MANUFACTURING OF DRY POWDER INJECTION OF CEFOPERAZONE + SULBACTAM 1.5gm IP

An internship report submitted for the

partial fulfilment of the degree of Master of science

By

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[M.Sc. Biotechnology]

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Under the supervision of

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DEPARTMENT OF BIOTECHNOLOGY

ATMIYA UNIVERSITY

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ATMIYA UNIVERSITY

(Established under the Gujarat Private University Act 11, 2018)

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C E R T I F I C A T E

This is to certify that this training report entitled "**Manufacturing of dry powder injection of Cefoperazone + Sulbactam 1.5gm IP**" was successfully carried out by **Miss. Mansi Amipara** 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 her own work, carried out by her under the guidance of Mr. Sukrut Patel for a period of three months from 05th Jan 2023 to 05th April 2023 during the academic year 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.

Sukrut Patel

Dr. Nutan Prakash Vishwakarma
(Head of the Department)

Mr. Sukrut Patel
(Supervisor)

Sanolet Lifecare Private Limited
CIN - U24304GJ2020PTC116691

DATE: 05th April 2023

CERTIFICATE

This is to certify that this training report entitled "**Manufacturing of dry powder injection of Cefoperazone + Sulbactam 1.5gm IP**" was successfully carried out by **Miss. Mansi Amipara** 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 her own work, carried out by her under the guidance of **Mr. Sukrut Patel** for a period of 3 months from 05th Jan 2023 to 05th April 2023 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.

We wish best of luck for her bright future.

Sanolet Lifecare Pvt. Ltd.

Authorized Signatory

SANOLET LIFECARE PRIVATE LIMITED • AHMEDABAD •

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D E C L A R A T I O N

I hereby declare that the work incorporated in the present Internship report entitled "MANUFACTURING OF DRY POWDER INJECTION OF CEFOPERAZONE + SULBACTAM 1.5gm IP" is my own work and is original. This work has not been submitted to any University for the award of any Degree or a Diploma.

05 April 2023 Mansi Amipara

Date

ACKNOWLEDGEMENT

The internship opportunity I had with Sanolet Life Care Private limited was a great chance for learning and development therefore I consider myself is a very lucky individuals as I was providing with opportunity to be a part of it, I am also great full for having a chance to meet so many wonderful people and professionals who lead me through the internship period.

Bearing in mind previous I am using the opportunity to express my deepest great attitude and special thanks to my guide Mr. Sukrut Patel, assistant production manager, who in spite of being extraordinarily busy with his duties, took time out to hear, guide and keep me on the correct path and allowing me to carry out my report it their organisation and extending during the internship.

Finally, I want to thanks to all staff members for give me some extra ordinary knowledge about pharmaceutical company and they all are very cooperative with me, so I have to thanks again.

I choose this moment to acknowledge is contribution gratefully.

MANSI AMIPARA

M.Sc. BIOTECHNOLOGY

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ABSTRACT

I pursued my training at sanolet lifecare private limited.

Pharmaceutical means which connected with the industrial production of medicines. There are different forms of medicines like oral or external, Intramuscular or Intravascular. Sanolet Life Care 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-lactam 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 Cefaperazone + Sulbactam 1.5gm IP for injection. 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 an 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.

COMPANY PROFILE

Sanolet Life care Private Limited is a Private incorporated on 21 September 2020. It is classified as Non-govt. Company and is registered at Registrar of Companies, Ahmedabad. Its authorized share capital is Rs. 11,000,000 and its paid-up capital is Rs. 10,100,000.

Directors of Sanolet Life care Private Limited are Kiran Bhai Kanu Bhai Bunde, Tejaskumar Maganlal Padodara, Hiren Vasantlal Shah and Sachin Ishvarbhai Sardava.

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.

LITERATURE REVIEW

Cefoperazone is used to treat bacterial infection in the different parts of the body. It works by killing bacteria or preventing their growth.

Sulbactam is a Beta-lactamase inhibitor antibiotic combined with other antibiotics to treat a variety of susceptible bacterial infection. Beta- lactamase, an enzyme produced by bacteria that destroys antibiotic activity.

Cefoperazone has bactericidal effects, and as a β-lactam antibiotic, it needs to be used together with a β-lactamase inhibitor such as sulbactam sodium. This can make the inactivation process of most β-lactamases produced by multi-drug resistant bacteria irreversible, thus enhancing the activity of cefoperazone.

