all operations are maintained.

3.2.S.2.6 Manufacturing Process Development

The manufacturing process development for Ceftriaxone Sodium has undertaken considerable modifications to ensure purity and stability. These changes are required and performed following the identification of impurities during crystallization and production. In order to develop improvements, researchers investigate different processes, which are recorded in this section. Improvements are considered for manufacturing Ceftriaxone Sodium to achieve high purity and low color absorbance to make it suitable for the formation of dosage forms.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and Characterization



Molecular Formula : C18 H18N8O7S3

Molecular Weight: 554.58 g/mol (PubChem, n.d.)

IUPAC Name:

(6*R*,7*R*)-7-[[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-[(2-methyl-5,6-dioxo-1*H*-1,2,4-triazin-3-yl)sulfanylmethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

3.2.S.3.2 Impurities

The two common impurities of Ceftriaxone are the Triazine compound and Methoxyimino geometric isomer (Tange et al., 2016).

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specifications

One specification for Ceftriaxone Sodium is an antibiotic that must meet strict quality standards for impurities. Each impurity has a limit, and the total amount of impurities in the drug cannot exceed 0.6%. This ensures the medication is safe and effective.

3.2.S.4.2 Analytical Procedures

Testing for impurities and High-Performance Liquid Chromatography (HPLC) are two analytical techniques that might be applied to Ceftriaxone Sodium.

3.2.S.4.3 Validation of Analytical Procedures

In order to determine the impurities, High-Performance Liquid Chromatography can be used. A Karla Fischer Titrator can be used to determine moisture content.

3.2.S.4.4 Batch Analysis

Batch analysis is a vital element when it comes to quality assurance in manufacturing Ceftriaxone Sodium. It includes comprehensive data for each batch of drug to use for nonclinical studies and testing. (CDER, 2004, p. 35). Each batch is assigned a unique batch identification number, including but not limited to manufacturing date, production site, and other necessary information. The batch analysis for Ceftriaxone Sodium includes pH, sterility, and assay tests. The NLM specifies that the assay for ceftriaxone sodium demonstrated good linearity, precision, and accuracy at concentrations ranging from 15.0 to 60.0 μg/mL, therefore being acceptable (Aléssio & Salgado, 2012).

3.2.S.4.5 Justification of Specification

The specifications for Ceftriaxone Sodium are set to ensure and enhance its safety, quality, and effectiveness until its shelf life. Bacterial endotoxins are one of these requirements; because they are injectable, they must be treated carefully. This ensures that such drugs do not yield adverse reactions if not directed carefully (*Ceftriaxone Sodium USP Reference Standard Sigma-Aldrich*, n.d.). Another important specification is about ensuring dosage consistency. The use of Karl Fischer titration aims to increase patient safety by ensuring that the drug's component includes the appropriate amount of endotoxins and water content.

3.2.S.5 Reference Standards or Materials

A well-researched material utilized as a benchmark in the pharmaceutical industry is called a reference standard. It helps to determine a drug's efficacy and purity. Maintaining the safety and efficacy of medications depends on laboratories utilizing a reference standard to make sure their test findings are accurate and consistent across batches and locations.

3.2.S.6 Container Closure System

Ceftriaxone for Injection, USP, is available in 100-gram Pharmacy Bulk Package bags. Each bag contains sterile ceftriaxone sodium equivalent to 100 grams of ceftriaxone. The SmartPak® system does not contain natural rubber latex. Reconstituted ceftriaxone may darken with storage but remains powerful. Only use if the solution is clear and free of particles. Store the sterile powder at room temperature (20º-25ºC or 68º-77ºF) and protect it from light until reconstitution (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.).

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

Stability analyses are essential to approving pharmaceutical medications because they ensure their long-term safety and efficacy. These studies follow the World Health Organization (WHO) and International Council for Harmonization (ICH) guidelines (Bajaj et al., 2012). Stability testing determines a drug's shelf life by analyzing its performance in different environments, such as temperature and humidity. A long shelf life for a drug substance benefits manufacturers because it means they can avoid discarding it if production delays occur, as long as it is stored correctly (Bajaj et al., 2012). Stability studies are essential because they can show issues with the drug material, which can lead to complications with the final product.

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

The PIL does not contain shelf life information.

3.2.S.7.3 Stability Data

The PIL does not contain shelf life information.

The elimination half-life of ceftriaxone is 5.8-8.7 hours. The half-life of ceftriaxone in the middle ear fluid has been estimated to be 25 hours (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.).

3.2.P Drug Product

Name: Ceftriaxone Sodium

Dosage Form: Sterile powder for injection

Ceftriaxone for Injection USP, Pharmacy Bulk Package bag SmartPak should be used only in patients who require a 1-gram dose and not any fraction thereof.

Ceftriaxone for injection is dosed based on the type of infection. Adults typically receive 1 to 2 grams once daily or divided into two doses every 12 hours, with a maximum of 4 grams per day. For surgery, 1 gram is given 30 minutes to 2 hours before the procedure. For skin infections, the dose is 50 to 75 mg per kilogram, not exceeding 2 grams in total. In meningitis cases, the dose increases to 100 mg per kilogram, still not exceeding 4 grams daily. For other serious infections, 50 to 75 mg per kilogram is given every 12 hours, with a 2-gram limit (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.).

3.2.P.1 Description and Composition of the Drug Product

Ceftriaxone sodium is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6*R*, 7*R*)-7-[2-(2-Amino-4-thiazolyl) glyoxylamido]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-*as*-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2-(*Z*)-(*O*-methyloxime), disodium salt, sesquaterhydrate.

Ceftriaxone sodium is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. The color of ceftriaxone sodium solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Ceftriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.).

