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Review of Aseptic Filling and Quality control testing of Cefuroxime Sodium IP in the pharmaceutical Industry

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ABSTRACT

Cefuroxime Sodium IP is a widely used antibiotic in the pharmaceutical industry, and its proper filling and quality control testing are crucial to ensure the safety, efficacy, and compliance of the final product. This review aims to provide an overview of the filling process and quality control testing methods employed in the industry for Cefuroxime Sodium IP. The filling process involves several critical steps, including formulation preparation, sterilization, filling, and packaging. Each step requires strict adherence to good manufacturing practices (GMP) and meticulous control to avoid contamination and ensure accurate dosage. Aseptic techniques are employed to maintain sterility during the filling process, and specialized equipment is used to ensure accurate volume and weight measurements. Quality control testing plays a vital role in assessing the integrity and quality of Cefuroxime Sodium IP. Various tests are performed throughout the manufacturing process to verify the identity, potency, purity, and quality of the drug. These tests may include appearance inspection, pH determination, assay of active ingredient, microbial limit testing, endotoxin testing, and stability studies. Compliance with pharmacopeial standards, such as the Indian Pharmacopoeia (IP), is essential during quality control testing. In addition to the filling process and quality control testing, the review also highlights the importance of documentation, record-keeping, and regulatory compliance. Comprehensive batch records and documentation of all activities are essential to ensure traceability, accountability, and compliance with regulatory requirements. Overall, the filling and quality control testing of Cefuroxime Sodium IP in the pharmaceutical industry require strict adherence to GMP guidelines and rigorous testing procedures. Robust quality control measures and accurate filling processes are essential to produce a safe and effective antibiotic product that meets the stringent regulatory standards. Continuous monitoring, validation, and improvement of these processes are essential to ensure the consistent quality of Cefuroxime Sodium IP in the industry.

Keywords: manufacturing, production, quality control, safety

INTRODUCTION

A third-generation cephalosporin antibiotic called cefuroxime sodium is used to treat various diseases, such as pneumonia, meningitis, and urinary tract infections. For injection, it is offered as a dry powder that is reconstituted with sterile water.

For dry powder injectables, the filling procedure is a crucial step in ensuring the product's quality and safety. In order to prevent contamination and guarantee that the powder is evenly distributed in the diluent, care must be taken when handling it. When making dry powder injectables, it's crucial to keep in mind that the excipients shouldn't conflict with the drug's stability or effectiveness and should instead work in harmony with it.

To make sure that dry powder injectables satisfy the necessary quality standards, they must be evaluated. Sterility, potency, and stability testing are all included in this.

The following are some of the procedures for filling, creating, and analyzing dry powder injectables:

- Filling: The powder is measured and put into a clean vial. An aluminum crimp and rubber stopper are then used to close the vial.

- Formulation: For injection, the powder is reconstituted with sterile water. After that, the solution is filtered to get rid of any impurities.
- Evaluation: The sterility, potency, and stability of the solution are examined.
- Dry powder injectables filling, formulation, and evaluation is a complex procedure requiring close attention to detail. You can contribute to ensuring that your goods are secure and efficient by following to these procedures.

The evaluation's findings will be utilized to establish the safety and effectiveness of cefuroxime sodium's dry powder injectable form and to support its use to the management of infections.

1. It comes in vials that have 750 mg or 1.5 g of cefuroxime sodium in them.
2. For injection, sterile water is used to reconstitute it.
3. Injections into the muscles or veins are used to administer it.
4. It is normally administered once or twice each day.

The type of infection being treated determines the length of the course of treatment. The majority of people tolerate cefuroxime sodium well. Nausea, vomiting, diarrhea, and rash are the most frequent side effects linked to its use. Allergies, liver damage, and kidney damage are a few serious side effects that have been linked to cefuroxime sodium.

Cefuroxime Sodium Inj IP:
Cefuroxime is a sterile semisynthetic, broad-spectrum, cephalosporin antibiotic for parenteral administration. It is the sodium salt of (6R,7R)-3-[(carbonyloxy)methyl]-7-[[(Z)-(furan-2-yl) (methoxyimino)acetyl] amino]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate. The empirical formula is C16H15N4NaO8S, representing a molecular weight of 446.37.

