# Manufacturing of dry powder injection of Ceftriaxone 1000 mg USP

A Internship Report submitted

for the partial fulfilment of the Degree of Master of Science

By

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**2022-23**

# ***CERTIFICATE***

This is to certify that this training report entitled **"Manufacturing of dry powder injection of Ceftriaxone 1000 mg USP''** was successfully carried out by **Miss. Nirali Hitenbhai Raja** towards the partial fulfilment of requirements for the degree of Master of Science in Biotechnology of Atmiya University, Rajkot. It is an authentic record of his/her own work, carried out by him/her under the guidance of **Mr. Sukrut Patel** for a period of 3 months during the academic year of 2022-23.The content of this report, in full or in parts, has not been submitted for the award of any other degree or certificate in this or any other University.

| | |
|---|---|
| Signature | Signature |
| **Dr. Nutan Parakash Vishwakarma** | **Mr. Sukrut Patel** |
| (Name of the Head of the Department) | (Name of the Supervisor) |

## ***D E C L A R A T I O N***

I hereby declare that the work incorporated in the present dissertation report entitled "**Manufacturing of dry powder injection of Ceftriaxone 1000 mg USP"** is my own work and is original. This work (in part or in full) has not been submitted to any University for the award of any Degree or a Diploma.

05/04/2023 Nirali Hitenbhai Raja

Date (Name and signature of Student)

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# ABSTRACT

Pharmaceutical means which connected with the industrial production of medicines. There are different forms of medicines like oral or external, Intramuscular or Intravascular.Sanolet Lifecare Private Limited is a private company. It have parental manufacturing drugs which given direct in IM or IV. This company have manufacturing plant for beta-lactum dry powder injections. This company include different departments like production department, QC department, QA department, engineering department & packaging & storage department. As I had worked on the product named Ceftriaxone for injection USP-1000 mg. Ceftriaxone belongs to the class of medicines known as cephalosporin antibiotic under the third generation. Ceftriaxone is given as an injection, either intramuscularly or intravenously. It is used for the treatment of bacterial infections in various locations, such as in the respiratory tract, skin, soft tissue, and urinary tract. Different tests that we observed and performed like Sterility test, BET test (LAL test), environmental analysis Sterility test are done to check the quality of the product. The study of this concept is necessary for getting real time practical experience before completing the studies. In this report I had given a introduction about my internship field along with the activities which I had performed during my internship period. I also learn practical with the theoretical concepts that observed during my internship.

## ABBREVIATIONS

- Annual General Meeting (AGM)
- Ministry of Corporate Affairs (MCA)
- No(Number)
- United State Pharmacopeia(USP)
- Manufacturing(Mfg.)
- Master Formula Record(MFR)
- Batch Manufacturing Record(BMR)
- Batch Packaging Record(BPR)
- Not Applicable(NA)
- Quality Assurance(QA)
- Quality Control(QC)
- Expiry(Exp.)
- Raw Material(RM)
- Packaging Material(PM)
- In Process Quality Assurance(IPQA)
- Bacterial Endotoxin Test(BET)
- Regulatory Affairs(RA)
- Standard Operating Procedure(SOP)
- Soyabean Casein Digest Medium(SCDM)
- Fluid Thioglycollate Medium(FTM)

## COMPANY INFORMATION

- Sanolet Life care Private Limited is a Private incorporated on 21 September 2020. It is classified as a private limited company and is located in Ahmedabad, Gujarat. Its authorized share capital is Rs. 11,000,000 and its paid up capital is Rs. 10,100,000.
- Sanolet Life care Private Limited's Annual General Meeting (AGM) was last held on 30 November 2021 and as per records from Ministry of Corporate Affairs (MCA), its balance sheet was last filed on 31 March 2021.
- Directors of Sanolet Life care Private Limited are Kiranbhai Kanubhai Bunde, Tejaskumar Maganlal Padodara, Hiren Vasantlal Shah and Sachin Ishvarbhai Sardava.
- Location : Plot No - 10 , survey No-151, Inside Varmora Plastech, P.O. Vasna Chancharwadi, Bavla-changodar Highway , Ahmedabad , Gujarat 382213,
- Website : **www.sanolet.co.in**