3.2.P.2 Pharmaceutical Development

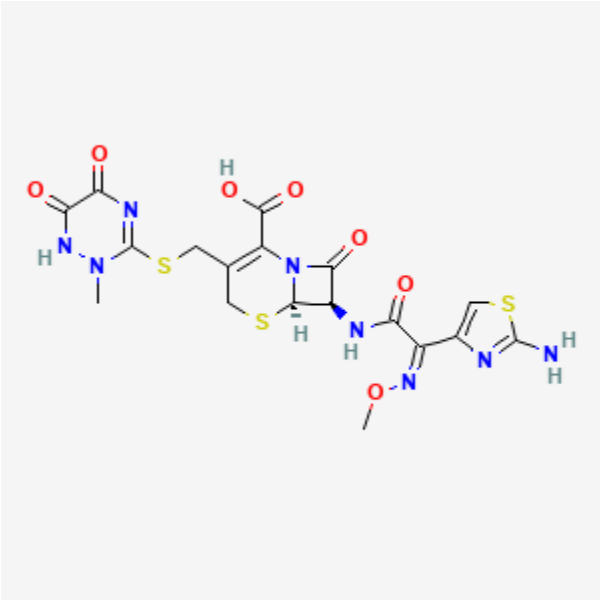
Pharmaceutical development is the phase after a new medicine is discovered, during which the pharmaceutical industry collects the necessary data to begin with laboratory and clinical testing. This stage is essential to produce a high-quality product since it involves developing and implementing the drug's formulation and the procedures required for its manufacture. Plans for the drug's manufacture and usage start to build, ensuring that it will be safe and effective for patients in the future.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The manufacturers of Ceftriaxone sodium are Hospira Healthcare India Pvt. Ltd and Samson Medical Technologies, L.L.C.

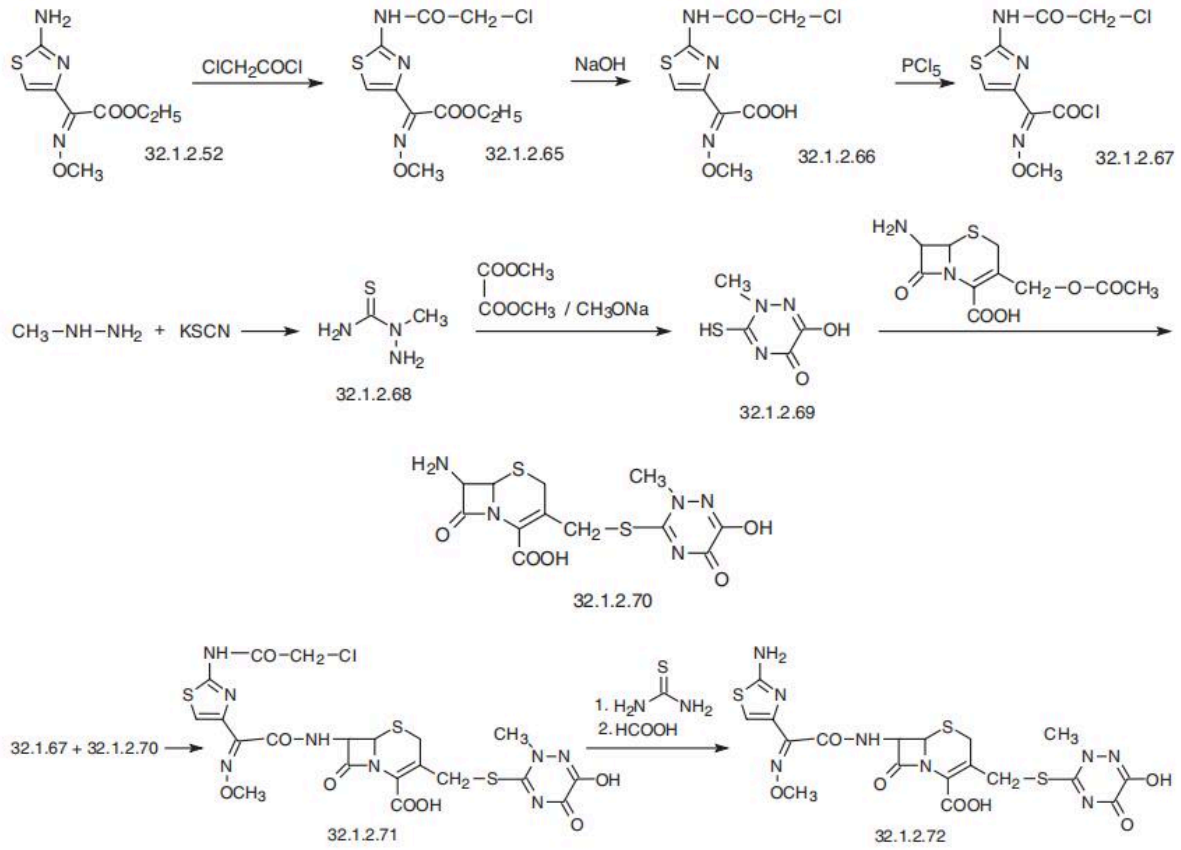
3.2.P.3.2 Batch Formula



Molecular Formula : C18 H18N8O7S3

3.2.P.3.3 Description of Manufacturing Process

The production of Ceftriaxone sodium powder for injection starts with the sterile synthesis and purification of the active ingredient. A sterile white to yellowish powder is obtained by filtering and crystallizing the product, produced by various highly regulated chemical processes. The following image contains the flow map for the synthesis of Ceftriaxone Sodium:



(CEFTRIAXONE synthesis)

(*CEFTRIAXONE | 73384-59-5*, n.d.)

The powder is transferred to a specialized cleanroom where everything is regulated and sterile once made. The powder is carefully weighed in this setting before being put into glass vials that have already undergone sterilization. Automated machines control the process of maintaining hygienic and high-quality requirements. Once the vials are filled, they are partially sealed with sterile rubber plugs to keep the contents safe.

The filled vials are preserved in the freezer to improve stability and minimize moisture. Following this procedure, the vials are entirely sealed and have metal caps bonded on them. The vials are then packed, labeled, and visually examined. Each batch is reviewed for physical characteristics, efficiency, purity, pH, sterility, and endotoxin levels before the shipment, and

quality checks are carried out at different stages to ensure products follow Good Manufacturing Practices ("Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice," 2004).

3.2.P.3.4 Controls of Critical Steps and Intermediates

The production of ceftriaxone sterile powder involves several essential steps to ensure its quality and regulatory compliance. In order to analyze microorganisms, the active ingredient is first sterilized and purified. The medication is then stored in the freezer to minimize moisture without destroying it. Sterilization conditions and fill quantity are checked during the aseptic filling into vials. Controls ensure that stoppers and seals are placed appropriately after filling. The entire solution is tested for sterility, efficiency, pH, and purity before drying. These procedures follow FDA regulations to maintain product quality.

3.2.P.3.5 Process Validation and/or Evaluation

All critical steps in manufacturing Ceftriaxone Sodium, such as sterilization, crystallization, and disinfectant packaging, require careful validation. To ensure sterility safety, these procedures are verified by conducting purity tests, chromatographic behavior, and chemical reactivity (European Medicines Agency, 1995). According to Center for Drug Evaluation and Research (CDER) industry guidance, information regarding the validation or assessment of crucial manufacturing process steps must be provided. The Common Technical Document (CTD) for Ceftriaxone will contain all necessary actions that have been verified or assessed in order to meet market approval requirements.