Cefuroxime for Injection, contains approximately 54.2 mg (2.4 mEq) of sodium per gram of cefuroxime activity.
Cefuroxime Injection is a sterile material consisting of Cefuroxime Sodium, with or without auxiliary substances. It is filled in a sealed container.The injection is constituted by dissolving the contents of a sealed container in the requisite amount of Water for Injections immediately before use.The constituted solution complies with the requirements for Clarity of solution and Particulate matter stated under Parenteral Preparations (Injections).The constituted solution should be used immediately after preparation but, in any case, within the period recommended by the manufacturer. Cefuroxime Injection contains a quantity of Cefuroxime Sodium equivalent to not less than 90.0 per cent and not more than 120.0 per cent of the stated amount of cefuroxime, $C_{16}H_{16}N_4O_8S$

IUPAC name: (6R,7R)-3-{[(Aminocarbonyl)oxy]methyl}-7-{[(2Z)-2-(2-furyl)-2-(methoxyimino)acetyl]amino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Usual strengths:
The equivalent of 250 mg, 750 mg and 1.5 g of cefuroxime.
Dose per Vial: strength /potency X 1000 = Dose (mg)

Description:
A white or faintly yellow powder. The contents of the sealed container comply with the requirements stated under Parenteral Preparations (Powders for Injection) and with the following requirements.

Identification:
A. In the Assay, the principal peaks in the chromatogram obtained with the test solution corresponds to the peaks in the chromatogram obtained with the reference solution.
B. It gives the reactions of sodium salts.

Tests:
1. pH: - 6.0 to 8.5, determined in a 10.0 per cent w/v solution.
2. Related substances: - Determine by liquid chromatography

Test solution. Dissolve a quantity of the mixed content of 10 containers containing 0.1 g of cefuroxime to 100 ml of water.
Reference solution (a). A 0.1 per cent w/v solution of cefuroxime sodium RS in water.
Reference solution (b). Heat 20.0 ml of reference solution (a) in water bath at 60° for 10 minutes, cool. Reference solution (c). Dilute 1.0 ml of reference solution (a) to 100.0 ml with water.

3. Chromatographic system: -
-a stainless steel column 12.5 cm x 4.6 mm packed with silica chemically bonded to hexylsilane groups (5 µm) (such as Spheris orb S5 C6).
-mobile phase: a mixture of 1 volume of acetonitrile and 99 volumes of acetate buffer pH 3.4.
-flow rate: 1.5 ml per minute

-spectrophotometer set at 273 nm,
-injection volume: 20 ul.

Inject reference solution (b) The chromatogram obtained shows peaks corresponding to cefuroxime and dicarbamoyl-cefuroxime. The test is not valid unless the resolution between the two principal peaks is not less than 2.0.

Inject reference solution (c) and the test solution. Run the chromatogram 3 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of peak due to dicarbamoyl-cefuroxime is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent). The sum of areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (e) (3.0 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

4. Bacterial endotoxins: - Not more than 0.1 Endotoxin Unit per mg of cefuroxime.
Water: - Not more than 3.5 per cent, determined on 015g
Assay: - Determine by liquid chromatography

Test solution. Weigh a quantity of the mixed contents of the 10 containers containing about 25 mg of cefuroxime and dissolve in sufficient water to produce 25.0 ml. Immediately transfer 5.0 ml of the resulting solution to a 100-ml volumetric flask, add 20.0 ml of a 0.15 per cent w/v solution of orcinol (internal standard) in water, dilute to volume with water and mix.

Reference solution. Treat a quantity of cefuroxime sodium RS equivalent to 25 mg of cefuroxime in a similar manner.
Chromatographic system:
- a stainless steel column 15 cm x 4.6 mm, packed with hexylsilane chemically bonded to totally porous silica particles (5 µm).
- mobile phase: a mixture of 91 volumes of acetate buffer pH 3.4 and 9 volumes of acetonitrile.
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm.
- injection volume-10 ul.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 per cent
Inject the reference solution and the test solution
Calculate the content of $C_{16}H_{16}N_4O_8S$ in the injection.

Storage:
Store in tightly-closed containers protected from moisture at a temperature not exceeding 30°.
Labelling:
The label on the sealed container states the quantity of Cefuroxime Sodium contained in it in terms of the equivalent amount of cefuroxime.

Preclinical safety data: - non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.

Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

Clinical Pharmacology:
After intramuscular (IM) injection of a 750-mg dose of cefuroxime to normal volunteers, the mean peak serum concentration was 27 mcg/mL. The peak occurred at approximately 45 minutes (range, 15 to 60 minutes). Following IV doses of 750 mg and 1.5 g, serum concentrations were approximately 50 and 100 mcg/mL, respectively, at 15 minutes. Therapeutic serum concentrations of approximately 2 mcg/mL or more were maintained for 5.3 hours and 8 hours or more, respectively. There was no evidence of accumulation of cefuroxime in the serum following IV administration of 1.5-g doses every 8 hours to normal volunteers. The serum half-life after either IM or IV injections is approximately 80 minutes.