Figure 1 – Flow of Production

**DEPARTMENTS OF COPMANY:**

- Production Department
- QA Department
- QC Department
- Engineering Department

# PRODUCT INFORMATION

- Ceftriaxone is a broad-spectrum cephalosporin antibiotic used for the treatment of bacterial infections in various locations, such as in the respiratory tract, skin, soft tissue, and urinary tract.
- **Chemical Formula :** $C_{18}H_{18}N_8O_7S_3$
- **Properties :**

  1. Solid in nature
  2. Melting Point - >155 °C
  3. CaCo2 Permeability - (-6.88)
  4. Molecular Weight -544.6

- **Medical uses include :**
  - Lower respiratory tract infections , skin and skin structure infections, urinary tract infections , pelvic inflammatory disease, bacterial sepsis , intra-abdominal infections.

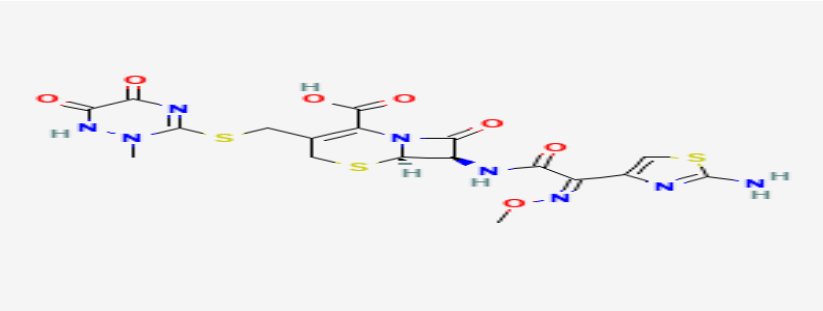

Figure 2 – Chemical Structure Of Ceftriaxone

https://pubchem.ncbi.nlm.nih.gov/compound/Ceftriaxone

- **Pharmacodynamic**s:
  - Ceftriaxone is a cephalosporin/cephamycin Beta-Lactam antibiotic used in the treatment of bacterial infections caused by usually gram-positive, organisms.
  - It has in vitro activity against gram-positive aerobic, gram-negative aerobic, and anaerobic bacteria.
  - The bactericidal activity is mediated through ceftriaxone binding to penicillin-binding proteins (PBPs).
- **Mechanism of action :**
  - Ceftriaxone mechanism is similar to that of other beta-lactam antibiotics. It inhibits the peptidoglycan layer of the bacterial cell wall catalyzed by transpeptidases. D-alanyl-D-alanine is structurally similar to ceftriaxone; however, transpeptidases irreversibly bind to ceftriaxone. Therefore, the final cross-linking of peptidoglycan is blocked, which collapses the bacterial cell wall leading to eventual bacterial cell lysis.

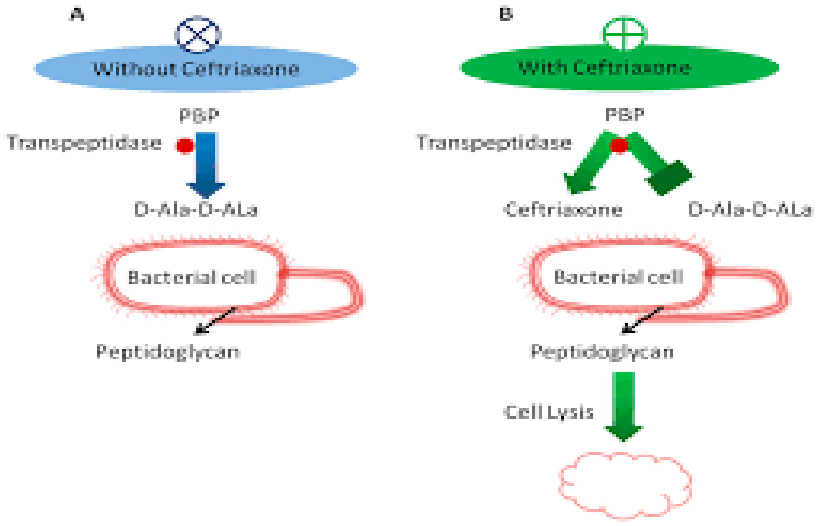


Figure 3 – Mechanism of Ceftriaxone on bacteria

tandfonline.com/doi/pdf/10.1080/21553769.2018.1491427

# PRODUCTION DEPARTMENT

- A production department is a group of functions within a business that is responsible for the manufacture of goods**.**
- Production department includes documents like Batch Manufacturing Record (BMR) & Batch Packaging Record (BPR)**.**