3.2.P.4 Control of Excipients

Ceftriaxone Sodium

3.2.P.4.1 Specification(s)

Two specifications for excipients are identification and purity level.

3.2.P.4.2 Analytical Procedures

Testing for impurities and High-Performance Liquid Chromatography (HPLC) are two analytical techniques that might be applied to Ceftriaxone Sodium.

3.2.P.4.3 Validations of Analytical Procedures

High Performance Liquid Chromatography (HPLC), Karl Fischer Titration, and GC instruments

3.2.P.4.4 Justification of Specifications

Excipients must meet pharmaceutical quality and safety criteria to verify their identification, purity, and functionality. They help regulate endotoxins and microbiological limits in intravenous medications and prevent interactions with the active component.

3.2.P.4.5 Excipients of Human or Animal Origin

Lactos and Gelatin

3.2.P.4.6 Novel Excipients

Ceftriaxone does not contain novel excipients.

3.2.P.5 Control of Drug Product

Store Ceftriaxone Sodium at 20º C to 25º C or room temperature and protect from moisture and light. Store in original packaging.

3.2.P.5.1 Specification(s)

One specification for Ceftriaxone Sodium is an antibiotic that must meet strict quality standards for tests, procedures, and guidelines. This ensures the medication is safe, quality, and effective.

3.2.P.5.2 Analytical Procedures

Testing for impurities and High-Performance Liquid Chromatography (HPLC) are two analytical techniques that might be applied to Ceftriaxone Sodium.

3.2.P.5.3 Validations of Analytical Procedures

It is determined by verifying that the analytical process offers a satisfactory level of linearity, accuracy, and precision when used on samples that contain analyte concentrations within or at the extremes of the analytical procedure's designated range (European Medicines Agency, 1995).

3.2.P.5.4 Batch Analyses

Batch analysis involves three key steps to ensure product quality and safety. First, a visual inspection verifies that the container is intact and looks for any particles. High-Performance Liquid Chromatography (HPLC) is used for chemical analysis to determine the product's efficiency and purity. Lastly, the product's sterility and lack of harmful components

are ensured by microbiological testing. These steps work together to maintain safety and effectiveness.

3.2.P.5.5 Characterization of Impurities

The three common impurities of Ceftriaxone are the Triazine compound, 7-Aminocephalosporanic acid (7-ACA), and Methoxyimino geometric isomer (Tange et al., 2016).

3.2.P.5.6 Justification of Specifications

Specifications are crucial to ensure a drug's identification, potency, quality, and purity. The production facility's manufacturing capabilities, safety evaluations from clinical studies, and data from validation procedures are all used to create these standards (INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, 1999). Their primary objective is to ensure that the medication regularly provides patients with the desired therapeutic advantages.

3.2.P.6 Reference Standards or Materials

A well-researched material utilized as a benchmark in the pharmaceutical industry is called a reference standard. It helps to determine a drug's efficacy and purity. Maintaining the safety and efficacy of medications depends on laboratories utilizing a reference standard to make sure their test findings are accurate and consistent across batches and locations.

3.2.P.7 Container Closure System

Ceftriaxone sodium is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available: Vials containing 500 mg equivalent of ceftriaxone. Vials containing 1 gm equivalent of ceftriaxone. Vials containing 1 gm equivalent of ceftriaxone (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.).

Ceftriaxone for Injection, USP is available in the following SmartPak® Pharmacy Bulk Package bags of 100 gram Pharmacy Bulk Package bag contains sterile ceftriaxone sodium equivalent to 100 grams of ceftriaxone (*DailyMed - CEFTRIAXONE- Ceftriaxone Sodium Injection, Powder, for Solution*, n.d.).

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The PIL does not contain this information.

The elimination half-life of ceftriaxone is 5.8-8.7 hours. The half-life of ceftriaxone in the middle ear fluid has been estimated to be 25 hours (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.).

3.2.P.8.2 Post-Approval Stability Protocol and Stability

The PIL does not contain this information.

3.2.P.8.3 Stability Data

The PIL does not contain this information.

3.2.A Container Closure System

3.2.A.1 Facilities and Equipment

Hospira Healthcare India Pvt. Ltd.

Irungattukottai - 602 105, India

Mfg. for:

Apotex Corp.

Weston, FL 33326

DATE OF REVISION: JUNE 2010

SmartPak is a registered trademark of Samson Medical Technologies, L.L.C.

C6100d

SAMSON

MEDICAL TECHNOLOGIES L.L.C.

Cherry Hill, NJ 08003, USA

by

ACS Dobfar S.p.A.

20067 Tribiano (Milano) Italy

Manufactured for

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form)

Possible adventitious agents' safety risks are viruses, endotoxins, and fungal contaminations.

3.2.A.3 Novel Excipients

The PIL does not contain this information.

3.2.R Regional Information

This section is not applicable because Ceftriaxone is not a combination product and does not require administering a medical device.

3.3 Literature References

Aléssio, P. V., & Salgado, H. R. N. (2012). Development and validation of a successful microbiological AGAR assay for determination of ceftriaxone sodium in powder for injectable solution. *Pharmaceutics*, *4*(3), 334–342. https://doi.org/10.3390/pharmaceutics4030334

Bajaj, S., Singla, D., & Sakhuja, N. (2012). Stability testing of pharmaceutical products. *Journal of Applied Pharmaceutical Science*. https://doi.org/10.7324/japs.2012.2322

CEFTRIAXONE | 73384-59-5. (n.d.). ChemicalBook. *https://www.chemicalbook.com/ChemicalProductProperty_EN_CB9114533.htm*

Ceftriaxone: Uses, interactions, mechanism of action | DrugBank Online. (n.d.). DrugBank. *https://go.drugbank.com/drugs/DB01212*

Ceftriaxone sodium USP Reference Standard Sigma-Aldrich. (n.d.). https://www.sigmaaldrich.com/US/en/product/usp/1098184?srsltid=AfmBOopWRW-j6Z7J-SNm2SvkHTgj0mJ6xI3SBsSUB1SwM2mKTMeE4Cy4

Chong, X., Wang, L., Hu, C., & He, L. (2023). Quality control and consistency evaluation of ceftriaxone sodium for injection. *Journal of chemotherapy (Florence, Italy)*, *35*(6), 477–490. https://doi.org/10.1080/1120009X.2022.2153314