Approximately 89% of a dose of cefuroxime is excreted by the kidneys over an 8-hour period, resulting in high urinary concentrations.

Following the IM administration of a 750-mg single dose, urinary concentrations averaged 1,300 mcg/mL during the first 8 hours. Intravenous doses of 750 mg and 1.5 g produced urinary levels averaging 1,150 and 2,500 mcg/mL, respectively, during the first 8-hour period.

The concomitant oral administration of probenecid with cefuroxime slows tubular secretion, decreases renal clearance by approximately 40%, increases the peak serum level by approximately 30%, and increases the serum cof-life by approximately 30%. Cefuroxime is detectable in therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, and aqueous humour.

Cefuroxime is detectable in therapeutic concentrations in cerebrospinal fluid (CSF) of adults and paediatric patients with meningitis. The following table shows the concentrations of cefuroxime achieved in cerebrospinal fluid during multiple dosing of patients with meningitis.

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

Indications and Usage:
Cefuroxime for Injection is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. Lower Respiratory Tract Infections, including pneumonia, caused by Streptococcus pneumoniae, Haemophilus influenzae (including ampicillin-resistant strains), Klebsiella spp., Staphylococcus aureus (penicillinase- and non-penicillinase- producing strains), Streptococcus pyogenes, and Escherichia coli.
2. Urinary Tract Infections caused by Escherichia coli and Klebsiella spp.
3. Skin and Skin-Structure Infections caused by Staphylococcus aureus (penicillinase- and non-penicillinase-producing strains), Streptococcus pyogenes, Escherichia coli, Klebsiella spp., and Enterobacter spp.
4. Septicaemia caused by Staphylococcus aureus (penicillinase- and non-penicillinase- producing strains), Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae (including ampicillin-resistant strains), and Klebsiella spp.
5. Meningitis caused by Streptococcus pneumoniae, Haemophilus influenzae (including ampicillin-resistant strains), Neisseria meningitidis, and Staphylococcus aureus (penicillinase- and non-penicillinase-producing strains).
6. Gonorrhoea: Uncomplicated and disseminated gonococcal infections due to Neisseria gonorrhoeae (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. Bone and Joint Infections caused by Staphylococcus aureus (penicillinase- and non- penicillinase-producing strains).

Clinical microbiological studies in skin and skin-structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Cefuroxime for Injection, has been used successfully in these mixed infections in which several organisms have been isolated.

In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Cefuroxime for Injection, may be used concomitantly with an aminoglycoside. The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefuroxime for Injection, and other antibacterial drugs, Cefuroxime 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.

Prevention:
The preoperative prophylactic administration of Cefuroxime for Injection, may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Cefuroxime for Injection, should usually be given one-half to 1 hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of Cefuroxime for Injection, has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that therapy with Cefuroxime for Injection, be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism, and appropriate antimicrobial therapy should be instituted.

Contraindications:
Cefuroxime for Injection is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Adverse Reactions: Cefuroxime for Injection is generally well tolerated. The most common adverse effects have been local reactions following IV administration. Other adverse reactions have been encountered only rarely.

Local Reactions:
Thrombophlebitis has occurred with IV administration in 1 in 60 patients.

Gastrointestinal:
Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhoea (1 in 220 patients) and nausea (1 in 440 patients). The onset of pseudomembranous colitis may occur during or after antibacterial treatment.

Hypersensitivity Reactions:
Hypersensitivity reactions have been reported in fewer than 1% of the patients treated with Cefuroxime for Injection and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in fewer than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, drug fever, erythema multiforme, interstitial nephritis, toxic epidermal necrolysis, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in haemoglobin and haematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (fewer than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies. As with other cephalosporins, there have been rare reports of thrombocytopenia.

Hepatic:
Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney:
Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

Post marketing Experience with Cefuroxime for Injection:
In addition to the adverse events reported during clinical trials, the following events have been observed during clinical practice in patients treated with Cefuroxime for Injection and were reported spontaneously. Data are generally insufficient to allow an estimate of incidence or to establish causation.

Immune System Disorders:
Cutaneous vasculitis, angioedema, acute myocardial ischemia with or without myocardial infarction may occur as part of an allergic reaction.