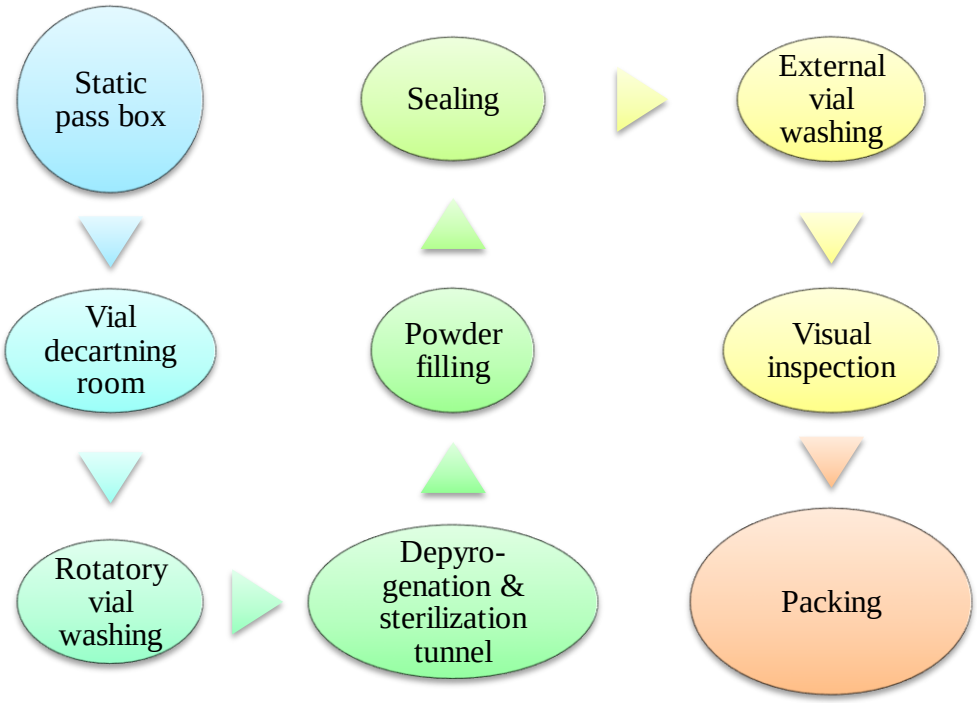


Figure 4 - Production line flowchart

# BATCH MANUFACTURING RECORD (BMR)

**BMR NO:** BMR/SC0018/00

**Product Name:** Ceftriaxone for injection USP-1000 mg

**Generic Name:** Ceftriaxone for injection USP-1000 mg

**Product Code:** SC0018

**Batch NO:** 22EC035

**Effective Date:** 20/05/2022

**Composition:** Each pack contain – one vial of Ceftriaxone for injection USP

**Product Description:** 10 ml clear glass vial USP II IHS, 20mm grey butyl rubber stopper with 20 mm CL blue flip off seal IHS containing a white coloured powder.

**Storage condition**: Store below 30°C, protect from light and moisture.

**Effective date:** 20/05/2022

**Effective Batch NO:** NA

**Product Specification:** USP

**Shelf Life:** 36 months.

**Standard Batch size**: 10000 vials

**Superseded version NO:** NA

**Reason for change:** New product

**MFR NO:** MFR/ SC0018/00

**Actual Batch size:** 12000 vial

**Mfg Date:** 01/2023

**Exp. Date:** 12/2025

**Fill weight:** As per calculation +_2%-

**BMR Issued by (QA):** done

**BMR Received by (Production):** done

**Batch Start Date:**

**Batch Completion date: -**

# Table of Content


1. List of abbreviations
2. Signature log sheet
3. Bill of raw material
    i. Before start the process line clearance shall be taken as per SOP No.
    ii. Name of area: RM store, previous product name, previous product batch number.
    iii. Line clearance
    iv. Raw material requirement, standard fill weight.
    v. Required quantity of RM
4. Bill of primary packing material
    i. Clearance of dispension
    ii. Number of area
    iii. Packaging material details
5. General instruction
6. Equipment & machine cleaning record\
    - Name of equipments :
        i. Rotary vial washing machine
        ii. Sterilization and depyrogenation tunnel
        iii. Vial filling and rubber stopping machine
        iv. Cap sealing machine
        v. External vial washing machine
        vi. Visual inspection booth
        vii. Weighing balance and Analytical balance
        viii. Dynamic pass box
7. Glass vial washing