DailyMed - CEFTRIAXONE- ceftriaxone sodium injection, powder, for solution. (n.d.). https://www.dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5cd2d96f-83e5-4326-ae87-d0ede4ba493a#section-12

DailyMed - CEFTRIAXONE SODIUM injection, powder, for solution. (n.d.). https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=473ab78d-5015-4a4a-8a2c-8f594b8de41d

European Medicines Agency. (1995). *Validation of Analytical Procedures: text and Methodology*. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q2r1-validation-analytical-procedures-text-and-methodology-step-5-first-version_en.pdf

Guidance for industry Sterile drug products produced by aseptic processing — Current good manufacturing practice. (2004). In *U.S. Department of Health And Human Services Food And Drug Administration*. https://www.fda.gov/media/71026/download

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE. (1999). *SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS*. https://database.ich.org/sites/default/files/Q6B%20Guideline.pdf

PubChem. (n.d.). *Ceftriaxone*. PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/Biotrakson#section=Hazard-Classes-and-Categories

U.S. Department of Health and Human Services Food and Drug Administration. (2004). Guidance for Industry Drug Substance Chemistry, Manufacturing, and Controls information. In *U.S. Department of Health And Human Services Food And Drug Administration*. https://www.gmp-compliance.org/files/guidemgr/3969DFT.pdf

Tange, M., Yoshida, M., Nakai, Y., & Uchida, T. (2016). The Role of an Impurity in Ceftriaxone Sodium Preparation for Injection in Determining Compatibility with Calcium-Containing Solutions. *Chemical and Pharmaceutical Bulletin*, *64*(3), 207–214. https://doi.org/10.1248/cpb.c15-00538

Module 4 Nonclinical Study Reports

4.2 Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

In nonclinical studies, primary pharmacodynamic studies play a crucial role in drug development. These studies determine how a drug works in the body and its effects, particularly concerning its intended medical use or benefits. Primary pharmacodynamics aims to uncover the specific ways a new drug can achieve the desired results for treating a condition (*Basic Principles of Non-clinical Development: Pharmacodynamics (PD) | EUPATI Open Classroom*, n.d.). These studies use animal models to imitate diseases, helping researchers find the best drug candidates and determine the proper trial dosages. They can be done in living organisms (in-vivo) or controlled environments (in vitro) and are usually conducted in the discovery phase without following Good Laboratory Practice (GLP) guidelines.

Ceftriaxone sodium is a third-generation antibiotic that works by inhibiting with the bacterial cell wall's production (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.). It binds to proteins that help form the cell wall, leading to bacterial cell death. It works well against several Gram-positive and Gram-negative bacteria. The usual dose for adults is 1–2 g daily, given by injection.

4.2.1.2 Secondary Pharmacodynamics

Secondary pharmacodynamics (PD) focuses on understanding the effects of a drug that go beyond its intended therapeutic target. These studies aim to explore how the drug acts in the

body in ways that are not directly related to the primary condition it is meant to treat (*Basic Principles of Non-clinical Development: Pharmacodynamics (PD) | EUPATI Open Classroom*, n.d.). These studies are conducted in lab settings (in vitro) and living creatures (in vivo) to investigate the drug's more significant impacts and interactions beyond its primary usage. Sometimes, if the body of current literature already tells researchers enough about these impacts, they may not need to perform any further secondary PD investigations.

4.2.1.3 Safety Pharmacology

Safety pharmacology studies, particularly analyzing both the positive and negative effects of a new medicine, are often designed with the help of primary and secondary pharmacodynamic studies. The primary goal of safety pharmacology research is to evaluate the drug's mechanism of action to determine if it causes a risk to human health (U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), ICH, 2001). It analyzes how the drug affects vital organs and body systems and determines the exposure levels that could lead to adverse events. It is essential to understand a substance's primary and secondary pharmacodynamic effects as well as how it functions in the body in order to determine if it is safe for humans. This understanding, along with safety study results, helps identify any potential risks or harmful effects.

4.2.1.4 Pharmacodynamic Drug Interactions

Pharmacodynamic drug interactions happen when the effect of one drug is changed by another drug taken at the same time. Considering their common harm, drug interactions are usually can be antagonistic, additive, or synergistic (Niu et al., 2019). An interaction mechanism

may take place at the same target or via several paths within a complicated pathophysiological system. Understanding these interactions is essential for ensuring the safe and efficient distribution of medications in combination treatments (Niu et al., 2019). Because medication interactions can also result in unfavorable reactions and adverse effects.

4.2.2 Pharmacology

4.2.2.1 Analytical Methods and Validations Reports

Analytical methods measure drugs and their breakdown products in biological samples like blood or urine. They are essential for understanding how drugs are absorbed in the body, how similar different versions of a drug are, and how the body processes them, and the methods must be validated (Shah et al., 1992). Researchers must document all experiments in a method validation report when they make claims based on these methods. Method validation confirms that an analytical method gives reliable and accurate results, ensuring the data collected is reliable.

4.2.2.2 Absorption

Drug absorption is a crucial process because a medication needs to be taken up by the body to be effective. Ceftriaxone, an antibiotic, is administered only through injections, either into the muscle (intramuscular) or directly into the bloodstream (intravenous). If ceftriaxone were taken by mouth, less than 1% of the drug would be absorbed, meaning it wouldn't work effectively. Therefore, injections are necessary for this medication to have its intended effect (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.).

4.2.2.3 Distribution

After a drug is absorbed, it is distributed through the blood to various tissues. Factors like the type of cell the drug attaches to can affect how it spreads throughout the body. In healthy individuals, a dosage of Ceftriaxone administered by intravenous (IV) or muscle injection usually varies from 5.78 to 13.5 liters (Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online, n.d.). However, this distribution can increase significantly in patients with

sepsis, ranging from 6.48 to 35.2 liters. The drug ceftriaxone is a reliable therapy for bacterial meningitis because it can efficiently cross the blood-brain barrier (Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online, n.d.).

4.2.2.4 Metabolism

Metabolism is the process that occurs after a drug has been distributed throughout the body and reaches its target. During this stage, the body breaks down the drug to eliminate it. For ceftriaxone, a commonly used antibiotic, metabolism is quite limited. This means that only a small amount of ceftriaxone is processed by the liver. As a result, most of the drug remains unchanged in the body, making its metabolism negligible Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online, n.d.).

