# SITE MASTER FILE

**PHARMA DEVILS**

(Oral Solid Dosage & Injectable Facility)

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## APPROVAL & AUTHORIZATION

This Quality Document **"SITE MASTER FILE"** elaborates the Site, and describes the Manufacturing Facility and Quality Management System being followed in all the relevant areas in ……..

**PREPARED BY:**

| DESIGNATION | NAME | SIGNATURE | DATE |
|---|---|---|---|
| OFFICER/EXECUTIVE (QA) | | | |

**REVIEWED BY:**

| DESIGNATION | NAME | SIGNATURE | DATE |
|---|---|---|---|
| HEAD (OPERATIONS/PLANT) | | | |

**APPROVED BY:**

| DESIGNATION | NAME | SIGNATURE | DATE |
|---|---|---|---|
| HEAD (QUALITY ASSURANCE) | | | |

**AUTHORIZED BY:**

| DESIGNATION | NAME | SIGNATURE | DATE |
|---|---|---|---|
| HEAD (CQA) | | | |

## 1.0 GENERAL INFORMATION ON THE MANUFACTURER:

**……** is a professionally managed Pharmaceutical Company with operating Head Office in …….. The Plant is around …..Km from ……..and …….. Km from New Delhi.

**……** has facility for Manufacturing of Oral Solid Dosage & Small Volume Parenteral, Ointment and the plant is located at ……in Industrial Area. ……..establishes the quality of its products with strong support of well equipped Quality Control Laboratory situated in the Plant.

Products are manufactured under license number:
a) For Drugs Specified in Schedule C & C (1) - **……**
b) For Drugs other than those Specified in Schedule C & C (1) - **……**

### 1.1 Contact Information on the Manufacturer:

| REGISTERED OFFICE | MANUFACTURING UNIT | CORPORATE IDENTITY NUMBER (CIN) |
|---|---|---|
| | | |

### Telephone/Fax No. of Contact Persons:

| | REGISTERED OFFICE | WORKS |
|---|---|---|
| **Phone No.** | | |
| **Emergency No.** | | |
| **Fax** | | |
| **E-mail** | | |
| **Contact Person** | | |

## 1.2 Authorized Pharmaceutical Manufacturing Activities of the Site:

All the Pharmaceutical Manufacturing Activities are carried out as per revised Schedule-M of The Drugs & Cosmetics Act 1940 and Rules 1945. Licensing and Regulatory activities are controlled by Drug Licensing & Controlling Authority, Drug Controller …….and CDSCO (Central Drug Standard Control Organization), Ghaziabad, North Zone -India.

Manufacturing License is issued by Drug Licensing & Controlling Authority, ……..-India. Copy of Manufacturing License is shown in **Annexure-I**

### Type of Products Manufactured:

| DOSAGE FORM MANUFACTURED | | | |
|---|---|---|---|
| Tablet | Hard Gelatin Capsule | Soft Gelatin Capsule | Small Volume Parenteral (Glass Ampoules) |
| Powder in Sachet | Dry Syrup | Dry Powder Injection (Glass Vials) | Eye & Ear Drops (Three Piece Vials) |
| Ointment | Oral Liquid | Large Volume Parenteral | Liniment |

…….. is **WHO-GMP** certified Company. Copy of current GMP & WHO-GMP Certificates are shown in **Annexure-III.**

**List of GMP Inspections & Approvals for the Manufacturing Site:**

| S. No. | Certification | Date of Audit | Name of Competent Authority/ Name of Country |
|---|---|---|---|
| 1. | WHO-GMP | | CDSCO-India |

## 1.3 Any Other Manufacturing Activities carried out on the site:

No other manufacturing activities are carried out at the site.

## 2.0 QUALITY MANAGEMENT SYSTEM OF THE MANUFACTURER:

## 2.1 The Quality Management System of the Manufacturer:

Purpose of the Quality Management System is to ensure compliance of cGMP requirements as enforced by National and International Regulatory Bodies. The Quality Management System ensure that all activities related to manufacturing of drug Products are in compliance with cGMP and controlled by Standard Operating Procedure, so that the end product meets all the Predefined Specifications ensuring the Identity, Strength, Safety & Purity of the Products.

## Quality Policy:

- Understand and meet the customer's Expectations.
- Provide quality product to full satisfaction of the customer.
- Ensure value for Money.
- Ensure compliance of all legal requirements.
- Ensure continuous Business Growth.
- Ensure increased Profitability.
- Continually improve the effectiveness of Quality Management System.
- Achieve continual improvement through Motivated and Trained Work Force.
- Manufacture Products of World Class Quality.

## Responsibilities of Quality Assurance Function:

- In-Process Control.
- Implementation of Quality Systems.
- Directive and Controlling of cGMP Operations.
- Providing guidance for compliance to various International cGMP requirements.
- Approve Deviations or Changes in the System.
- Total Quality Management of the Plant.
- Control of Material Specifications.
- Monitoring and Control of the Manufacturing Environment.
- Qualification and Validation Activities.
- Employee Training.
- Approval and Monitoring of Suppliers of Materials.
- Designation and Monitoring of storage conditions for Materials and Products.
- Retention of Records.
- Internal Inspection, Investigation and Collection of Samples.
- Annual Product Review.
- Co-ordination with Regulatory Department.
- Investigation of Non-Conformances and Market Complaints.
- External Audit and Compliance of the findings.
- Authorization of Manufacturing Documents.
- Document Control.
- Batch Release / Rejection.

## Elements of Quality Assurance System:

Quality Assurance Head is mainly responsible for incorporating comprehensively designed and correct Systems of cGMP, whereby producing a product which is Safe, Pure and Effective.
Following are the job Responsibilities of Key Personnel of ……...