i. Line clearance for decartoning of vials
ii. Decartoning of vials
iii. Washing of vials and verification
iv. Clarity check (Minimum 8 vials to be checked at interval of 1hr)
v. No. of vials rejected during decartoning & washing
vi. No. of washed vials sent for Depyrogenation
vii. Check the parameters before starting the depyrogenation & sterilization

**8.** Depyrogenation & sterilization of washed vials
i. Line clearance for vial washing & depyrogenation of tunnel
ii. No. of vials rejected during depyrogenation
iii. No. of vials sent for filling

**9.** Flip Off seal sanitization record

**10.** Washing & sterilization of rubber stopper , blander & machine parts

**11.** Environmental control of sterile area
i. Fogging status
ii. Cleaning before start of filling
iii. Control checks
a. Working of AHU system and dehumidifier
b. Fogging with disinfectant solution containing 11% $H_2SO_4$ & 0.01%$AgNO_3$

**12.** Equipments stability record

**13.** Weighing & Bulk mixing record

**14.** Filling & sealing record

**15.** Visual Inspection & Rejection record

**16.** Batch Reconciliation

**17.** Batch yields details

**18.** Batch summary report

**19.** BMR review history

# BATCH PACKAGING RECORD

**Product Name:** Ceftriaxone & Sulbactam 1.5gm

**Generic Name:** Ceftriaxone 1000MG & Sulbactam 500MG for injection

**BPR NO:** BPR/SC0015/00

**Batch NO:** 22DC118

**Effective Date:** 20/05/2022

**Composition:** Each vial contains: Sterile ceftriaxone & Sulbactam IP Eq. to Ceftriaxone& Sulbactam anhydrous 1.5gm

**Storage condition**: Store below 25°C do not freeze, protect from light and moisture.

**Effective date:** 29/05/2022

**Effective Batch NO:** NA

**Product Specification:** IP

**Shelf Life:** 24 months.

**Standard Batch size**: 5000 vials

**Mfg License No:** G/28/1843

**Actual Batch size:** 5000 vial

**Mfg Date:** 01/2023

**Exp. Date:** 12/2024

**Fill weight:** As per calculation +_2%-

**BMR Issued by (QA)**

**BMR Received by (Production):**

**Batch Start Date** & **Batch Completion date:**

## Bowie-Dick Test

- A Bowie-Dick test is used in prevacuum type steam sterilizers (also called dynamic-air-removal sterilizers).
- The purpose of this test is to ensure all air is removed from the sterilizer and that there are no air leaks in the system.

**How to run Bowie-Dick Test?**

- Running a Bowie-Dick Test requires placing a small, disposable test pack into the autoclave and running a four-minute sterilization cycle, typically a Bowie-Dick Cycle. The test pack is placed in an empty chamber on the lowest shelf above the drain and the Bowie-Dick Cycle is initiated. The sterilization cycle typically consists of three to four prevacuum pulses, each of which involve injecting steam into the autoclave and then pulling out the air and steam through a vacuum, before reaching the set point of 270°F (or 132°C).

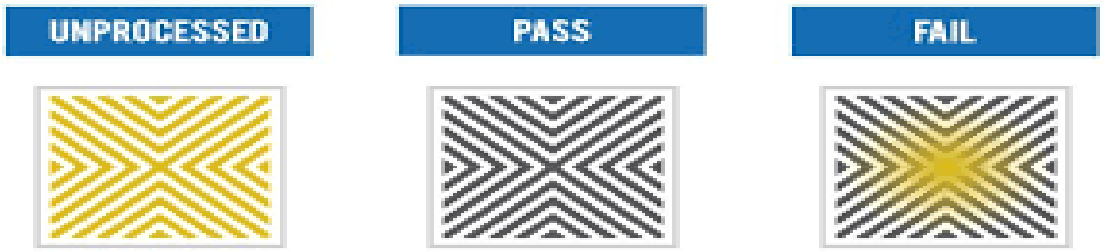


Figure - 5 Bowie-Dick Test Observation

https://consteril.com/bowie-dick-test/

**Interpretation:**

- A uniform color change to dark brown/black is a PASS.
- A non-uniform color change showing a lighter colored area in the center of the test sheet is a FAIL.