4.2.2.5 Excretion

Excretion is the final step in how our bodies process a drug. The metabolized process helps the body remove them through urine or bile, making it easier and safer to get rid of the drug. For ceftriaxone, a powerful antibiotic, most of it (about 33-67%) is removed from the body through urine (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.). The rest is cleared through bile, which is then excreted in the feces. This process ensures that the drug is effectively eliminated from the system after it has worked to treat an infection. The elimination half-life of ceftriaxone is 5.8-8.7 hours (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.). It has been estimated that ceftriaxone has a half-life of 25 hours in middle ear fluid.

4.2.2.6 Pharmacokinetics

Pharmacokinetic studies focus on how a drug moves through the body, including how it is absorbed, distributed, metabolized, and eventually excreted. When considering how the body processes ceftriaxone, a commonly used antibiotic, it's important to note that the way this medication works in older adults and individuals with kidney or liver problems is mainly similar to how it's processed in healthy adults (*Ceftriaxone: Package Insert / Prescribing Information*, n.d.). As a result, there is no need to change the typical dosage for these groups, even if they take up to 2 grams of ceftriaxone each day. This means that elderly patients and those with certain health conditions can safely take the standard doses without needing adjustments (*Ceftriaxone: Package Insert / Prescribing Information*, n.d.).

4.2.2.7 Other Pharmacokinetic Studies

In comparison to younger people, children's and older adults' bodies can handle drugs quite differently (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.). This includes how quickly the body clears the drug and how it distributes within the body. Because of these differences, paying close attention to the dosage of medications when treating these age groups is essential to ensure they receive the right amount for their needs.

4.2.3 Toxicology

4.2.3.1 Single Dose Toxicity (Ceftriaxone Sodium and Intravenous, Intramuscular)

Single-dose toxicity studies are essential in determining new medications' maximum tolerated dose (MTD). These studies are typically performed on animals receiving either a single large dose or several smaller doses over a 24-hour period (Rousseaux & Bracken, 2013). In one study, researchers found that patients who received a single dose of ceftriaxone sodium had lower rates of clinical recovery than those who underwent a 10-day course of oral treatment. (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.) However, another study showed that the cure rates from a single dose of ceftriaxone were similar to those achieved with an alternative treatment. It's essential to weigh the possibly lower effectiveness of ceftriaxone against the benefits of administering it through injection rather than orally (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.).

4.2.3.2 Repeat Dose Toxicity (Ceftriaxone Sodium, Inject, 4 to 14 Days)

Repeat-dose toxicology studies are essential for understanding how certain substances can negatively affect health when given to animals multiple times over an extended period (Thorsrud et al., 2012). These studies help identify the dosage that causes adverse effects and which organs are affected by toxicity. They also establish safe dosage limits for human trials and provide insight into the drug's long-term impact on the body. In studies where ceftriaxone was given daily for 14 to 28 days, some mild, temporary changes can be observed (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.). These changes may include slight increases in liver enzymes and some alterations in the kidney tissue, but these effects were only seen at higher drug doses.

4.2.3.3 Genotoxicity

The ability of certain chemicals to harm a cell's genetic material, which can result in mutations and perhaps cancer, is known as genotoxicity (Deng et al., 2022). Some compounds are genotoxic; however, not all mutagenic substances are genotoxic. Several experiments were carried out in the genetic toxicity research to assess the antibiotic ceftriaxone's safety. These tests included the Ames test, which checks for mutations in bacteria; a micronucleus test that looks for damage to genetic material in cells, and a test that examines chromosomal changes in human lymphocytes (a type of white blood cell) grown in the lab (DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution, n.d.). The results showed that ceftriaxone did not cause any genetic mutations or harmful changes in these tests, indicating it is not likely to be toxic to DNA.

4.2.3.4 Carcinogenicity

Carcinogenicity refers to substances or agents that can cause cancer. This includes chemicals, radiation, and some biological organisms. If something is carcinogenic, it means that being exposed to it raises the chance of getting cancer. Certain studies have not been conducted regarding the safety of ceftriaxone, a medication used to treat various infections (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.). Specifically, there have been no tests to check if ceftriaxone could cause cancer during long-term use since the drug hasn’t been tested in animals for longer than six months. This means that while we know how safe the drug is over limited periods, we don’t have information about its effects if used for extended periods (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.).

4.2.3.5 Reproductive and Developmental Toxicity

Reproductive toxicology is the study of how new drugs can affect fertility in both males and females, as well as how they impact childbirth and breastfeeding. In research involving rats, a drug called ceftriaxone was tested to see if it had any adverse effects on fertility (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.). There were no signs of fertility issues when administered at high daily doses up to 586 mg for each kilogram of the rat's weight. This dosage is around 20 times higher than the usual clinical dose given to humans, which is 2 grams daily (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.).

4.2.3.6 Local Tolerance

Local tolerance testing is an essential step in evaluating the safety of drugs, focusing on how well medicinal products are tolerated in specific areas of the body. Testing for medications usually occurs in labs before any human exposure (*Non-clinical Local Tolerance Studies - Creative Animodel*, n.d.). It’s essential to observe how patients react at the injection site. If they feel discomfort or side effects, it could prevent them from using the medication later. Knowing local tolerance is key to helping patients continue their treatment smoothly.

4.2.3.7 Other Toxicity Studies

Testing for toxicity is essential while developing new medications. It helps researchers understand how drugs affect various species, organs, and doses. This testing looks at accidental exposures, where unintentional contact with a substance occurs, as well as controlled experiments using cells in the lab (in vitro studies) and studies conducted on living animals (in vivo studies) (Parasuraman, 2011). These tests give essential details on the safety and effects of new medications before they are given to patients. Mutagenicity is a test for new drugs that looks

for DNA modifications that may cause cancer. Another study, neurotoxicity, searches for adverse effects on the nervous system that may result in neurological problems (Parasuraman, 2011).