## Job Responsibilities: Head-Operations

- Head of Unit.
- To ensure the adhering & implementation of current SOPs. Training of subordinates on the Standard Operating Procedures.
- To ensure the proper Production Planning & Execution in time.
- Allocation of Processing Operation, Supervision and Compliance of cGMP and Safety Requirements.
- Assistance in Documentation related to Production, cGMP.
- Maintenance of Good House Keeping, Cleanliness, Personal Hygiene and Work Discipline.
- Compliance to Entry / Exit Procedure and Gowning Procedures in Restricted Areas.
- Calibration and Maintenance of Equipment's. Assistance in Process and Equipment Validation.
- Exercise Preventive Measures to avoid Cross Contamination and Mix-Ups during Handling, Manufacturing and Preservation of Products / Materials.
- Maintenance of Good Industrial Relations.
- To Carry out Self-Inspection to maintain cGMP norms.
- Provide Co-ordination, Support to other departments as appropriate in their area of work.
- Achieving the Requirements of the Monthly Production Plan with Priorities if any.
- To ensure the Allocation & Supervision of Jobs to Subordinates.
- To ensure the Reduction of Production Cost.
- To ensure Proper Manpower Planning & Utilization.

## Job Responsibilities: Head-Quality Assurance (QA)

- Documentation for all QA Activities.
- Daily Monitoring of Quality Assurance Activities.
- Training on cGMP and Health Hygiene.
- To Review the MFR, BPCR, SOPs and Protocols.
- Handling of Products Complaints.
- Approval of Vendors for RM & PM.
- Periodical Quality Audit.
- Activities related to Drug Control Authorities.
- Co-ordination with various Departments to implement cGMP in Plant.
- Stability Study of Finished Products.

- Product Recall.
- Validation and Qualification.
- cGMP Training to Staff.
- cGMP Implementation in the Factory.
- Release of Finished Products for Sale.

## Job Responsibilities: Head-Quality Control

- Analysis of RM, PM, In-Process Sample, Finished Product.
- Release of Raw Material, Finished Products and Packaging Materials.
- To review the STP, Specifications and SOPs of Quality Control Department.
- To Perform Calibration of Instruments routinely and Maintenance of Records.
- To Perform Stability Sample Analysis as per the Stability Study Program.
- Maintenance of Reference Standards.
- To review documents of analysis carried out routinely.
- Daily Monitoring of QC Activities.
- Validation Activities.
- Analytical Method Validation.
- GLP implementation in Laboratory.

## Job Responsibilities: Head-Engineering

- To follow Good Engineering Practices (GEP) in Plant.
- Maintenance and Management of Oral Solid Dosage & Injectable Facility including Compliance and Good Engineering Practices.
- Implementation of Clean Room Concepts (HVAC & Water System).
- Co-ordination with Production and Engineering Department for Productivity.
- To assist QA Department during Audits.
- Indigenization of Imported Equipment Spares and Developing Local Vendors.
- Design and Implementation of measures like Inventory Control and Energy Conservation for Cost Minimization.
- Developing Systems & Procedures, Maintenance Manuals and Training Programs.
- Establish Maintenance Systems and Procedures for New Manufacturing Facility and to implement the Systems of Basic Engineering.
- Development of Systems and Methodologies in line with Regulatory Body Requirements in Co-ordination with QA Department for any Regulatory Audit.
- Training the team members for the latest Regulatory requirements from engineering aspects.
- Design and implementation of Energy Conservation Techniques.
- Close Monitoring and Implementation of Preventive Maintenance Schedules and Down Time Analysis.

## 2.2 Release Procedure of Finished Products:

- After completion of Packing and In-Process release, Finished Goods are transferred from Packing Department to Finished Goods Store after due Terminal inspection and by raising Finished Goods Transfer Note (Transfer Ticket).
- After complete review of the relevant batch record and confirming the availability of all necessary Certificates of Analysis, the Quality Assurance Head or his designee authorizes the release of the finished Goods for Sale / Distribution.
- List of Key Persons is given in section 3.0.

## 2.3 Management of Suppliers and Contractors:

### ❖ Summary of Supply Chain / External Audit Program (Vendor Approval)

Vendors of all Active Pharmaceutical Ingredients as well as Excipients and Packaging Materials are assessed for cGMP compliance. Following are most important aspects of procurement of materials:

- ➢ Material Specifications.
- ➢ Vendor Audit/Development.
- ➢ Vendor Approval/Certification.
- ➢ Periodic Vendor Audit.

- All the Manufacturers/or Vendors (RM/PM) and Contractors (Analytical Lab. and Calibration Agency) are evaluated for compliance to cGMP/GLP Standards.
- Pre- Audit Questionnaires are initially sent to vendors and filled Questionnaires are evaluated for expected level of Technical Competence and adherence to Regulations pertaining to the respective business.
- On satisfactory evaluation of Pre-Audit Questionnaire and reference documents provided by the vendor along with COAs, facility approval certificates & TSE/BSE free certificates (If applicable), Vendor Audit is conducted by CQA. Audit is conducted as per checklist and Audit Observations are recorded in specified format.
- Audit Report is sent to the Vendor for Compliance.
- On the basis of Compliance Report received from the Vendor, its evaluation and Verification of Audit Observations at Vendor site (if required), Vendor (Supplier/Analytical Lab/Calibration Agency) is Approved/Rejected.
- All the Vendors are periodically audited for compliance status as per Vendor Audit Schedules.
- List of Approved Vendors/Analytical Lab/Calibration Agency is prepared on the basis of Vendor Audit Program and the same is available at Manufacturing Site.

### ❖ Use of Outside Scientific, Analytical and Calibration Agency:

**…….**is well equipped to manufacture all above mentioned dosage forms. Facilities to test Raw Materials, Intermediate Products, Packaging Materials and Finished Products are available in Quality Control Department however Analytical and Calibration assistance is also taken from Government Approved Analytical Lab & Calibration Agency for Analysis & Calibration of a few specific tests that cannot be carried out at the site.

**Following are Outside Scientific & Analytical Agencies:**

| | Name & Address of Outside Scientific & Analytical Agencies | Type of Services |
|---|---|---|
| **1.** | | |

### ❖ Responsibility of Contract Giver and Acceptor:

- Contract giver is responsible for sending the samples (Along with Method of Analysis - if required) for analysis to the Contract Acceptor.
- Contract acceptor shall be responsible to perform the analysis as per Pharmacopoeial Specification/ In-House method provided by the contract giver.
- Contract giver is responsible to inform the Calibration Agency for due date of Calibration as and when required.
- The COA and Calibration Certificates shall be used by the Contract Giver for further processing steps and may be audited and referred for and by Regulatory / Legal authorities.