Cefoperazone exerts its bactericidal effect by inhibiting the bacterial cell wall synthesis, and Sulbactam acts as a beta-lactamase inhibitor, to increase the antibacterial activity of cefoperazone against beta-lactamase-producing organisms.

LIST OF ABBREVATION

BMR – Batch Manufacturing Record

BPR – Batch Packaging Record

No – Number

Exp. – Expiry

A. R. No – Analytical Reference Number

PM – Packaging Material

MFR – Master Formula Record

IPQA – In Process Quality Assurance

CAPA – corrective action and preventive action

RLAF – Reverse laminar air Flow

IPA – isopropyl alcohol

RH – Relative humidity

NLT – Not less than

WFI – water for injection

PPM – primary packaging material

UV – Ultra violet

BOPP – Biaxially oriented polypropylene

MRP – Maximum Retail Price

LIC – licence

IP – Indian Pharmacopoeia

DEPARTMENTS IN COMPANY

1) Store

2) Production

3) Quality control

4) Quality assurance

5) Engineering

Store:

In store including Raw material, Primary packaging material (PPM), Secondary packaging material (SPM), Tertiary packaging material (TPM).

1) Primary packaging material: In primary packaging includes vials, seal, and rubber stoppers.

2) Secondary packaging material: In secondary packaging includes label for vials, Carton, insert leaflet.

3) Tertiary packaging Material: In tertiary packaging includes box for package, plastic Shrink.

1. PRODUCTION

Providing information regarding the procedure currently adopted for manufacturing, operating equipment (sop's) and any modification if required in the current procedure adopted for manufacturing operating equipment with justification.

Production Protocol:

1. Receiving Cefoperazone 1000 mg & Sulbactam 500 mg order for 10000 vials.
2. RMS department where all Raw materials transport from warehouse now this material keeps in quarantine section.
3. The entry of received material in register. And check the A.R No., Batch No., MFG and Exp. Date.
4. QC department take material for sampling to check and the received material and label the containers or tanks as UNDER TEST.
5. After test if material is ok then they labelled it is APPROVED. And if not labelled as REJECT.
6. Approved material can transfer to Production department as per order received 10000 vials.
7. All required materials (RM, PPM, SPM, and TPM) in production pass through static pass box.
8. Vial decanting Room: In vial decanting room defective vials are removed and push forward and move into washing (Effect on vials: white particles, black particles, mould effective, crack vial).
9. Rotatory vial washing machine: washing with 3 waters (purified water, WFI water, recycle Water).
10. Depyrogenation & sterilization tunnel: 4 zone (Dry zone, Hot zone, cool zone, Stabilize zone)
11. Powder filling and stoppering
12. Sealing machine
13. External vial cleaning machine
14. Visual inspection (High fill or low fill and sealing rejection)
15. Vial labelling (Batch No., Mfg. Date, exp. Date, MRP)
16. Packaging the vials

1.1 In process check parameters:

1.1.1 Cleanliness of the area and line clearance:

Visually check area and equipment are cleaned and all cleaning records are filled.

Ensure that temperature 24.0°c (23±5°c), RH 53% (50±5%) of the area is within the limit.

Ensure that differential pressure of the room is within the limit NLT 10 Pascal.

Ensure area is free from previous product.

1.1.2 Vial washing machine check point:

Vial washing with three types of water: i) Recycle water

ii) Purified water

ii) WFI water

Compressed air pressure: NLT 1.0 kg/cm²

Recycled water pressure: NLT 1.0 kg/cm²

Purified water pressure: NLT 1.0 kg/cm²

WFI pressure: NLT 1.0 kg/cm²

1.1.3 in process weight check:

Stranded weight to fill vial: 1.058 g

Minimum weight to fill vial (-2%): 1.477g

Maximum weight to fill vial (+2%): 1.538 g

1. Leakage Test:

It is desirable that all the parental preparation which are filled in vial must be hermetically sealed.

The vial is immersed in 1% methylene blue solution in a vacuum chamber under negative pressure. When the vacuum is released, the coloured solution will enter those vials having defective sealing. The presence of dye in the vial confirms the leakage and hence rejected.

2. Clarity check:

Minimum 8 vials to be checked for clarity at interval 1hour.

Particulate matter is defined as unwanted insoluble matter other than gas bubbles present in the product. The presence of foreign matter in parenteral preparation is very dangerous especially when its particle size is larger than the RBC size. It can block the blood vessel.