4.3 Literature References

Basic principles of non-clinical development: Pharmacodynamics (PD) | EUPATI Open Classroom. (n.d.). https://learning.eupati.eu/mod/book/view.php?id=308&chapterid=159

Ceftriaxone: Uses, interactions, mechanism of action | DrugBank Online. (n.d.). DrugBank. https://go.drugbank.com/drugs/DB01212

Ceftriaxone: package insert / prescribing information. (n.d.). Drugs.com. https://www.drugs.com/pro/ceftriaxone.html#s-34092-7

DailyMed - CEFTRIAXONE SODIUM injection, powder, for solution. (n.d.). https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=473ab78d-5015-4a4a-8a2c-8f594b8de41d#i4i_clinical_studies_id_12a633f3-a385-4948-9e10-19c30895eba4

Deng, R., Gao, J., Yi, J., & Liu, P. (2022). Could peony seeds oil become a high-quality edible vegetable oil? The nutritional and phytochemistry profiles, extraction, health benefits, safety and value-added-products. *Food Research International*, *156*, 111200. https://doi.org/10.1016/j.foodres.2022.111200

Niu, J., Straubinger, R. M., & Mager, D. E. (2019). Pharmacodynamic Drug–Drug interactions. *Clinical Pharmacology & Therapeutics*, *105*(6), 1395–1406. https://doi.org/10.1002/cpt.1434

Non-clinical Local tolerance studies - Creative Animodel. (n.d.). https://www.creative-animodel.com/Toxicology/Non-clinical-Local-tolerance-studies.html

Parasuraman, S. (2011). Toxicological screening. *Journal of Pharmacology and Pharmacotherapeutics*, *2*(2), 74–79. https://doi.org/10.4103/0976-500x.81895

Rousseaux, C. G., & Bracken, W. M. (2013). Overview of drug development. In *Elsevier eBooks* (pp. 647–685). https://doi.org/10.1016/b978-0-12-415759-0.00021-2

Shah, V. P., Midha, K. K., Dighe, S., McGilveray, I. J., Skelly, J. P., Yacobi, A., Layloff, T., Viswanathan, C. T., Cook, C. E., McDowall, R. D., Pittman, K. A., Spector, S., Albert, K. S., Bolton, S., Dobrinska, M., Doub, W., Eichelbaum, M., Findlay, J. W. A., Gallicano, K., … Yuh, L. (1992). Analytical methods validation: Bioavailability, bioequivalence and pharmacokinetic studies: Sponsored by the American Association of Pharmaceutical Chemists, U.S. Food and Drug Administration, Fédération Internationale Pharmaceutique, Health Protection Branch (Canada) and Association of Official Analytical Chemists. *International Journal of Pharmaceutics*, *82*(1), 1–7. https://doi.org/10.1016/0378-5173(92)90065-A

Thorsrud, B. A., Faqi, A. S., Beck, M. J., & Morford, L. L. (2012). Juvenile toxicity testing to support clinical trials in the pediatric population. In *Elsevier eBooks* (pp. 383–394). https://doi.org/10.1016/b978-0-12-387815-1.00015-0

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), ICH. (2001). *Guidance for Industry S7A Safety Pharmacology Studies for Human Pharmaceuticals*. https://www.fda.gov/media/72033/download

Module 5 Clinical Study Reports

5.2 Tabular Listing of All Clinical Study Information

Type of Study	Column Author	Study ID	Clinical Site	Study Status
Pharmacokinetics (PK)	Janki Patel	001	Clinical Solution Center, Arizona	Completed
Pharmacodynamics (PD)	Janki Patel	002	Clinical Solution Center, Arizona	Completed
Bioavailability (BA)	Janki Patel	003	Advance Research Center, California	Completed
Bioequivalence (BE)	Janki Patel	004	Advance Research Center, California	Completed
Efficacy and Safety	Janki Patel	005	Advance Research Center, California	Completed
Postmarketing Reporting	Janki Patel	006	Advance Research Center, California	Completed

5.3 Clinical Study Reports and Related Information

5.3.1 Reports of Biopharmaceutical Studies

5.3.1.1. Bioavailability (BA) Study Reports and Related Information

Bioavailability describes the rate and amount of a drug's active component that enters the bloodstream and reaches the body's intended area of action. Bioavailability (BA) studies are essential for demonstrating that a drug can effectively treat specific conditions (Chen et al., 2001). It is important for understanding this idea for efficient medicine use since a drug that has poor bioavailability may not be helpful for the conditions it is intended to treat. Studies of bioavailability (BA) evaluate a drug's absorption, distribution, metabolism, and excretion within the body. They also estimate how different formulations perform compared to the original drug tested in clinical trials, which is essential for ensuring safety and efficacy (Chen et al., 2001). Based on their specific goals and designs, these studies can focus on pharmacokinetic information or product quality.

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports and Related Information

Bioequivalence (BE) testing compares how well two or more drug products work in the body. It focuses on bioavailability (BA), which is how quickly and effectively a drug enters the bloodstream. By ensuring that patients and medical professionals have access to safe and effective therapies, studies such as these are essential in preserving confidence in the drugs that are currently on the market (Chen et al., 2001). Bioequivalence (BE) means that two drug products deliver the same active ingredient to the body at the same rate and extent when given in the same dose under similar conditions. BE is assessed through a comparative study of the two products. The quality of a drug's bioavailability (BA) must be established, but BE frequently

includes a formal test that compares a test product to a reference product using predefined limitations and specific criteria (Chen et al., 2001).

5.3.1.3 In Vitro - in Vivo Correlation Study Reports and Related Information

In vitro-in vivo correlation (IVIVC) is a method that uses a drug's distribution in laboratory experiments to anticipate how it will behave in the body. It considers the drug's properties and how it reacts in the body. Dissolution testing is done on drugs taken orally to see how well and quickly they dissolve (Lu et al., 2011). Researchers can modify the drug's structure to improve patient absorption and efficacy by examining these findings. The most effective medication version is chosen for clinical trials due to the In Vitro-In Vivo Correlation (IVIVC). This procedure helps researchers in understanding the differences between a drug's reaction in the laboratory (in vitro) and its physiological effects (in vivo) (Lu et al., 2011). However, since Ceftriaxone is given through injections rather than taken orally, the IVIVC approach is not as crucial in its development.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

In bioanalytics, specific substances in biological fluids, such blood or urine, are measured (Kadian et al., n.d.). Drug development and treatment efficacy monitoring depend heavily on these data. Bioanalytical methods are essential for quantitative determination that measures small drug molecules and larger macromolecules (Kadian et al., n.d.). Quantitative determination helps evaluate pharmacokinetics, bioavailability, drug interactions, bioequivalence, and compatibility. Validating analytical methods ensures they are reproducible, stable, sensitive, robust, and reliable for analyzing blood, plasma, urine, serum, and feces. Bioanalytical validation provides high-quality data for regulatory submissions and supports drug discovery and development.