Nervous System Disorders: Seizure

Cephalosporin-class Adverse Reactions:
In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics Adverse Reactions

Vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anaemia, haemolytic anaemia, haemorrhage

Dosage:
Adults The usual adult dosage range for Cefuroxime for Injection is 750 mg to 1.5 grams every 8 hours, usually for 5 to 10 days. In uncomplicated urinary tract infections, skin and skin-structure infections, disseminated gonococcal infections, and uncomplicated pneumonia, 750-mg dose every 8 hours is recommended. In severe or complicated infections, 1.5-gram dose every 8 hours is recommended.

In bone and joint infections, 1.5-gram dose every 8 hours is recommended. In clinical trials, surgical intervention was performed when indicated as an adjunct to therapy with Cefuroxime for Injection. A course of oral antibiotics was administered when appropriate following the completion of parenteral administration of Cefuroxime for Injection.

In life-threatening infections or infections due to less susceptible organisms, 1.5 grams every 6 hours may be required. In bacterial meningitis, the dosage should not exceed 3 grams every 8 hours. The recommended dosage for uncomplicated gonococcal infection is 1.5 grams given intramuscularly as a single dose at 2 different sites together with 1 gram of oral probenecid. For preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5-gram dose administered intravenously just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg intravenously or intramuscularly every 8 hours when the procedure is prolonged.

For preventive use during open heart surgery, a 1.5-gram dose administered intravenously at the induction of anaesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

Paediatric Patients Above 3 Months of Age:
Administration of 50 to 100 mg/kg/day in equally divided doses every 6 to 8 hours has been successful for most infections susceptible to cefuroxime. The higher dosage of 100 mg/kg/day (not to exceed the maximum adult dosage) should be used for the more severe or serious infections.

In bone and joint infections, 150 mg/kg/day (not to exceed the maximum adult dosage) is recommended in equally divided doses every 8 hours. In clinical trials, a course of oral antibiotics was administered to paediatric patients following the completion of parenteral administration of Cefuroxime for Injection.

In cases of bacterial meningitis, a larger dosage of Cefuroxime for Injection is recommended, 200 to 240 mg/kg/day intravenously in divided doses every 6 to 8 hours.

In paediatric patients with renal insufficiency, the frequency of dosing should be modified consistent with the recommendations for adults.

Preparation of solution and suspension:

For Intramuscular Use

Each 750-mg vial of Cefuroxime for Injection should be constituted with 3 mL of Sterile Water for Injection. Shake gently to disperse and withdraw completely the resulting suspension for injection.

a Note: Cefuroxime for Injection is a suspension at IM concentrations.

For Intravenous Use

Each 750-mg vial should be constituted with 8.3 mL of Sterile Water for Injection. Withdraw completely the resulting solution for injection.

Each 1.5-gram vial should be constituted with 16 mL of Sterile Water for Injection, and the solution should be completely withdrawn for injection.

Table: Dosage Indications

Strength	Amount of Diluent to be Added (mL)	Volume to be Withdrawn	Approximate Cefuroxime Concentration (mg/mL)
750-mg Vial	3 (IM)	Total	225
750-mg Vial	8.3 (IV)	Total	90
1.5-gram Vial	16 (IV)	Total	90

Instruments used in Filling:

1)Vial washing and sterilization assembly:

an NPK linear vial washing machine to wash vials and even coat silicon on vial internally or externally. Most of them are externally coated by silicon to reduce friction produced between vials.

The complete process is of 45-60 mins which includes vial washing with pure water, water for injection and drying with dry air. Followed by silicon coating and dry heat sterilization at 350- 375 ℃ for minimum 8 mins and after that there is a cooling passage to cool vials which are directly passed to the filling area without human touch or interference.
Model Name: SteriPACK V - 900 (NK VW 250H)
Production Rate: Up to 240 Vials/Min.

2)vial filling and sealing machine:

As we need sterile conditions, we use conveyor belts to transport and keep vials away from human touch. This machine can fill 50 Mg to 1.5 Grams. single dose (with help of change parts).1.5 Grams. to 6 Grams. double, triple and four doses. Fill range depending upon vial opening and bulk density of powder.

Model Name: NKPF 125
Production Rate: Up to 120 Fills/Min. for a single dose.
Up to 60 Fills/Min. for a double dose.
Up to 40 Fills/Min. for a triple dose.
Up to 30 Fills/Min. for four doses.

This assembly has vertical laminar air flow equipped with 0.22-micron HEPA filters which keep the filling & sealing area class 100 (Class 100 is a class of air purity which can be defined as Number particles in air should be below 100 per cubic square) which should be maintain to keep produce sterile.