Particulate Matter: (A): ≥ 10 µm: ≤ 300 Pc/g

(B): ≥ 25 µm: ≤ 300 Pc/g

Figure No.-1 clarity check

3. Bowie Dick Test:

Done to check autoclave is working properly or not. The purpose of pressure and vacuum pulse is to effectively remove air from the chamber because air is a bad conductor of heat Colour changes of indicators sheet is from red to black. If there is any problem in the autoclave colour will not change.

Figure No.: 2 Bowie Dick test

1.2 Environmental monitoring:

Environmental monitoring is the system allows pharmaceutical manufacturers to monitor and control the viable environmental contamination in their clean rooms.

Settle plates typically consists of petri dishes filled with a culture media are opened and exposed to the air in different production area for specified period of time to determine what microbiological particle may be present in the environment, as they may settle out of the ambient air, and onto the media surface of the petri dish.

These plates are then incubated and analysed.

2. QUALITY CONTROL

Providing information regarding the test procedure and equipment to be adopted to be used or to be developed for the testing of samples.

Sampling of RM & Packing materials, analysing and result declaration all samples.

To carry out environmental monitoring.

Review and evaluation of batch analysis as well as preparation and approval of certificate analysis.

Microbiology & Stability testing.

Quality control Analysis: A. Chemical

B. Microbiological

2.1 Instrument used in quality control:

1. pH meter

A pH meter is a scientific instrument in pharmaceutical industry that measures the hydrogen – ion activity in a solution, indicating the acidity or alkalinity and expressed as pH.

Take to 25 gm substance of Cefoperazone & sulbactam sodium in 100 ml volume flask and final make up with water and check the pH (limit – 4.5 to 6.5).

2. Polarimetry:

Polarimetry can be used to determine product purity by measuring specific rotation and optical rotation of compounds.

Instrument which measures the angle of rotation by passing polarized light through an optically active substance.

3. Bursting Strength Tester:

It measures the bursting strength by applying hydraulic pressure, use to measure the resistance to rupture or burst material like paper, corrugated boxes, and these tests helpful to prove quality, performance and strength of the material to assure the toughness of material.

It is used to measure the force needed to burst the board. It ranges from 0 to 40 kg/cm²

Figure No. 3: Bursting Strength Tester

4. Hot Air Oven:

Dry the glass vials

Hot Air Oven is a dry heat sterilization Oven. Uses high temperature 150°c, 200°c. They are also called forced air circulating Oven and widely used to dry glassware.

5. Melting point apparatus:

Melting point apparatus is designed to determine the melting points with high accuracy, and is supplied with a silicon oil bath with heater for heating the bath.

As heat is applied to a solid, its temperature will increase until the melting point is reached.

6. Vacuum Oven:

A vacuum Oven is most often used for delicate drying processes, such a drying tiny part or removing flammable solvents. A standard vacuum Oven can operate at temperatures as high as 200°c to 250°c.

The vacuum Oven method requires a temperature of 100°c to a point of constant weight at 25 mm of Hg. When compared with the same samples dried to constant weight in an atmospheric oven at 100°c the vacuum dried product will show a 10 to 50 % greater loss of weight depending on carbohydrate content.

7. Muffle Furnace:

Used to heat material to extremely high temperature and the determine the percent of ash content in those material. And determine how much non – combustible and non – volatile content is present in a sample.

Figure No.4: Muffle Furnace

8. Tap Density Tester:

The tapped density is a very popular measure for powder characterization because of the both simplicity and rapidity of the measurement. The ability of a powder sample to pack under taps gives a measure of powder cohesiveness which can be linked to its flowability.

9. Centrifuge:

Separate insoluble particle

10. Karl Fischer Titrator:

KF Titrator used to determine the amount of water in sample. The principal of Karl Fischer titration is based on the oxidation reactions between iodine and sulphur dioxide. Water reacts with iodine and sulphur dioxide to form sulphur trioxide and hydrogen iodide. An endpoint is reached when all the water is consumed. Karl Fischer reagents consists of iodine, sulphur dioxide, a base solvent

such as alcohol. The original Karl Fischer method used pyridine as organic base because pyridine is basic nature while Hydrogen iodide is acidic in nature so Pyridine neutralize the Hydrogen iodide and reaction is not reversible. Methanol used as alcohol because methanol forms stable complex Pyridine and Sulphur Trioxide.