5.3.2 Reports of Studies to Pharmacokinetics Using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports and Related Information

Plasma protein binding studies help determine how much of a drug attaches to proteins in the blood versus how much remains free. In studies on ceftriaxone, a new antibiotic, researchers found similar binding patterns in humans and animals like baboons, rabbits, dogs, and rats (Popick et al., 1987). At lower concentrations of less than 100 micrograms per milliliter, about 90-95% of ceftriaxone binds to proteins. However, at higher concentrations of over 400 micrograms per milliliter, this drops to around 60% (Popick et al., 1987). This shows that the drug's binding to plasma proteins varies with its concentration in the blood.

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

Hepatic metabolism is the process by which the liver transforms drugs and other substances into simpler products that the body can easily remove. This process often reduces the effectiveness of the original compound, meaning the drug's action may not last as long or be as strong as intended (*Hepatic Drug Metabolism and Anesthesia*, 1980). Taking two different drugs at the same time can change how the liver processes each one. This interaction may reduce their effectiveness in treating the condition. The liver is key in how medications work in the body.

5.3.2.3 Reports of Studies Using Other Human Biomaterials

Scientists use biomaterials to help repair injured tissues and organs since the human body sometimes finds it challenging to heal serious injuries independently. One of the studies has looked into how using different human biomaterials can improve the effectiveness and delivery of the antibiotic Ceftriaxone. For instance, researchers have explored using chitosan nanoparticles, small particles made from a natural substance found in shellfish (Zaki & Hafez,

2012). When these nanoparticles are loaded with Ceftriaxone, they can more effectively deliver the medication to infected cells, enhancing its healing properties.

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports and Related Information

Investigational medications are tested for pharmacokinetics and early tolerability in phase 1 clinical trials and first-in-human (FIH) investigations on healthy volunteers. Such Phase 1 study was conducted by dispensing Predictable PK behavior was demonstrated by Ceftriaxone Sodium under all skin layers of healthy participants utilizing the recommended delivery method, with constant half-life and dose-proportional plasma concentrations (Karakunnel et al., 2018). Certain criteria are set for selecting healthy volunteers who can tolerate the treatment well, with only mild local adverse effects reported. Such trials are critical for assessing systemic exposure, tolerability, and safety before advancing into patient populations (*Study Details | Study to Evaluate the Safety, Tolerability, PK, and PD of PB2452 in Healthy Volunteers | ClinicalTrials.gov*, n.d.).

5.3.3.2 Patient PK and Initial Tolerability Study Reports and Related Information

Pharmacokinetic studies in sick people are necessary in some circumstances, such as when researching antibiotics that target resistant diseases, even though first-in-human (FIH) clinical trials are often conducted in healthy volunteers. Ceftriaxone Sodium has primarily been evaluated for its PK profile and acceptability in a range of patient groups, particularly those suffering from pneumonia and infections that were obtained in public. Although these studies are similar to those with healthy volunteers, they help researchers understand how disease conditions vary with drugs (Shen et al., 2019). Also, tolerability examinations in patients help determine the most suitable dosing regimens and identify any side effects linked to disease-mediated changes in drug handling (Shen et al., 2018).

5.3.3.3 Intrinsic Factor PK Study Reports and Related Information

Intrinsic factors are hard-coded into a person's DNA, such as biological sex, race, ethnicity, and hereditary medical conditions that can affect the pharmacokinetics (PK) of a drug (Sehta & Sehta, 2025). For Ceftriaxone Sodium, PK studies have shown variations in drug metabolism and elimination across distinct populations. For example, newborns and elderly patients may show longer half-lives due to reduced renal or hepatic clearance. Also, few studies have found variations based on sex, but they are usually insignificant for beta-lactam antibiotics such as Ceftriaxone. Understanding these intrinsic influences is critical for dose adjustment and personalized treatment strategies (Reyner et al., 2020).

5.3.3.4 Extrinsic Factor Study Reports and Related Information

The pharmacokinetics (PK) of ceftriaxone sodium can be significantly impacted by extrinsic factors, which operate externally, including environmental exposures, smoking status, correlated drugs, and food (Reyner et al., 2020). For example, smoking can impact through compounds in tobacco smoke that are potent inducers of drug-metabolizing enzymes and can accordingly increase the metabolism of such drugs (Sehta & Sehta, 2025). Therefore, understanding how these external factors alter drug metabolism, distribution, or absorption is critical in improving dosing regimens and assuring patient safety.

5.3.3.5 Population PK Study Reports and Related Information

Population PK studies are vital as they provide an integrated examination of PK across analyses and aim to justify variability in PK due to intrinsic and extrinsic factors. PopPK studies of Ceftriaxone Sodium study how patient variability affects drug disposition across diverse groups (Research, 2022). The results navigate to optimal dosing in subpopulations, support

labeling decisions by identifying optimal dose adjustments and supporting critical drug development conclusions. PopPK modeling also helps indicate appropriate dosing for various subgroups and supports labeling decisions by identifying optimal dose adjustments (Sehta & Sehta, 2025).

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports and Related Information

Pharmacokinetics (PK) looks at how a medication travels and is processed in the body over time, focusing on the drug's concentration at different moments. Pharmacodynamics (PD) examines a drug's effects on the body throughout that same timeframe (Tuntland et al., 2014). PK/PD studies combine these two domains to determine their efficacy by analyzing how the body reacts to new medicines. Ceftriaxone helps fight bacteria by blocking their cell wall synthesis through binding to penicillin-binding proteins (PBPs), leading to bacterial death (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.).

5.3.4.2 Patient PD and PK/PD Study Reports and RElated Information

PK/PD studies help evaluate how effective a new drug is. Pharmacokinetics (PK) examines how the drug moves through the body, while pharmacodynamics (PD) examines how it affects the body. PK/PD modeling predicts how these two processes are connected, helping find the right dosage and timing for the best treatment outcomes (Tuntland et al., 2014). Ceftriaxone shows similar pharmacokinetics and pharmacodynamics in patients as in healthy individuals, but infection severity and changes in physiology can affect its effectiveness (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.). It is effective against various aerobic and anaerobic bacteria by binding to penicillin-binding proteins (PBPs) and blocking cell wall synthesis. However for some individuals, resistance mechanisms, including reduced permeability of the membrane, modified PBPs, or beta-lactamase synthesis, might affect how well they respond to treatment (*Ceftriaxone: Uses, Interactions, Mechanism of Action | DrugBank Online*, n.d.).