**Common Causes of Bowie-Dick Test Failures Include:**

- Inadequate vacuum
- Clogged drain line, vent lines or water supply strainer.
- Leak caused by a faulty door gasket or other defect.
- Low steam pressure or water pressure.
- Water temperature too high.
- Poor steam quality (i.e., non-condensable gases or superheating).

# QUALITY CONTROL DEPARTMEMNT

- The aim of QC in the pharmaceutical industry is to verify and test the medicines at various stages of production to ensure every product is of the good quality.
- Quality control also involves identifying any defects in products and fixing these problems with corrective techniques and measures.

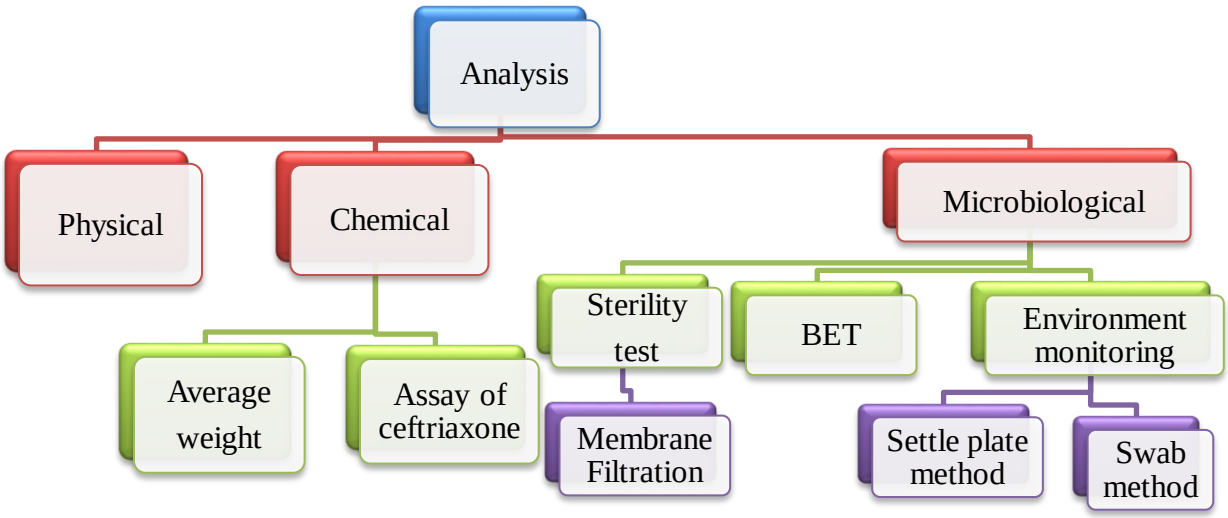


Figure 6 – Classification of test

## PHYSICAL ANALYSIS

- Physical testing examine physical attributes of the drug form , such as colour , particle size, dissolution, disintegration. Physical testing is performed on raw materials, intermediates and final product.

## CHEMICAL ANALYSIS

1. **Average weight:** Cefoperazone & Sulbactam

**Materials:**

- Sample
- Ethanol
- Hot air oven

**Procedure:**

i. Remove seal and weigh powder present in vial (pre-weight).
ii. Wash the vial with ethanol
iii. Dry the vial
iv. Weigh it again (post-weight).

**Result:**

- Pre-weight - Post-weight (29111.53 mg – 27526.47mg )
- Average weight -1591.06 mg

2. **Assay of ceftriaxone & sulbactam:**

- The assay is based on the inhibitory effect of ceftriaxone on the strain of *Bacillus subtilis* is used as test organism.
- Assay of sulbactam a beta lactamase inhibitor, in serum in the presence of ampicillin were compared.
- Method –Agar Diffusion Bioassay

## MICROBIOLOGICAL ANALYSIS

1. **Sterility Test:**

- Sterility testing is required to ensure viable contaminating microorganisms are not evident in a product.
- This testing is conducted by direct inoculation or membrane filtration methods and can be performed in an isolator or clean room environment.