This titrimetric method commonly used in a pharmaceutical industry for the determination of water content in different substance.

Figure No. 5: KF Titrator

11. UV spectrometer:

UV visible spectrometer measure the intensity of light passes through the sample and amount of UV or visible light absorbed by the compound. The analysis of Cefoperazone sodium was between 220 nm and range of calibration is 10 – 35 mg/L.

12. Laminar Air Flow:

Laminar Air Flow system equipped with HEPA (High Efficiency Particulate Air) filters removes 99.97% of particulate > 0.3 µm.

Laminar air flow unit works by the use of inflow laminar Air Flow drawn through one or more HEPA filters, designed to create a particle free working environment and provide product protection.

13. Incubator:

Used to grow and maintain microbiological culture.

14. Autoclave:

The autoclave is used remove microorganisms using high pressure and high temperature steam sterilization.

In the production department Autoclave used to sterilization of rubber stopper, machine part assembly (piston, Hopper, star wheel).

2.2 Microbiological test in QC:

2.2.1 Limulus Amoebocyte Lysate (LAL) test:

The LAL test is also known as Bacterial Endotoxin Test or BET test. It is in vitro assay used to detect the presence of bacterial Endotoxin in aqueous parenteral preparation.

The reagent used in this test is Amoebocyte Lysate from RBC extract of horseshoe crab, *Limulus polyphemus.*

The gel-clot technique is used for detecting Endotoxin based on clotting of the Lysate reagent in test tube in presence of Endotoxin.

If Endotoxin are present, it can lead to a pyrogenic response (Fever) or symptoms of septic shock.

Endotoxin range: 0.25 EU/ml

Methods of Gel – clot technique:

1) Prepare test tubes of 4 sample dilution.
2) Then LAL reagents are added to the equal volume of test tubes.
3) Incubate for 1hour at 37°c.
4) After incubation the tubes are inverted.
5) If the clot remains intact the product is considered to contain Endotoxin.

2.2.2 Sterility test:

Sterility testing is defined as testing which confirms that products are free from the presence of viable microorganism. The test sterility is based upon the principle that if microorganism is placed in a medium which provides nutritive materials and water and keep at a favourable temperature,

the microorganism will grow and their presence can be indicated by turbidity in the originally clear medium.

Culture media:

1. Fluid thioglycolate medium (FTM) – For anaerobic bacteria
2. Soya bean casein digest medium (SCDM) – Suitable for the culturing of both Fungi and anaerobic bacteria

Sterility test by Membrane Filtration method:

1) Filter the dissolve product and 3 times rinse with peptone water (100 ml).
2) Remove the Filter Membrane and membrane cut the help with sterile forceps and into half.
3) Incubate 1 half in SCDM and other half in FTM broth.
4) Incubate SCDM tube (20 – 25 °C) for 14 days.
5) Incubate FTM tube (30 – 35 °C) for 14 days.
6) Observed the tubes for turbidity every day till 14 days.

2.2.3 Turbidity check:

Turbidity is a measure of how cloudy water is.

Procedure:

1. SCDM & FTM 2 media present, 2 plate.
2. Sample streak in plate 7 days incubation.
3. Check turbidity of plate anaerobic bacteria present water is not pure.

2.2.4 Microbial Limit Test:

This test is performed for the estimation of the number of viable microorganisms present in sample.

TOTAL BACTERIAL COUNT:

10 gm of substance is added to 90 ml of buffered sodium chloride Peptone solution (sample preparation) With the help of sterile pipette, 1.0 ml of sample is aseptically transfer to petri dish. Now add 15- 20 ml Soyabean Casein Digest agar. Now the plate is allowed to solidify. Incubate the plate at 35 – 37 °c for 5 days.

TOTAL FUNGAL COUNT:

1. With the help of sterile pipette, 1.0 ml of sample is aseptically transfer to Petri dish.
2. Instead of SA and SD medium is used and plates incubated at 20 – 25 °c for 3 days.
3. After the compilation period colonies are counted and multiply by dilution factor to get count per gm.

2.2.5 Test for *Escherichia coli:*

These include identification of *Escherichia coli* bacteria pathogenic to human body and cause infection of stomach.