## 2.4 Quality Risk Management (QRM):

Risk is defined as the combination of the probability of **occurrence of harm** and the severity of that harm & Quality Risk Management Principles as per ICH Q9 are effectively utilized and implemented in all areas of manufacturing site.

**Basic Methodology for Quality Risk Management is:**

- Basic Risk Management Facilitation Methods (Flowcharts, Check Sheet etc.).
- Failure Mode Effects Analysis (FMEA).
- Fault Tree Analysis (FTA).
- Hazards Analysis and Critical Control Points (HACCP).
- Hazards Operability Analysis (HAZOP).
- Preliminary Hazard Analysis (PHA).
- Failure Mode Effects Criticality Analysis (FMECA).
- Risk Ranking and Filtering.
- Supporting Statistical Tools.

Quality Risk Management Methods and supporting statistical tools may be used in combination (e.g. Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

## 2.5 Product Quality Review:

We ensure the Quality, Efficacy and Safety by necessary control on starting materials, Intermediates and Finished Products. All manufacturing process are clearly defined, systematically reviewed, meeting the quality that complies with their specifications and also by maintaining proper Storage condition at all the manufacturing steps.

Annual Product Review is Performed / Carried out for all the Batches Manufactured, Packed and Released or Rejected in the previous Calendar Year.

## 3.0 PERSONNEL:

Diagrammatic representation of Organizational Structure is shown in **Annexure-V.**

List of Key Personnel's showing the arrangements for Quality Management, Production and Quality Control is given below:

| S.No. | Name | Designation | Qualification | Experience | Responsibility |
|---|---|---|---|---|---|
| 1. | | | | | |

### Number of Employees engaged in the Quality Management System, Production, Quality Control, Storage and Distribution:

……have well experienced Qualified and Competent, Dedicated Technical Personnel in various departments like Quality Assurance, Quality Control, Production, Personnel & Administration, Engineering & Warehouse.

All the Employees engaged in Production are subjected to Periodic Health Checks and Records are maintained. Systems are in place for use of clean factory uniforms provided to employees working at various Levels.

### Following Dedicated Manpower is engaged in ……..

| DEPARTMENTS | STAFF | WORKERS + OPERATORS | TOTAL |
|---|---|---|---|
| **Quality Assurance** | | | |
| **Quality Control** | | | |
| **Production** | | | |
| **Warehouse** | | | |
| **Engineering** | | | |
| **Others** | | | |
| **Total Number of Employees** | | | |

## 4.0 PREMISES AND EQUIPMENT:

### 4.1 Premises:

Premises have been designed, keeping cGMP, safety and manufacturing capacity in consideration. Premises and equipment are located, designed, constructed, adapted and maintained to suit the operation to be carried out. Their layout and design is in such a way that it is aimed to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, any adverse effect on the Quality of Products.

The premises used for manufacturing, Processing, Labeling, Packing and Testing, Storage purposes are well maintained and adequate to allow orderly and logical placement of Equipment and Materials.

**Description of the Site:** **Refer Annexure-VI for Site Map.**

Plant is surrounded by:

**North** : …… **East** : ……..

**South** : …… **West** : ……..

Plant is located in a Green Belt and Clean Area. It has facilities for Manufacture of **Tablet, Hard Gelatin Capsule, Soft Gelatin Capsule, Powder in Sachet, Dry Syrup, Dry Powder Injection (Glass Vials), Small Volume Parenteral (Glass Ampoules) and Eye & Ear Drops (Three Piece Vials) ,Ointment.** There are total …… blocks and manufacturing activities

**BLOCK:**

| DEPARTMENT/SECTION | AREA IN SQ. METER (APPROX.) |
|---|---|
| **Floor** | |
| Area | |
| **Total Area** | |
| **Total Covered Area** | |
| **Total Open Area** | |

Layouts of Production Area showing the Man Movement Plans, Material Movement Plans, HVAC Zoning Layouts, Area Classification Plans, Pressure Differential Plans of different Blocks & Floor Plans are shown in **Annexure-VI**

Pressure differentials are maintained across adjacent areas in the facility for the respective dosage forms. General Temperature in core area is NMT 25°C and is also maintained as per product requirement.

Relative humidity in different Section of Blocks is mentioned below:

| Section | Relative Humidity* |
|---|---|
| All Manufacturing Areas | NMT 55% |
| Low RH Area | As Per Product Requirement |

| | |
|---|---|
| Small Volume Parenteral Area | As Per Product Requirement |

* Environmental conditions (Room Temperature & Relative Humidity) of individual area in the above mentioned sections are designed and maintained to meet the requirement of in-process products at different manufacturing stages.

The Ventilation System design is based on re-circulation of air, 90% of the air is re-circulated and 10% fresh air is taken in. Air changes in the Grade-B area is not less than 60/Hr and for Grade-D are not less than 20/Hr.

**Nature of Construction:**

The entire building is constructed by using RCC & Pre-Engineered Steel Structure and is adequate and suitable for manufacturing of drug products. Excellent Ventilation, Cooling and Air Conditioning are provided to all the area as per requirement and similarly Water, Waste Water Removal, Electricity, Fuel services & other utilities are provided adequately. All the Utility facilities kept separate from main building and have adequate capacity. The internal walls of Production areas and sampling & dispensing areas are made of PUF insulated modular panels.

**Finishing:**

**Epoxy Flooring:** Core Areas, Packing Area, Production Areas & Microbiology Laboratory have epoxy flooring. Epoxy floor gives a smooth finish without joints, chemical resistance and dust-free

**Kota Flooring:** Kota Stones are fixed in Canteen and Toilets are provided with ceramic tiles.

**Coving:** To avoid vertical joints, coving is being done from floor to wall, wall to wall & wall to ceiling by using Epoxy/PVC/Aluminium coving to minimize the risk of dust deposition and microbial growth.