5.3.5 Results of Efficacy and Safety Studies

5.3.5.1 Study Reports and Related Information of Controlled Clinical Studies Pertinent to the Claimed Indication

Controlled clinical studies are carefully designed experiments that test how well a new drug works. They are called "controlled" because researchers compare the new drug's effects against a control group, which usually receives a placebo or an existing treatment. This comparison helps determine the drug's effectiveness more accurately. A clinical study focused on pediatric patients with acute bacterial otitis media compared a single IM dose of ceftriaxone to a 10-day course of oral antibiotics (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.). The study involved U.S. trials with children aged 3 months to 6 years. Additionally, an open-label study of ceftriaxone included 108 patients, with 79 having positive cultures for common bacteria (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.).

5.3.5.2 Study Reports and Related Information of Uncontrolled Clinical Studies

In uncontrolled clinical research, patients are not assigned to different groups but receive the same treatment. Because these trials lack a control group for comparison, it is challenging to determine the drug's effectiveness. The absence of a control group limits the ability to fully understand the efficiency of the therapy, even though they can offer helpful information. Usually, these types of studies are conducted during Phases I and II, the initial stages of clinical research. They are often used to observe how the treatment works or evaluate how well it works for specific patient groups.

5.3.5.3 Reports of Analysis of Data From More Than One Study

Multiple studies have been conducted throughout clinical trials to determine the safety and efficacy of an innovative medication. By looking at the results from different studies together, they can determine if the drug works differently for various groups of people. For example, systematic reviews indicate that Ceftriaxone is a reliable treatment preference due to its significant efficacy and low resistance rates when consumed correctly.

5.3.5.4 Other Study Reports and Related Information

Several studies have been conducted throughout the clinical research of ceftriaxone; however, not all of them fit into the other categories of CTD Module 5. Many research studies look into different aspects of ceftriaxone, a commonly used antibiotic. These studies examine how well ceftriaxone works, how safe it is for patients, and the best ways to use it. Some studies specifically compare ceftriaxone to other antibiotics to see how effective it is in treating certain infections.

5.4.6 Reports on Postmarketing Experience

In addition to the adverse reactions noted in clinical trials, some side effects have been reported during regular use of ceftriaxone. There have been a few cases of fatal outcomes in newborns who received ceftriaxone along with calcium-containing fluids (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.). Some of these cases involved a crystalline material found in the lungs and kidneys at autopsy, often linked to using the same IV line for both drugs. One fatality occurred even when ceftriaxone and calcium were given at different times and through separate lines, with no crystals found at autopsy. No similar issues have been reported in patients other than neonates (*DailyMed - CEFTRIAXONE SODIUM Injection, Powder, for Solution*, n.d.).

5.4 Literature Reference

Chen, M., Shah, V., Patnaik, R., Adams, W., Hussain, A., Conner, D., Mehta, M., Malinowski, H., Lazor, J., Huang, S., Hare, D., Lesko, L., Sporn, D., & Williams, R. (2001). Bioavailability and bioequivalence: an FDA regulatory overview. *Pharmaceutical Research*, *18*(12), 1645–1650. https://doi.org/10.1023/a:1013319408893

DailyMed - CEFTRIAXONE SODIUM injection, powder, for solution. (n.d.). https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=473ab78d-5015-4a4a-8a2c-8f594b8de41d#i4i_clinical_studies_id_12a633f3-a385-4948-9e10-19c30895eba4

Hepatic drug metabolism and anesthesia. (1980, February 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/6990824/

Kadian, N., Raju, K. S. R., Rashid, M., Malik, M. Y., Taneja, I., & Wahajuddin, M. (2016). Comparative assessment of bioanalytical method validation guidelines for pharmaceutical industry. *Journal of Pharmaceutical and Biomedical Analysis*, *126*, 83–97. https://doi.org/10.1016/j.jpba.2016.03.052

Karakunnel, J. J., Bui, N., Palaniappan, L., Schmidt, K. T., Mahaffey, K. W., Morrison, B., Figg, W. D., & Kummar, S. (2018). Reviewing the role of healthy volunteer studies in drug development. *Journal of Translational Medicine*, *16*(1). https://doi.org/10.1186/s12967-018-1710-5

Lu, Y., Kim, S., & Park, K. (2011). In vitro–in vivo correlation: Perspectives on model development. *International Journal of Pharmaceutics*, *418*(1), 142–148. https://doi.org/10.1016/j.ijpharm.2011.01.010

Popick, A. C., Crouthamel, W. G., & Bekersky, I. (1987). Plasma protein binding of ceftriaxone. *Xenobiotica*, *17*(10), 1139–1145. https://doi.org/10.3109/00498258709167406

Research, C. F. D. E. A. (2022, February 3). *Population Pharmacokinetics*. U.S. Food And Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/population-pharmacokinetics

Reyner, E., Lum, B., Jing, J., Kagedal, M., Ware, J. A., & Dickmann, L. J. (2020). Intrinsic and Extrinsic Pharmacokinetic Variability of Small Molecule Targeted Cancer Therapy. *Clinical and Translational Science*, *13*(2), 410–418. https://doi.org/10.1111/cts.12726

Sehta, S., & Sehta, S. (2025, April 1). *Intrinsic and extrinsic factors in drug development*. Allucent. https://www.allucent.com/resources/blog/intrinsic-and-extrinsic-factors-drug-development

Sehta, S., & Sehta, S. (2025, April 3). *What is Population Pharmacokinetic (popPK) Analysis?* Allucent. https://www.allucent.com/resources/blog/what-population-pharmacokinetic-poppk-analysis

Shen, J., Swift, B., Mamelok, R., Pine, S., Sinclair, J., & Attar, M. (2018). Design and conduct considerations for First‐in‐Human trials. *Clinical and Translational Science*, *12*(1), 6–19. https://doi.org/10.1111/cts.12582

Study details | Study to evaluate the safety, tolerability, PK, and PD of PB2452 in healthy volunteers | ClinicalTrials.gov. (n.d.). https://clinicaltrials.gov/study/NCT03492385

Tuntland, T., Ethell, B., Kosaka, T., Blasco, F., Zang, R. X., Jain, M., Gould, T., & Hoffmaster, K. (2014). Implementation of pharmacokinetic and pharmacodynamic strategies in early

research phases of drug discovery and development at Novartis Institute of Biomedical Research. *Frontiers in Pharmacology*, *5*. https://doi.org/10.3389/fphar.2014.00174

Zaki, N. M., & Hafez, M. M. (2012). Enhanced Antibacterial Effect of Ceftriaxone Sodium-Loaded Chitosan Nanoparticles Against Intracellular Salmonella typhimurium. *AAPS PharmSciTech*, *13*(2), 411–421. https://doi.org/10.1208/s12249-012-9758-7

Appendix