Procedure:

1. Take 10 ml of sample of product and inoculate in to 90 ml Soyabean Casein Digest Medium.
2. Incubate at 30 – 35 °c for 18 – 24 hours.
3. Observe the above SCDM tube for growth. If the growth is present. After incubation shake the broth and transfer 1 ml of Soyabean Casein Digest Medium to 100 ml of MacConkey broth and incubate at 42 – 44 °c for 24 – 48 hours.
4. Subculture on a plate of MacConkey agar and incubate the plates at 30 – 35 °c for 18 – 72 hours.
5. Growth of pink, non-mucoid colonies the presence of E. coli.
6. If there is no growth of such types of colonies, it indicates absence of E. coli.

2.2.6 Test for *salmonella:*

1. After incubation shake the broth & transfer 0.1 ml of Rappaport Vassiliadis Salmonella Enrichment Broth and Incubate at 30 – 35 °c for 18 – 72 hours.
2. Subculture on a plate of xylose Lysine Deoxycholate Agar and Incubate at 30 – 35 °c for 24 – 48 hours.
3. Growth of red colonies with or without black centre indicates the presence of *salmonella.*
4. If there is no growth of such types of colonies, it indicates absence of *salmonella*.

2.2.7 Test for *Pseudomonas aeruginosa:*

1. After incubation subculture on a plate of Cetrimide Agar and Incubate at 30 – 35 °c for 18 – 72 hours.

2. A Green colour indicates the presence of *Pseudomonas aeruginosa*

Review and test results of Cefoperazone & sulbactam

Test	Results	Standard
Description	A white crystalline powder	A white or almost white crystalline powder.
pH	5.082	Limit: 4.5 to 6.5
Solubility	Soluble	Freely soluble in water
Water	3.2%	NMT 5.0% determine 0.5g
Average weight	1.501	Std. Weight: 1.508 ± 2%
Assay	99.26%	Limit: NLT 95% and NMT 10.2 %
Related substance	0.27%.	Any individual impurities present ≤ 1.5 %
	0.97%	Total impurities ≤ 4.5 %
Particulate matter	160 PC/g 4 PC/g	≥ 10µm: ≤ 300 PC/g ≥ 25µm: ≤ 300 PC/g
Visible particle	Not present	No foreign matter observed on visual inspection
BET test	Not present	NMT 0.20 EU/mg
Sterility test	No growth observed	No growth found in the sample containing media up to 14 days observation results.
Tapped density	0.55 /ml	

3. QUALITY ASSURANCE

Providing technical information regarding the GMP treads to be incorporated in the protocols for the validation activities.

Preparations and approval of validation master plan validation protocols, site master file, QA Manual, SOP, etc.

QA: SOP, RA regulatory, Master file

1. QA – SOP
2. RA – (Regulatory) – Review
3. Design (art work) – carton, Sticker

In case of any unexpected event occurred during the manufacturing process or documentation of product then QA is responsible for the investigation of the event, including the root cause and taking appropriate action to prevent the occurrence and recurrence of the event.

QA ensures that the product is safe for the market prior to the batch release.

3.1 Department which includes:

Maintenance of quality control of manufacturing procedure for each batch manufactured.

Record of release, quarantine or rejection of components and finished products, containers, labels on quality control test result.

Manufacturing process and process checks

Production Record Review

Stability testing and evaluation of shelf – life of products

Line clearance before the start of any manufacturing process IPC person ensures proper line clearance.

QA in-process team is Responsible for this activity and ensures compliance of all floor activities related to storage of raw material to final product dispatch.

4. ENGINEERING

4.1 Air Handling Unit:

AHUs in cleanrooms performs the following basic function control airborne particle, dust and microorganism through air filtration Using efficiency particulate air (HEPA) filters.

Maintain room pressure areas that must remain cleaner than surrounding areas must be kept under a positive.

Main purpose of the AHU is to ensure comfort to the staff and employee.

HEPA (High efficiency particulate air) filters will be acceptable only if they are capable of removing all particulate matter 0.3 micron in size with an efficiency 99.97 %.

These filters can remove microscopic substance from the air like dust and pet dander.

4.2 HVAC (Heating ventilation and air conditioning)

They control the manufacturing environmental, which can impact the strength, identify, safety, purity, and quality of product.

Main purposes of a heating, ventilation and air conditioning system are to help maintain good indoor air quality through adequate ventilation with filtration and provide thermal comfort.

4.3 Pour Steam Generator:

Pure steam generator as per CGMP requirement it is recommended to use pure steam in place or filtered plant steam. This steam is used for all in situ. Like sterilization of vessels, piping distribution system, autoclaves and for humidification of sterile rooms.