**Painting:**

**PU (Polyurethane)** is used in Entrances, Toilets, Change Rooms, Passages and Storage Areas. It is applied in all other areas which are not covered with modular Panels. It is characterized by Excellent Chemical, Oil, Water Resistant, Smooth Finish and Excellent, Algae and Fungi Growth Resistance.

**Doors & Windows:** All doors are sandwiched modular doors with view Panels and windows are Aluminum body with wall flushed double layered glasses.

**Specific Storage Conditions:**

Storage areas are created to suit product requirement. All drug products and substances are stored in required storage conditions.

### 4.1.1 Heating, Ventilation and Air Conditioning (HVAC) System:

Plant has separate and dedicated HVAC System for all Block.

| S.No. | SECTION/AREA | No. of AHU | No. of DHU | No. of FDV |
|---|---|---|---|---|

| S.No. | SECTION/AREA | No. of AHU | No. of DHU | No. of FDV |
|---|---|---|---|---|
| 1. | Ground Floor | | | |
| 2. | First Floor | | | |
| 3. | Third Floor | | | |

All the areas are provided with appropriate ventilation system to maintain the required room condition with respect to the temperature & relative humidity. To maintain proper Ventilation System in the Plant AHU, DHU, FDV and Exhaust are provided.
The Schematic drawings of Ventilation System along with relevant details are attached in **Annexure-IX**

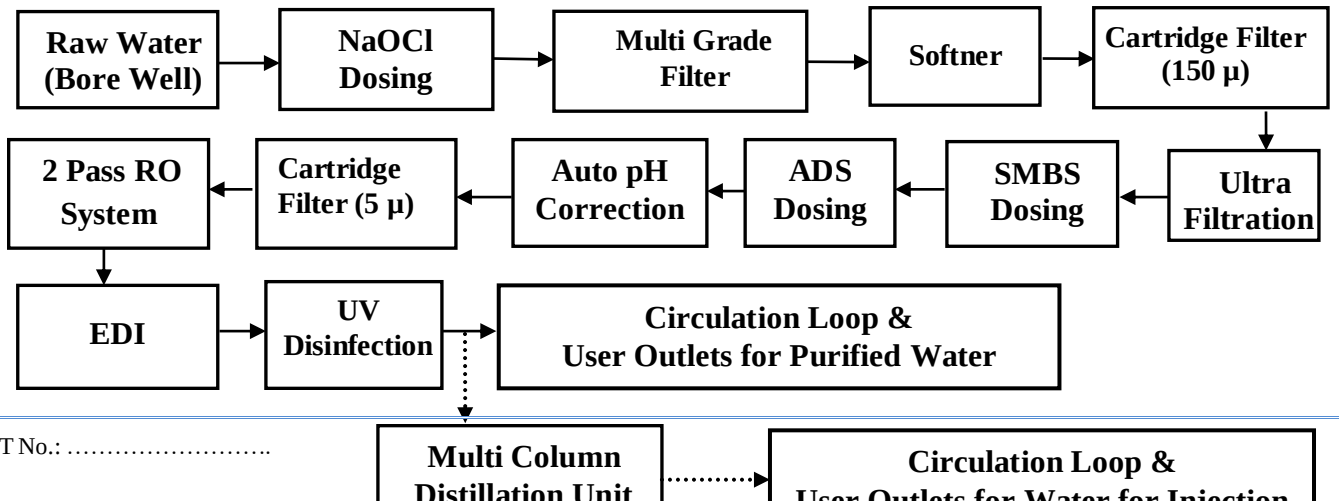
- **Filters for different Grades of Area in Blocks:**

| Grade of Areas | Fresh Air Filter | Return Riser Filter | Pre-Filter | Micro-Vee Filters | Final Filter |
|---|---|---|---|---|---|
| **Grade-A** | Not applicable | Not applicable | 5 µ (EU-5) | Not applicable | 0.3 µ (EU-13) |
| **Grade-B** | 10 µ (EU-4) | 10 µ (EU-4) | 5 µ (EU-5) | 3 µ (EU-7) | 0.3 µ (EU-13) |
| **Grade-C** | 10 µ (EU-4) | 10 µ (EU-4) | 5 µ (EU-5) | 3 µ (EU-7) | 0.3 µ (EU-13) |
| **Grade-D** | 10 µ (EU-4) | 10 µ (EU-4) | 5 µ (EU-5) | 3 µ (EU-7) | 0.3 µ (EU-13) |
| **Unclassified** | 10 µ (EU-4) | 10 µ (EU-4) | 5 µ (EU-5) | Not applicable | 3 µ (EU-7) |

- **Filter Replacement Policy:**
  All ventilation filters are changed or claimed for maintenance, as soon as the pressure differential across filters deviates from the design range. Such replacement of filter is done according to the Standard Operating Procedure.

**Effluent Treatment Plant:**
We have contract with Private Operator UEM India Pvt. Ltd., who maintains and operates Industrial Liquid waste discharge by Common Effluent Treatment Plant (CETP) situated in SIDCUL Industrial Area for disposal & Treatment of Waste.