Automatic high speed vial sealing machine, is a very handy and proficient machine as it comes with compression pressure indication & rejection system. The raw material used for the construction of the machine possesses high strength that imparts a sturdy structure. This makes the high-speed vial machine extremely durable, capable of performing operations for a longer period of time.
Model Name: NKCS - 350PR
Production rate: 250 Vials/Min. For 5 ML to 10 ML Vial
No. of sealing Head: 8

3) Vial Labelling Machine:

High Speed Fully Automatic Labelling Machine for all sticker application requirements by Maharshi Ltd. this equipment has separate drives for conveyor, wrap around unit and space creator is useful for precise labelling to multi products with different label size.

Production rate: The machine operates at the speed of 100 - 200 - 300 containers / min. (depending upon the labels length).

4) In process Quality Checking:

This includes three main tastings as Weight, clarity and Seal test.
For Weight testing:
we take 10-20 vials and check individual weight of vial.
For Clarity:
we get 10 vials and water for Injection to each vial and check clarity for any development of foreign particle.
For Seal test:
we take 10 random vial samples and check for seal is packed and not tampered.

Quality Control Report:

1.Raw material and finished goods

The analysis of various raw materials, bulk drugs and finished products are checked for conformance for specifications laid down by official compendium or Internal Standard Committee (ISC).
These materials are tested chemically, microbiologically and pharmacologically in respective laboratories. The analytical reports from various labs are received and compiled by QC office.

The test performed should be recorded and the records should include the following data:

- Name of the material or product, type of dosage form (if applicable)
- Batch number, lot number, mfg./exp date etc.
- References to the relevant specifications and testing procedures

- Test results, including observations and calculations etc.
- Date of testing the material
- Remark of released or not released
- Name and sign of the analyst and verifying officer.

2.Packaging materials

The analysis of various packaging materials (primary/secondary/tertiary) are checked for conformance for specifications laid down by official Compendium or Internal Standard Committee (ISC). These materials are tested Physically, chemically and pharmacologically.

The test performed should be recorded and the records should include the following data:

- Name of the material
- Lot number/receipt no.
- References to the relevant specifications and testing procedures
- Test reports including test, norms, observations, calculations and results.
- Date of testing the material
- Remark of released or not released.
- Name and sign of the analyst/technician and verifying officer.

3.BET (bacteria Endotoxin Test)

A pyrogenic molecule called endotoxin (lipopolysaccharides) is present in the cell walls of gram-negative bacteria. A pyrogen material when injected into the blood can cause fever. Use the LAL (limulus Amoebocyte Lysate) assay to identify pyrite. This substance is obtained from horseshoe crabs. The blue hue of crabs is caused by copper hemocyanin. A gel-like structure is created when the Lal reagent interacts with the lipopolysaccharides of gram-negative bacteria.

Methods for bet:

1. Gel clot limit test method
2. Semi quantitative gel clot method
3. Kinetic turbid metric method
4. Kinetic Chromogenic method
5. Endpoint chromogenic method

Procedure of Gel clot limit test :

1. Gel clot limit test Is performed using the LAL(Limulus Amoebocyte Lysate) reagent to detect the presence and concentration of bacterial endotoxins in drugs
2. LAL reagent Limulus amoebocyte lysate (LAL) is an aqueous extract of blood cells (amoebocytes) from the horseshoe crab, Limulus polyphemus. LAL reagent reacts with bacterial endotoxin and lipopolysaccharide (LPS), which is a membrane constituent of Gram-negative bacteria.
3. Preparatory Testing
   i. Confirmation of labelled lysate sensitivity
   a) Prepare of 4 standards (2λ, λ, 0.5 λ and 0.25 λ) – 4 replicates of each conc.
   b) Mix equal amount of Lysate (LAL) as the standard
   c) Incubate the mixture (usually for 60 ±2 mins at 37°C)
   d) Invert the tube (in one smooth motion) NPCB •
   ii. Test for interfering factors –
   Prepare of solutions A, B, C and D
   Solution A & B: 4 replicates
   solution C & D: 2 replicates.
   Repeat steps b) to d) from Confirmation of labelled lysate sensitivity.
4. Limit test
   Prepare of solutions A, B, C and D (refer Table 1.2) – min 2 replicates for all solutions • Repeat steps b) to d) from Confirmation of labelled lysate sensitivity
   MVD = Endotoxin limit x Product concentration/ λ
5. Maximum Valid Dilution = the maximum allowable dilution of a sample at which the endotoxin concentration can be determined
6. To Carry LAL test we need to neutralize the Product using Penicillinase For 6 Gm of Sample 11 ml Penicillinase is required.
7. LAL test is carried on product as:
   Local manufacturer – CoA for 1 batch of finished products •
   Oversea manufacturer – CoA for 3 batches of finished products •
   Must contain (in relation to LAL test):

i. Product name and strength
ii. Batch number
iii. Specification for BET
iv. Results for BET
v. Appearance
vi. Ph
vii. Name, signature, and date of approval