Clean steam is the steam generated from treated water, free from volatile additives, such as amines, hydrazides.

4.4 Water purification system:

Purified water is highly pure water produced from raw water. Firstly, the pre-treatment of water is done. Borewell water is first treated with Sodium hypochlorite dosing system for chlorination of bore well and thus water disinfects. And then the pre-treated water is stored in Storage tank. After

this the water is passed through the sand filter (Pressure sand filter) for the removal of suspended matters. Waste water then flows vertically through the bed of sand and gravel, and particles are thus removed adsorption. Pressure sand filter contains pure graded silver quartz as a filtering media and thus after this filtered water is obtained. Filtered water is then treated with Sodium Meta bi-sulphite (SMBS) for dichlorination of water as chlorine free water will not attack on the softener resin and RO membrane. Simultaneously, Antiscalant dosing (E.g. - Polyacrylic acid) is given to the treated water for scale prevention. Then it is passed through Micron cartridge filter which is of 10 Microns. The high suspended particles in water may choke the membrane passage and may also damage the membranes thus affecting performance and life of RO system. Two types of water is generated: Permeate or fixed water and Rejected water. The rejected water is again sent for recycling and the permeate water is passed through a Mix- bed unit which is used for polishing water to achieve demineralized water quality. It consists of a strong acid cationic exchanger, which removes cations and a strong Base anionic exchanger which removes anions of the filtered water, which results in demineralized water. Furthermore, the water is also passed through 1 micro meter cartridge filter which prevents the impurities of water which is greater than 1 micro meter size. Followed by which the water passes through the UV system which emits 254nm wavelength for microbial control. After the final treatment with UV, purified water is generated which is stored in a storage tank and further used for various purposes.

4.5 Water system:

4.5.1 Raw water:

Bore well supplies adequate water which store tank of 55k litre capacity and 16k litre.

4.5.2 CSRO (Chemically sanitization RO):

CSRO from the 5k litre raw water store tank, water supplies to MFG, membrane and softener for primary treatment to remove dissolved organic & inorganic impurities in RO and store in 2k litre HDPE storage tank.

4.5.3 Purified water:

RO water after chlorination & filtrations uses as feed water for purified water system. The system involves passing of the feed water through activated charcoal filters followed by cation exchanger,

weak base anion exchanger, storage base anion, UV purifier mix bed, finally UV purifier allowed by filtration through 25 µ filters in sequencer.

4.5.4 Specification water:

Purified water complies with the specification as per IP/BP with regards to chemical and microbiological testing.

4.5.5 Sampling point:

Sample of water for analysis is withdraw from loop and 27 sample points in water system.

4.5.6 Sanitations:

Wall defined program exists for sanitation of purified water system. Sanitations of purified water system is done at temperature more than 80°C to 85°C at a frequency of once in 30 days ± 2 days.

5. DOCUMENTATION WORK OF MANUFACTURING PROCESS

5.1 Batch Manufacturing Record (BMR):

A BMR is an important document for process manufacturers. It includes Information about like product name, weight and records the entire production process, from start to finish.

There are several stages of the pharmaceutical product manufacturing process. All stages are included in the batch manufacturing records from the issuance of the Raw material to the final packaging.

A good Batch Manufacturing Record format should contain following parts:

1) Batch records:

A very first page of the BMR has all information about batch as batch number, product name, batch size, composition, Effective Date, product description, storage conditions, product specifications, manufacturing date, expiry date, shelf life, date of starting and date of completion.

2) Abbreviations:

List of the abbreviations used in the document should be made to understand the BMR easily.

3) Bill of Raw material:

In the bill of raw material

Calculation of Raw material for fill weight

Line clearance:

Areas and equipment should be cleaned.

Ensure that temperature and RH of area within the limit and recorder in BMR.

Temperature: 21.4°c (23 ± 2°c)

RH: 22% (20 ± 5 %)

Check differential pressure of dispensing area.

Check cleanliness and quantification status to RLAF.

Ensure all material are approved from QC.

Check utensils required for the dispensing and available & cleaned.

Check that RLAF is switched on 30 min before the dispensing activity.

4) Bill of Raw material:

List of the raw material should have the quantity of the materials with their A.R.No. weights of the materials should be verified by quality assurance.