### 4.1.2 Water System Description:



Schematic Diagram of Purified Water System (Generation & Distribution) for Blocks is shown in **Annexure-VII**

## Purified Water System:

- The Raw water is collected from Bore wells in HDPE Storage Tank.
- From these Tanks water is pumped, while on line dosing with up to 3 ppm of free chlorine using Sodium Hypochlorite. Water is then fed to Multi Grade Filter (MGF).
- From the MGF, the water is passed through Softeners (Having stand by units such that while one unit is under use, the other unit is re-generated and kept ready for use). Now the soft water is collected in 5 KL SS 316-L Tank. From this Tank the Water is pumped through 150 µ Cartridge filter and supplied to Ultra filtration Unit. The water from UF (Ultra filtration) is collected in 5 KL SS 316-L Tank.
- This water is subjected to SMBS dosing, ADS Dosing System & Auto pH Correction systems after which it is passed through 5 µ filters and pumped into 5 Nos. of RO membranes for first pass. The Water of first pass RO is again pumped into 3 Nos. of RO membranes for Second Pass.
- One 3 KL SS tank with continuous circulation loop system having 26 user points provides purified water to 'I' block and 'Q' block at ambient condition whereas the other 3 KL Tank is connected to two separate continuous circulation loops supplying Purified water to 'G' block at ambient condition having 25 and 24 user points respectively. All the loops are made with SS 316-L pipe with 0.4 Ra inner finish and the joints are argon welded and each joint is checked using boroscopy for quality of welded joint.

| Capacity (Liters) | Quantity | Make |
|---|---|---|
| | | |

## Water for Injection (WFI):

Water for injection (WFI) generation and distribution system is provided for manufacturing Facility of Small Volume Parenteral. Multi Column Distillation Plant (MCDP) of 110 Liters/Hr capacity (**Make: Pharmalab**) is available to produce high quality water for injection which is collected in a SS 316-L Tank fitted with Circulation Systems supplying WFI to various user points in Small Volume Parenteral manufacturing facility. The WFI in the Storage Tank and loop is maintained at temperature NLT 80ºC, while maintaining continuous Circulation.
Schematic Diagram of Water for Injection System (Generation & Distribution) for Blocks is shown in **Annexure-VII**

## Pure Steam Generator (PSG):

Pure Steam Generator (PSG) 300 Kg/Hr Capacity (**Make: Pharmalab**) is provided to meet requirements of Pure Steam in manufacturing Facility of Small Volume Parenteral. The Pure Steam is used for Sterilization of Machine Parts, Aseptic Area Garments, Rubber Bungs & Aluminium Seals in Bung Processor cum HPHV steam Sterilizer.
Schematic Diagram of Pure Steam Generation & Distribution System is shown in **Annexure-VII**

### 4.1.3 Description of Relevant Utilities:

#### Compressed Air:

Plant has a Compressed Air System to serve all manufacturing locations in Blocks , which provides oil free compressed air for process & equipment with following capacities:

| Capacity (CFM) | Quantity | Make |
|---|---|---|
| | | |

The Compressed Air is stored in an air receiver, filtered by 5 micron filter at suction and the air dried using refrigerant type air drier before supplying to various user points at 6 bar pressure. The header and distribution legs are kept under pressure.

#### Nitrogen Gas Plant:

Nitrogen Gas is procured from in house Nitrogen Gas generation & distribution system which is PSA(Pressure Swing Adsorption) based Nitrogen plant having following description.
**1. Capacity:** 10$Nm^3$/hr. **2. Purity**: 99.5%. **3. Outlet Pressure**: 5.5 Kg/$cm^2$.**4. Dew Point**: (-) 40$^0$C.

#### Chilling Plant:

Chilling Plant having five Chillers is provided for supply of Chilled water for Blocks to meet the requirement of Chilled Water in HVAC System and Process.

| Capacity (TR) | Quantity | Total TR | Make |
|---|---|---|---|
| | | | |

#### Steam System:

Steam is provided to the facility as a utility and does not come in contact with product. The Plant Steam is generated by one oil fired boilers of following capacity and make:

| Capacity (Kg / Hr.) | Quantity | Make |
|---|---|---|
| | | |

#### Electricity Supply:

**……..** has an electricity connection of **3300 KVA,** supplied by ……. Apart from Govt. Supply, ……..has its own electricity generation facility by following generator:

| Capacity (KVA) | Quantity | Make |
|---|---|---|

| | | |
|---|---|---|
| | | |

### Dust Extraction System:

Dust Extraction System has been provided to minimize the particles, generated during processing and all other dust generating areas are provided with Dust Extraction Units dedicated for each area, located in Manufacturing Area.

### Maintenance:

Preventive Maintenance of all AHUs and Water Treatment Plant is carried out as per the respective Preventive Maintenance Procedure. The Annual Plan for Preventive Maintenance of all AHUs and Water System is Prepared at the beginning of the Calendar Year. This Annual Plan is prepared with the proposed date of preventive maintenance as per defined frequency in Standard Operating Procedure.

Record of the Preventive Maintenance is maintained in the respective checklist prepared as per the corresponding procedure for Preventive Maintenance.

## 4.2 Equipment:

### 4.2.1 Major Production and Quality Control Laboratory Equipment:

Manufacturing Equipment are designed, located and maintained to suit their intended purpose. These are designed so that can be easily and thoroughly cleaned.

The equipment are cleaned according to written procedures and stored only in a clean and dry condition. All the product contact parts are made up of SS316 Stainless Steel.

All equipment are designed as per cGMP for ease of Cleaning and Maintenance.

### Major Production Equipment:

Major Production Equipment for Oral Solid Dosage Manufacturing, Small Volume Parenteral & Ointment Manufacturing are shown in **Annexure-VIII**

### Major Quality Control Instruments /Equipment:

…… has separate and dedicated Quality Control & Microbiology Laboratory and the Equipment/Instruments list of quality control laboratory is shown in **Annexure-VIII**

### Maintenance:

Preventive Maintenance of all equipment is carried out as per the respective Preventive Maintenance Procedure. The Annual Plan for Preventive Maintenance of all Equipment and Instruments is prepared at the beginning of the Calendar Year. Such Annual Plan gives the proposed date of Preventive Maintenance as per defined frequency in Standard Operating Procedure.

All the Utility and process related equipment are taken into consideration as per the Standard Operating Procedure of Planned Preventive Maintenance. The Engineering Department is responsible for carrying out maintenance and servicing of the Equipment.
Record of such Preventive Maintenance is maintained in the respective checklist prepared as per the corresponding procedures for Preventive Maintenance.

### Qualification, Validation and Calibration:

All Processes, Analytical Methods, Cleaning Methods, Equipment and Utilities are validated as per the Validation Master Plan. There are written procedures for Validation of Equipment and Processes, along with Protocols.
Following is the approach for Qualification/Validation:

### Design Qualification (DQ):

The designs of all equipment used in manufacturing of products are qualified. Design qualification is done for all utilities also. These design qualification documents ensures the equipment are manufactured on predefined specification laid down in URS document.