Table: Results of Gel Clot Limit Test

	Content	**Conclusion**	**Pass/Fail**
Solution A	Sample A (25µL) + LAL Reagent (100µL)+ water (75 µL)	Gel Clot Not Formed	Pass
Solution B	Sample B (25µL) + LAL Reagent (100µL)+ water (75 µL)	Gel Clot Not Formed	Pass
Solution C	Sample C (25µL) + LAL Reagent (100µL)+ water (75 µL)	Gel Clot Not Formed	Pass
Positive Product Control	Sample (25µL) + LAL Reagent (100µL)+ CSE (Control Standard Endotoxins) (50 µL)	Gel Clot Formed	Pass

Conclusion Of Gel Clot Limit Test :
Negative Product Control which are Sample A,B&C have not formed any gel clot which is favourable and confirms that no bacterial endotoxins are present in final product Positive product control has Gel clot so it confirms that Anti biotic was neutralized and test procedure was carried perfectly

4.Bioassay
A bioassay is an analytical method to determine the concentration or potency of a substance by its effect on living animals or plants (in vivo), or on living cells or tissues(in vitro). A bioassay can be either quantal or quantitative, direct or indirect. If the measured response is binary, the assay is quantal, if not, it is quantitative.

A bioassay may be used to detect biological hazards or to give an assessment of the quality of a mixture. A bioassay is often used to monitor water quality as well as wastewater discharges and its impact on the surroundings. It is also used to assess the environmental impact and safety of new technologies and facilities.

Principle:
A bioassay is a biochemical test to estimate the potency of a sample compound. Usually, this potency can only be measured relative to a standard compound. A typical bioassay involves a stimulus (ex. drugs) applied to a subject (ex. animals, tissues, plants). The corresponding response (ex. death) of the subject is thereby triggered and measured.
When standard and lower dilutions of Antimicrobial Drugs are inoculated on AGAR culture Trey then they produce zone of inhibition which defines the potency of the Anti-Microbial Drug.

Procedure:
1. Preparation of Agar Tray
This preparation plays important role in testing as this tray serves as base for both sample as well as culture. 200ml of agar preparation is sterile for 5 mins at 170 °C then cooled to 40-45°C Then 3ml of culture is added to it and poured it in a tray. 64 vials can be tested at same time due to this process.

2. Principle of The Latin square and quasi-Latin square lay-out
Yates (1937) has given a design for carrying out an experiment of the form 25 (five factors all at two levels) in an 8 × 8 square, which involves the partial confounding of the higher order interactions. This design can be adapted to our purpose. We consider that we have one factor at two levels (the high and low dilutions) and one factor at eight levels. This factor at eight levels can be regarded as made up as

(1) standard preceding unknowns,
(2) unknown 1 succeeding the standard by one time interval,
(3) unknown 2 succeeding the standard by two-time intervals,
(4) unknown 3 succeeding the standard by three-time intervals,
(5) unknown 3 preceding the standard by three-time intervals,
(6) unknown 2 preceding the standard by two-time intervals,
(7) unknown 1 preceding the standard by one time interval,
(8) standard succeeding the unknowns.

Ideally this should be re-randomized every time it is used, but when doing 20–30 plates a day this is impracticable. The most satisfactory compromise is probably to construct about 20–30 arrangements, and have separate forms printed similar to for each. Appropriate templates for transferring the results from the main table to the smaller one and for filling the plates would also be needed. The arrangement to be used in any particular assay can be selected with a table of random numbers. which has been used in all the assays of this type reported in this paper, the restriction has been imposed that in all rows and all columns the high and low levels alternate. This was to assist the operator in filling the plate, but a completely random arrangement is to be preferred on theoretical grounds. Randomization in practice can be carried out by drawing numbers from 1 to 8 from a hat, and rearranging the rows in the order thus given, and repeating this process for columns.

3. Zone Reading

After Inoculating 0.1ml sample in tray with help of Latin square as odd numbers have standard dilutions and even numbers have lower dilutions. This Inoculated part shows 'Zone of Inhibition' by measuring this zone we can determine the potency and efficacy of the antimicrobial drug. Acral Zone Reader equipment is used to measure accurate area of 'Zone of Inhibition'.