Packing material details:

Name of material (glass vial, grey butyl rubber stopper, pista green flip off seal), date of issue, Quantity Required, A.R.No., Extra issue, Net issue.

5) General instructions for Manufacturing:

Health and safety instructions to the operators and the manufacturing are written those should be followed during the manufacturing process regarding the material and equipment used during manufacturing. All equipment used for manufacturing must be cleaned, dried and sterilized. Use appropriate labels at all the stages of production duly filled and signed by production with date. Operators must wear hand gloves and sterilized gowning throughout the sterile area operations.The relative humidity of whole sterile areas must be 20 ± 5 %, and temperature 23 ± 2°c.

6) Equipment and Machines Cleaning Records:

Checklist of the cleaning of all equipment is prepared, those are used in the manufacturing of the batch including the previous product, batch and date of cleaning. Cleaning of the equipment should be checked by the quality assurance.

Name of equipment: 1) Rotary vial washing machine

2) Sterilization and Depyrogenation tunnel

3) Vial filing and Rubber stoppering machine

4) Aluminium cap sealing machine

5) External vial washing machine

6) Double cone blender

7) Visual Inspection Booth

7) Glass vials washing:

Line clearance for De-cartoning of vials. Equipment should be checked and cleaned.

Temperature: 24°c (23±5°c)

RH: 53 (50±5%) of area

Decanting of vials: transfer vials from PPM store and remove corrugated boxes and then transfer in decartoning area in shrink PVC bag through static pass box. Load these vials on lifter and then remove the PVC shrink bag. Transfer on rotary vial washing machine.

Washing of vials

Vial washing verification

Clarity check

8) Flip off seal sanitization Record

Take flip off seals in SS container and sanitize the flip off seals using 70% IPA solution. Sanitization completed on date and note the time.

9) Environmental control of sterile area:

Fogging status (fogging with disinfectant solution containing 11% Hydrogen peroxide and 0.01% AgNO3.)**.** Cleaning before start of filing

10) Weighing and Bulk mixing record

11) Filing and sealing Record

12) Visual inspection and Rejection record

13) Batch Reconciliation

14) Yield:

Yield of the batch should be calculated at end of every stage to calculate the process loss. Final yield should be calculated at the end of manufacturing that should not be less than 99.00%.

5.2 Batch packaging Record (BPR):

Batch packaging Record is important documents because it contains all information about the packaging process of the batch.

A good Batch packaging Record contain following parts:

1) Batch Record:

A very first page of the BPR contain has all information about product name, Batch No., Composition, store conditions, shelf life, batch size, Manufacturing date, Expiry date.

2) List of abbreviations:

List of the abbreviations used in the document should be made to understand the BPR easily.

3) General instructions for packing:

Inspect the pre-printed Mfg.lic.no. Batch no., Manufacturing date, Exp.date and MRP on each label of the vials.

Pack vials as per the MFR specifications of packing.

Pack one vial in a carton and 10ml sterile water for injection IP ampoule.

Pack such monocartons in shrink bag and pass it through the shrinking machine.

Pack such shrink in one corrugated outer box. Close with 3-inch BOPP tap roll. Affix outer box label, pre-printed with details Mfg.lic.no. Batch no., MFG Date and Exp. Date.

4) Bill of Packing material:

List of the packing material should have the quantity of the materials with their A.R.No., Extra issue, and Net issue.

List of packing material: 1) 10ml vial sticker label

2) 10ml sterile water for injection IP ampoule

3) Monocarton for 1 vial

4) Shrink bag

5) BOPP tag Roll

5) Overprinting of packing material Records:

Vial labels

Carton label

6) Specimens of printed packing material

Affix sticker label specimen here (sticker of vials, carton contain all details about product)

7) Labelling and packaging Record:

Line clearance before starting the labelling and packaging procedure

Visually check area and equipment is cleaned and recorded in respective format

Verify the secondary packaging materials issued as per BPR.

Ensure the area free from previous product I.e., label, carton, insert, vials etc.

Ensure pervious batch record from the labelling machine is erased.

Labelling Record should contain Date, operator name, labelled quantity, checked by sign.

Packing Record contain labelled checked by, carton packed by, outer box packed by, quantity packed, checked by.

No. Of Carton packed

No. Of shrink packed

Total shippers to finish goods

8) **Batch yield Details**
9) **Dispatch log sheet**
10) **BPR Review History**

REFERENCE

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