### Installation Qualification (IQ):

The IQ is aimed at demonstrating that the equipment and components installed are in accordance with the specifications and that they have been properly identified and installed within the correct location in accordance with the Design Qualification. It has been initiated along with project concept, includes equipment and system specifications, fabrication inspection (where relevant) and completed following installation of the System / Equipment.

### Operational Qualification (OQ):

Initiated following completion of the System / Equipment IQ and may be combined with the IQ in certain circumstances (plant commissioning). All the measuring devices are calibrated against the Calibration Protocol and Certified. All the parameters are checked against the Specification and Protocol & Certified for Performance Qualification.

### Performance Qualification (PQ):

Following completion of OQ may be combined with the PQ in certain circumstances. The PQ is the final stage of qualification, which demonstrates how each system will perform when challenged under simulated or actual production operating conditions.

### Prospective Validation:

For new products, process validation is performed using the first three production batches to demonstrate the process capabilities of the manufacturing processes.

### Concurrent Validation:

Concurrent Validation is conducted during routine processing of products.

**Retrospective Validation:**

Site is not doing any retrospective Validation for Process or Cleaning . However Historical data trending is done for water parameter.

**Revalidation:**

Facilities, System, Equipment and Processes, including cleaning method are periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfills the need for revalidation. QA Department releases all validation batches after completion of the validation report, provided that they meet all specifications & have been manufactured in accordance with cGMP. All instruments being used for monitoring are taken into consideration as per the plan for instrument calibration.

**Calibration:**

A Plan for instrument calibration describes the identified instruments are calibrated as per the respective Standard Operating Procedure. Calibration Certificates of the instruments and the certificates of calibration of the references standards used during the calibration are preserved for the reference.

If any deviation is found, the Engineering Department informs to concern department and QA on intimation note and categorizes the defect as critical, non-critical, most critical breakdown.

The QA Department approves the corrective actions, if found appropriate with necessary recommendations.

### 4.2.2 Cleaning and Sanitation:

Each Area in Production undergoes cleaning as per the Standard Operating Procedure on cleaning. The SOPs clearly specify the type of detergents to be used and the sanitizing agents with their concentration and frequency. All the equipment are cleaned after use as per their cleaning procedure. The cleaning procedures are validated as per protocol. The cleaning of equipment is evaluated based on the rinse water/swab analysis of collected samples. The water lines are cleaned as per the Standard Operating Procedure. Sanitization is carried out using Hot Water at 80ºC for 30 min.

The Air Handling System is cleaned as per the Standard Operating Procedure. Pre-filter and Micro filters are cleaned with wet and dry cleaning method. HEPA filters are evaluated periodically and if found damaged they are replaced. Wet scrubbers are cleaned using water which goes to the primary treatment tank of ETP.

### 4.2.3 Validation of Critical Computerized Systems:

Computer Validation including Software Validation & PLC of Machines is done as per Validation Master Plan of LIMS & SAP by External Agency.

## 5.0 DOCUMENTATION:

The entire documentation systems of Manufacturing & Quality Control are very comprehensive & well controlled to avoid any ambiguity and uncertainty in the Plant.

……is maintaining all documents as per requirements of Quality Management System as means of ensuring that products manufactured conforms to specified requirements. Major documents include **Site Master File, Validation Master Plan, Quality Manual, Training Manual, Safety Manual, Master Formula of Products, Standard Operating Procedures** and supporting records.

### Preparation, Revision and Distribution of Documents:

### Master Formula Record:

Product Information, Packing Information, Composition, Processing, Manufacturing, Inprocess checks and other instructions, testing etc. are mentioned in all Master Formulas for individual products. These Master Formula's are approved by Head QA. The same contains specimen of Packing Material etc.

### Standard Operating Procedure:

Standard Operating Procedure (SOP) on Preparation, Review, Approval & Control of SOP is available. Separate SOP on Documentation & Data Control is also available which describes the entire documentation system. Standard Operating Procedure consists of documented procedures which define in detail the activities and responsibilities of all the personnel involved in administration and operation of the Quality System. Standard Operating Procedure are prepared by respective department representatives, checked by Head of the Department, Approved by Head QA. All CQA SOP shall be Approved by Head-CQA.

However, if any change is required due to any reason, the revision is done after getting permission from Head-CQA.

**Periodic Review of SOP's is done in every two years or when ever is required.**

### Product Quality Documents:

### Site Master File:

All details regarding Site are available in this particular document as per PIC/S and Schedule M of Drugs & Cosmetic Act 1940 and rules there under. It includes Company Profile, Employees, Quality Manual, Key Personnel and Job Responsibilities, Training, Premises, Manufacturing Operations,

Equipment and Machineries, QA/QC Activities, Flow Charts, Annexure etc. The SMF is prepared by QA Department, Reviewed by Approved by Head QA and Authorized head-CQA.

**The Revision of the Site Master File is done once in two year or whenever is required.**

## Quality Manual:

Company Quality Policy & Quality System Manuals are available which guides the Quality Management System to provide products & services of highest standards with total customer satisfaction. Company Quality System Manuals covers the following areas:

- Premises, Personnel Hygiene, Cleaning & Sanitation, Training, Introduction parameters for Quality System, Good Laboratory Practices & Laboratory Safety, Calibration, Contamination Control, Validation Policy, Water for Pharmaceutical use, Warehousing, Laboratory Controls, Packing and Labeling, Release of Semi-Finished and Finished Goods, Stability Studies, Vendor Approval, Out of Specification, Change Control, Deviations, Annual Product Review, Product Recall & Market Complaints, Documentation, Self Inspection.

All details regarding QA/QC activities of …… are included in this document as per requirement of WHO GMP norms.

The Quality Manual is Approved by Head QA and Authorized by Sr. General Manager-QA/General Manager-QA.