**What is a membrane filtration method?**

- Sterile, enclosed units allow for the filtration of equal volumes of test samples through two membrane filters. Samples are incubated, for the detection of both aerobic and anaerobic microorganisms.

**Requirements:**

- Sample
- Peptone water
- Filtration assembly
- SCDM media & FTM media

**Procedure:**

1. Take product vial and spray it with Isopropyl Alcohol
2. Mix sample with peptone water.
3. Pour through membrane filtration assembly.
4. Connect with vacuum pump.
5. Remove the filter membrane and cut it.
6. Put one part into in SCDM and other in FTM media.
7. Incubate it for 7-10 days.

**2. Bacterial Endotoxin Test (BET):**

**Principle:**

- LAL (Limulus Amybiocyte Lysate) + Endotoxin = Clotting

- Endotoxin testing (LAL test) ensures that sterile pharmaceutical products are safe for human use. Endotoxins are bacterial structural components. These components are toxic if administered to humans and/or animals (rise in body temperature).

**Requirements:**

- CSE (Controlled Standard Endotoxin)

- LAL (Limulus Amybiocyte Lysate)

- LRW (LAL Reagent Water)

- Test sample

- Standard endotoxin

- Heating block

**Procedure:**

1. Take 2 test tubes.

2. Add 100µL of sample to the tubes.

3. Now add 100µL of LAL reagent in assay tubes and incubate tubes for 60 minutes.

4. Now invert the tubes and observe the result.

5 .If solid medium remain intact the product is considered to contain endotoxin.

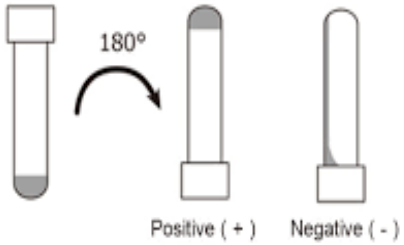


Figure 7 – Observation

https://labchem-wako.fujifilm.com/europe/category/general/pyrogen_detection/lysate_reagents/index.html

## Result:

Figure 8 - Sample (negative).

Figure 9 - Standard (positive).

### 3. Environment monitoring:

- It provides information of presence or absence of contaminants in the environment.
    - Settle plate method
    - Swab method

# QUALITY ASSURANCE DEPARTMENT (QA)

- Assuring the quality of raw materials.
- Assuring the quality of finished product.
- Quality improvement plan.
- Parental manufacturing - The compound of the drug substance, sterile filtration, and filling of drug solution into containers such as vials or syringes.