Conclusion:

Neat circular zone with large area is more effective and potent and zero growth in zone of Inhibition is ideal conditions for passing the test.

5. Microbiological Limit test

to carry limit test, we use Total Aerobic Microbial Count (TAMC) is equal to the number of colony-forming units (CFU) on Soybean-Casein Digest Agar. If fungal colonies are found, they are counted as a part of TAMC.

Procedure of TAMC:

To carry the test, we take 20 vials per batch and 20 Ampules of WFI. We need to neutralize the API as it will disturb the results. To neutralize 6 g of sample we use 11 ml of added penicillinase. Then we dilute the Final product till 100 ml

Now using Millipore method, we wash the membrane three times with our sample.
In total Four Millipore assembly are used to three for negative Control Product and One for Positive control product to ensure the Complete Neutralization of API. Then in Aseptic conditions these membranes are shifted to the Media plate and incubated for 48 hours.

To determine specific bacterial endotoxins, we use special media as

- For E-coli we use MacConkey Broth
- For Salmonella we use Selenite Broth
- For Pseudomonas we use cetrimide Broth

This method is called selective media Culture

Table: Results of Microbiological Limit Test

Sr.No	Media Plate	Observation	Conclusion	Pass Or fail
1.	MacConkey Broth	No Growth in media plate	E-Coli is not present	Pass
		Pink Colony growth is observed	E-Coli Present	Fail
2.	Selenite Broth	No Growth In media plate	Salmonella Is not Present	Pass
		Black Yellow Colony growth is Observed	Salmonella is Present	Fail
3.	Cetrimide Broth	No growth in media plate	Pseudomonas is Not present	Pass
		Bluish Green colony growth is observed	Pseudomonas is present	fail

Conclusion:

This test is Conducted to determine the presence of bacterial endotoxins, presence of these endotoxins as harmful for product life, as well as patients' life. There should not be presence of any endotoxins maintained above to insure the product life and patient safety. If any test is failed by product, then whole batch is recalled and discarded

CONCLUSION

1. Filling Process: The filling process for Cefuroxime Sodium IP in the industry is generally satisfactory. The review found that the industry follows standard procedures and guidelines for filling, ensuring accuracy and consistency in the dosage form. The filling equipment appears to be in good working condition, allowing for efficient and precise filling of the drug.

2. Quality Control Testing: The industry's quality control testing measures for Cefuroxime Sodium IP demonstrate a commitment to ensuring product quality and compliance with regulatory standards. The review found that the industry conducts comprehensive testing throughout the manufacturing process, including raw material analysis, in-process testing, and final product testing. These tests help identify any potential deviations or impurities, ensuring the safety and efficacy of the drug.

3. Compliance with Regulatory Requirements: The review indicated that the industry adheres to regulatory requirements and guidelines for the filling and quality control testing of Cefuroxime Sodium IP. This commitment to compliance helps ensure that the drug meets the necessary quality standards for market distribution.

4. Product Quality: Overall, the review suggests that the filling and quality control testing processes contribute to the production of high-quality Cefuroxime Sodium IP. The industry's attention to detail and rigorous testing protocols helps minimize the risk of product defects and ensure that the drug meets the desired specifications.

Based on the review of filling and quality control testing of Cefuroxime Sodium IP in the industry, it can be stated that the industry demonstrates a strong commitment to maintaining product quality and compliance with regulatory standards. The filling process and quality control measures are effective in ensuring accurate dosage form and high-quality Cefuroxime Sodium IP.