**The Revision of Quality Manual is done in every two years or whenever is required.**

## Validation Master Plan:

Validation Master Plan is available which covers all aspects of Qualification & Validation of facilities, Equipment, Process, Calibration, and Revalidation etc. and documented for future reference.

**Review of Validation Master Plan is done in every two years or whenever is required.**

Documentation has categorized like Product/Process Specification, Raw Material Specifications, Packaging Component Specifications, Standard Process Instructions including Packing, Batch Manufacturing Records and Packing Records, Analytical Methods Validation and Qualifications Documents etc. All the Master Documents are controlled by QA Department with regulated distribution as per the Standard Operating Procedure.

## Training:

Training Manual & Written Standard Operating Procedure for Training of Employee is available.

All the personnel working in plant and whose job is directly or indirectly associated with Product Quality are given continuous cGMP training, appropriate to their respective job activities. The Head QA in consultation with the Head Operations as well as Head HR develop comprehensive training modules and programs for employees at all levels.

Following types of training are conducted in ……..:

- Internal Training, Induction Training, On the Job Training, cGMP/Technical Training, Refresher Training, External Training, Training Needs Identification, Re-training.

### Documentation & Records:

The documentation of different type of training shall be done by the departments as mentioned below:

| | | |
|---|---|---|
| Induction / Behavioral Training | : | HR Department |
| On the Job Training | : | Concerned Department |
| cGMP / Technical Training | : | Quality Assurance Department |
| External Training | : | Quality Assurance Department |
| Refresher Training / Requalification | : | Concerned Department |
| Re-training | : | Respective department as mentioned above |

Training to all employees is provided with the objective to perform activities to produce quality products. In QA / QC department regular training is imparted by Head QA to all Staff, workmen on various topics to maintain GLP and cGMP other activities and records are maintained. Records of all such training are maintained in QA Documentation.

### Stability Study:

…… Utilize Services of Central Stability Study Facility at Central Warehouse of parent company ……., where Samples are placed at different conditions for Stability Studies.

### Retention & Storage of Control Samples:

All the Control/Retention Samples of Finished Product for Domestic & Export are stored at dedicated space available for storage at ……..They are reviewed Periodically to verity any physical observation.

## 6.0 PRODUCTION:

### 6.1 Type of Products: **Refer Section 1.2 and Annexure-II**

**……** meets all National & International regulatory requirements with respect to Current Good Manufacturing Practices. Facility for Production of Oral Solid Dosage, Small Volume Parenteral & Ointment is available at manufacturing site. The manufacturing of batch is carried out in accordance with Master Formula Record (MFR). Reconciliation is done at critical steps of manufacturing and on completion of Packing Operations.

**Manufacturing Capacity for '…' Block**

| S.No. | Dosage Form | Capacity Per Day (In Millions) |
|---|---|---|
| 1. | Tablets | |
| 2. | Hard Gelatin Capsule | |
| 3. | Soft Gelatin Capsule | |
| 4. | Powder in Sachet | |
| 5. | Dry Syrup | |

## 6.2 Process Validation:

Process Validation is done as per the Validation Master Plan, first three production batches are validated & the following parameters are considered while performing Process Validation.

1. Raw Material Specifications.
2. Physical characteristic of Raw Material.
3. Critical Process Steps & Variables.
4. Critical Process Equipment.
5. cGMP Requirements.
6. Review of Process Issues, if any.
7. Any Modifications, Process improvement.

Equipment, Processes & Procedures undergo periodic critical revalidation to ensure that they are capable of achieving intended results. A detailed SOP is prepared describing the detailed process of Validation Procedure.

### Re-Processing or Re-Work:

Written Procedures are established and Approved for Reprocessing that specifies the conditions and limitations of repeating any process. Separate area is designated for rejected material and materials to reprocessed or recovered. Reprocessing Procedure is properly documented and recorded. Reprocessed batch is subjected to the stability study and released for sale only after proper evaluation. No re-processing performs in Injectables.

## 6.3 Material Management and Warehousing:

We have separate dedicated facility with dedicated Staff & Worker to handle Raw Materials, Packaging Materials, Bulk and Finished Products, including Sampling, Quarantine, Release & Storage for Oral Solid Dosage & Small Volume Parenteral.
Each consignment of material (RM / PM) received is examined visually. Damaged Goods are labeled as hold and kept aside for Quality Assurance's instructions either for disposal or return to party. On verification of received Quality and Batch Wise segregation, the details of receipts are entered in register called inward register and Goods Receipt Note (GRN) is generated with unique serial number.

All the containers are placed at designated **'QUARANTINE'** area with details of GRN No. of containers, manufacturer name, material code etc. Samples are drawn as per sampling plan and sampled containers are identified, samples are tested as per the respective material specifications by Quality Control Department. 100% containers are sampled for API identification and pooled samples are taken for complete analysis. √n + 1 Sampling Methodology is followed for Excipients & Packaging Material Sampling and Analysis.

After sampling under test labels are affixed on each containers having all the details like Material Code, Quantity, Total number of Containers, Manufacturer's Name, GRN No. etc and material is shifted to **"UNDER-TEST"** area. Analyst compiles the data after analysis & decides whether the material meets the Predefined / Compendial specification or not and accordingly, Approves / Rejects the material. **"APPROVED / REJECTED"** labels are affixed on the material containers & the same is transferred to designated storage area accordingly.

### Handling of Rejected Materials and Products:

Plant has separate dedicated facility to handle rejected material of 'Blocks.
All rejected materials are separated from **"APPROVED"** or **"UNDERTEST"** and the quality control persons affix **"REJECTED"** labels. The rejected material is transferred to a separate reject material area.
Quality Assurance decides the fate of such rejected material as to destroy or to be returned. No printed packaging materials are returned but are destroyed in the premises under supervision of Quality Assurance. The rejected materials are kept under lock and key and only authorized persons are allowed to handle such materials.