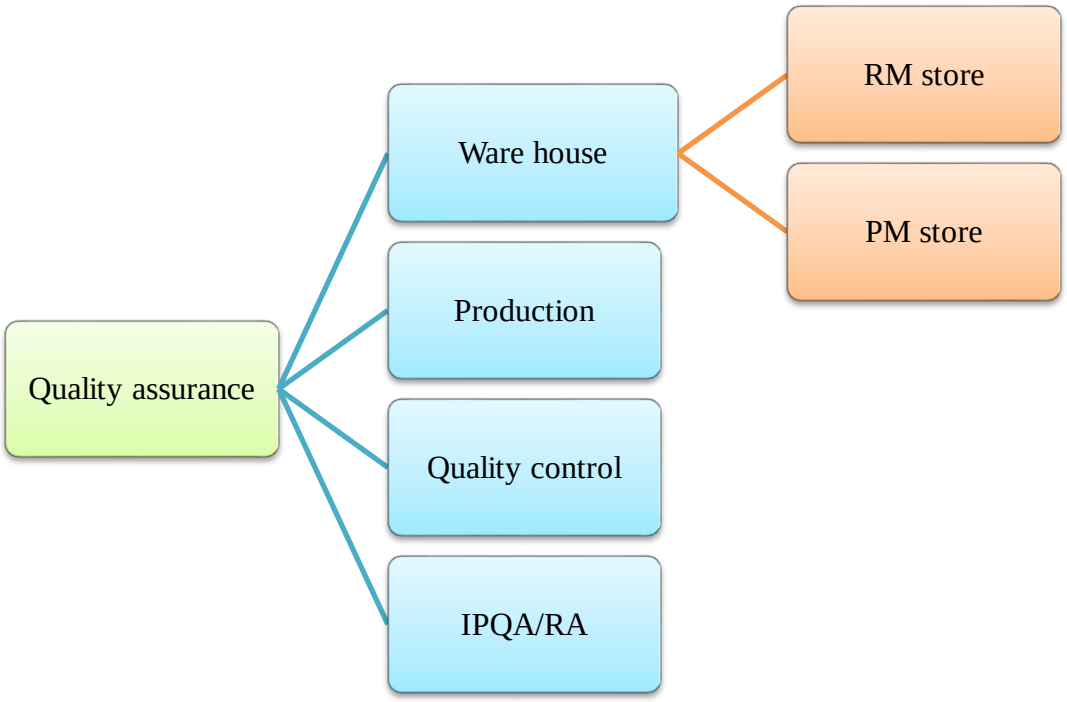


Figure 10 – Area under QA

- **Ware house**: RM (raw material)store and PM(packaging material)store.
- **Production department**: The process of Drug Manufacturing performed in Production Department in Pharmaceutical Unit into a series of unit operations, such as dispensing,, blistering, mixing, filling, and others.
- **Quality control**: It is a process by which the quality of all factors involved in production is tested.
- **IPQA**: In Process Quality Assurance plays a very important role in the quality of drugs or products during manufacturing.
- **RA**: The regulatory affairs (RA) department is responsible for obtaining approval for new pharmaceutical products and ensuring that approval is maintained for as long.

# ENGINEERING DEPARTMENT

- Pharmaceutical engineering focuses on designing, building, and improving
- Water system
- Air system

- **Air Handling Unit:**

- No cross contamination through air in product manufacture area.
- Air lock (cascade, bubble)
- Filters (HEPA,fine-filter,pre-filter)
- Validation (integrity-to know leakage)
- Particle count (0.5 to 5 micron)
- Recovery:

  Time – 10 min

  Instrument – Air borne particle counter

  Print out of result – Cycle per min (Viable/non-viable particle count)

## Water Hardness

### Principle

- Hardness of water is due to the presence of dissolved salts of calcium, magnesium and other metal ions.
- The determination of hardness is a useful analytical process for measuring the quality of water for household and industrial uses.

### Range

- 76 to 150 mg/L -moderately hard
- 151 to 300 mg/L-hard
- more than 300 mg/ - very hard
- Below 75 mg/L-soft

### Result

- Wine red to blue colour


Figure 11 – Kit For Test

https://thechemicalcenter.com/water-testing-kit-hardness-with-titrants-d-5-25

# PACKAGING & STORAGE DEPARTMENT

- **Primary packaging** :

- It is the material that first envelopes the product and holds it.
- Vials
- Seal rubber
- Stopper

- **Secondary packaging:**

- It is outside the primary packaging used to group primary package together.
- Label
- Carton

- **Tertiary packaging:**

- It is done for bulk handling and shipping.
- Raw material and Packing materials stored at required storage condition
- Shipper box
- Plastic shrink

## References


1. Ayman Ahmad Al kraiem, Guang Yang, Fahd Al kraiem & Tie Chen (2018) Challenges associated with ceftriaxone resistance in Salmonella, Frontiers in Life Science, 11:1, 26-34, DOI: 10.1080/21553769.2018.1491427 To link to this article: https://doi.org/10.1080/21553769.2018.1491427
2. Aléssio PV, Salgado HR. Development and validation of a successful microbiological agar assay for determination of ceftriaxone sodium in powder for injectable solution. Pharmaceutics. 2012 Jun 29;4(3):334-42. doi: 10.3390/pharmaceutics4030334. PMID: 24300294; PMCID: PMC3834915.
3. https://go.drugbank.com/
4. https://multimedia.3m.com/mws/media/660881O/comply-bowie-dick-interpretation-chart.pdf
5. https://consteril.com/bowie-dick-test/
6. http://pharmaceuticalmicrobiologi.blogspot.com/2017/10/gel-clot-test.html
7. https://thechemicalcenter.com/water-testing-kit-hardness-with-titrants-d-5-25
8. https://www.pharmaguideline.com/2007/02/principle-construction-working-uses-merits-demerits-membrane-filters.html
9. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 5479530, Ceftriaxone; [cited 2023 Apr. 11]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Ceftriaxone


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