REFERENCES

[1]. Indian Pharmacopeia 2018 volume 2, Page 1546-1548
[2]. Indian Pharmacopeia 2018 volume 1, Section 2.2.3 Page 28-33
[3]. Bioassay Techniques For Drug Development By Atta-ur-Rahman, M. Iqbal Choudhary & William J. Thomson, Page 13-22
[4]. Preparation and Evaluation of a Dry Powder Formulation of Cefuroxime Sodium (2014) by M.S. Al-Sulaiman
[5]. J.C. Boylan and A.L. Fites, “Parenteral Products,” in Modern Pharmaceutics, G.L. Banker and C.T. Rhodes, Eds. (Marcel Dekker Inc., New York, NY, 1979), p. 445.
[6]. P.P. DeLuca and J.C. Boylan, “Formulation of Small-Volume Parenterals,” in Pharmaceutical Dosage Forms: Parenteral Medications, Volume 1, K.E. Avis et al., Eds. (Marcel Dekker Inc., New York, NY, 1992), p. 215
[7]. R.J. Harwood et al, “The Processing of Small-Volume Parenterals and Related Sterile Products,” in Pharmaceutical Dosage Forms: Parenteral Medications, Volume 2, K.E. Avis et al., Eds. (Marcel Dekker Inc., New York, NY, 1993), p. 61.
[8]. S. Motola and S.N. Agarkar, “Preformulation Research of Parenteral Medications,” in Pharmaceutical Dosage Forms: Parenteral Medications, Volume 1, K.E. Avis et al., Eds. (Marcel Dekker Inc., New York, NY, 1992), p. 115.
[9]. D.G. Greene, “Preformulation,” in Modern Pharmaceutics, G.S. Banker and C.T. Rhodes, Eds. (Marcel Dekker Inc., New York, NY, 1979), p. 211.
[10]. W.C. Hinds, “Adhesion of Particles,” in Aerosol Technology: Properties, Behavior, and Measurements of Airborne Particles, W.C. Hinds, Ed. (Wiley, New York, NY), pp. 127–132 (1982).
[11]. J.C. Boylan and A.L. Fites, “Parenteral Products,” in Modern Pharmaceutics, G.L. Banker and C.T. Rhodes, Eds. (Marcel Dekker Inc., New York, NY), p. 445 (1979).
[12]. G. Stark et al., “Instrumental Evaluation of Color of Solid Dosage Forms during Stability Testing,” Int. J. Pharm. 143, 93–100 (25 Oct. 1996).
[13]. R.W. Jaehenke et al., “Interaction of Rubber Closures with Powder for Parenteral Administration,” J. Parenter. Sci. Technol. 44 (5), 282–288 (1990).
[14]. P.P. DeLuca and J.C. Boylan, “Formulation of Small-Volume Parenterals,” in Pharmaceutical Dosage Forms: Parenteral Medications, Volume 1, K.E. Avis et al., Eds. (Marcel Dekker Inc., New York, NY, 1992), p. 216.
[15]. “788” Particulate Matter in Injections,” in USP 24–NF 19 (United States Pharmacopeial Convention, Rockville, MD, 2000), pp. 1971–1977.
[16]. D.A. Parkins and A.J. Taylor, “Particulate Matter Content of 11 Cephalosporin Injections: Conformance with USP Limits,” Am. J. Hosp. Pharm. 44, 1111–1118 (May 1987).
[17]. Hung JC. Comparison of various requirements of the quality assurance procedures for (18)F-FDG injection. J Nucl Med. 2002; 43:1495–506
[18]. The Indian Pharmacopoeia Commission. 6th ed. 6.0. Ghaziabad: 2010. Index, Indian Pharmacopoeia Commission. ISBN 81-903436-4-5

[19]. Williams CC, Borchert RD, Clanton JA. The bacterial endotoxin test in the PET facility. J Nucl Med. 1993; 34:469–73.
[20]. Joiner TJ, Kraus PF, Kupiec TC. Comparison of Endotoxin Testing Methods for Pharmaceutical Products. Int J Pharm Compound. 2002; 6:408–9.
[21]. Hung JC, Iverson BC, Jacobson MS, Mahoney DW. Inhibtion evaluation for a 20-min. endotoxin limit test on FDG. Nucl Med Commun. 2005; 26:869–74.
[22]. Mitra A, Kulkarni S, Rajan MG. Rapid test for bacterial endotoxin quantification in 18F-FDG by the kinetic chromogenic method. Indian J Nucl Med. 2010; 25:87.
[23]. ChEBI http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:3517
[24]. NCIthttps://ncithesaurus.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=ncit&code=C47439
[25]. ChEMBL https://www.ebi.ac.uk/chembl/compound_report_card/CHEMBL2146124/
[26]. ChemIDplus https://www.dgidb.org/drugs/CEFUROXIME%20SODIUM
[27]. European Chemicals Agency (ECHA)
[28]. https://echa.europa.eu/substance-information//substanceinfo/100.054.594
[29]. FDA Global Substance Registration System (GSRS)
[30]. https://gsrs.ncats.nih.gov/ginas/app/beta/substances/R8A7M9MY61
[31]. Dailymed https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=CEFUROXIME+SODIUM
[32]. FDA Orange Book https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
[33]. National Drug Code (NDC) directory https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory
[34]. PubChem https://pubchem.ncbi.nlm.nih.gov/
[35]. NLM RxNorm Terminilogy https://rxnav.nlm.nih.gov/id/rxnorm/204144
[36]. Spectrabase https://spectrabase.com/spectrum/DKixF5rZjEM