## 7.0 QUALITY CONTROL (QC):

### Quality Control System:

Separate dedicated facility with dedicated Staff is assigned for Quality Control Lab & Microbiology Lab. The Lab is well equipped to perform analysis of Oral Solid Dosage & Small Volume Parenteral. The Quality Control System is an integral part of cGMP and ensures that necessary and relevant tests are performed. Quality Control Department is independent of Production Area.
Quality Control Department has the responsibility and authority to release or reject all Raw materials, Drug Product Containers, Closures, Packaging Material, Labels and Finished Products. Quality Control department is responsible for Sampling, Specifications, Testing, Documentation, release procedure which ensure that the necessary and relevant test is actually carried out and that the materials are not released for use or products not released for sale / supply until their quality has been judged to be satisfactory.
Head Quality Control investigates and records the Out of Specification with complete involvement of QA department. Head Quality Assurance Investigates and Records all the Product Complaints.

Each specification for Raw Materials, Intermediates, Final Products and Packing Materials is maintained and checked by Quality Control and finally approved by Quality Assurance Department.

## 8.0 DISTRIBUTION, COMPLAINTS, PRODUCT DEFECTS AND RECALLS:

### 8.1 Distribution:

…….is engaged in Contractual manufacturing activities for the manufacture of Drug Products on Third Party/Loan License basis.

Products manufactured in Plant prior to release for market are thoroughly checked for all the tests and then batch manufacturing records, analytical control records, In-process records are reviewed by QA responsible person who is given authorization for release of batches. After release, the Finished Goods Stores personnel reviews the orders and demands from Party / Sale depot and distribute as per requirements of Party/Sales depot which are located in various parts of the country.
……proposes to export its Products to Forgien countries after completion of necessary registration in respective Countries.

Recording of the documentation related to distribution are maintained on SAP Systems in Warehouse.

### 8.2 Complaints, Product defects and Recalls:

#### Complaints:

A System is established for dealing with complaints that include written procedures indicating the responsible person (s) through whom the complaints are channeled. The responsible persons have adequate knowledge, experience and authority to decide the action to be taken.

All complaints concerning a product defect are recorded with all the original details and thoroughly investigated. The responsible person decides whether and what subsequent action is necessary. Based on the investigation subsequent Corrective and Preventive Action is taken. Complaint records are regularly reviewed for any indication of specific and recurring problems requiring attention and possibly the recall of Marketed Products. Whenever complaints are received, the nature of complaint is recorded in the Complaint Log Register along with other available details in Register. The complaint is investigated and evaluated thoroughly.

If a sample is accompanied with complaint the defect in the product/container/pack/is observed. Reference Samples are checked for Visual Inspection of particular batch.
Depending upon the nature of Complaints particular tests are performed on Control Samples if required. All the records pertaining to the Product, Batch No., Batch Manufacturing Record (BMR) and Analytical Control records are checked thoroughly for the particular complaint. An immediate action is taken for show cause notices of Drug Authorities. On investigation and evaluation, if the

product recall is necessary, immediate withdrawal letter is sent to all the depots or stockiest. An appropriate follow up action is taken in case of product recall. Suitable replies to all concerned are made at an early date. The Head QA & Head-Operations are responsible for handling the product Complaints. Details are available in Handling of Product Complaint Record.

### Product Recall:

Recall refers to the removal of specific batch or batches of the product from market. The recall may be initiated by the manufacture or the distributor either following the reports of adverse reactions or as the failure of ongoing Stability Studies or under the directions of the Regulatory Authorities.
In case of Product Recall following Procedures are adopted.
The purpose of recall is to ensure rapid and effective withdrawal of the drug from the markets, depots, stockiest, institutions etc. In case if any complaint received to avoid any untoward effects to end user (Patients). First of all determine:

1. The reason of recall.
2. The degree of recall. (Type of complaint whether of serious nature or other external) damages to product container / packs / labels etc. This includes severe shivering, Anaphylactic Shocks or any other serious problems to any patient.

The Distribution Records are readily available to the person (s) responsible for recalls and contain sufficient information on wholesalers and customers (Addresses, emergency and 'Out of Hours' contacts and telephone numbers, batches and amount delivered), including exported products and medical samples. Recalled products should be identified and stored separately in a secured area while awaiting a decision. The progress of recall process is recorded and a final report is to be issued that includes reconciliation between the delivered and recovered quantities of the products.
Effectiveness of the recall is checked periodically to evaluate the recall process.

## 9.0 SELF INSPECTIONS:

### Short Description of Self Inspection:

The purpose of Self-Inspection is to evaluate the compliance with cGMP in all aspects of Production and Quality Control. The Self-Inspection program is designed to detect any shortcomings in the implementation of cGMP and to recommend the necessary corrective actions.
Self-Inspections are performed yearly and whenever required in case of product recalls, repeated rejections or before any inspection by regulatory authorities.
Self- Inspections Team is appointed by the Management from staff who are expert in their own field and familiar with GMP & cGMP requirements.
The Team consists of:

**i) Head-QA** **ii) Head- QC** **iii) Head-Operations** **iv) Head- Engineering**

The Team responsible for Self-Inspection consists of personnel from CQA department who can evaluate the implementation of cGMP. All recommendations for corrective action are implemented.

The Procedure for Self-Inspection is documented and effective follow-up program is taken within a fixed time period for implementation of Corrective Action and Preventive Action.
The Standard Operating Procedure is in place that defines frequency, Planning, Selection of Team, Execution and Reporting System.

### Frequency for Self Inspection:

Self-Inspections are performed yearly for Production/Quality Assurance/Quality Control Department /HR/Utility Sections, including Water System and Air Handling System. Self-Inspections may also performed whenever required in case of product recalls, repeated rejections or before any inspection by regulatory authorities.

### Points for Self Inspection:

Following items are included in routine Self Inspection Program:

- Personnel, Premises including Personnel Facilities, Maintenance of Building and Equipment, Storage of Starting Material and Finished Product, Equipment, Production and In-process Controls, Quality Control, Documentation, Sanitation and Hygiene, Validation and Revalidation Programs, Calibration of Instruments or Measurement System, Recall of Product (if any), Complaints Management, Labels Control, Results of previous Self Inspections and Corrective steps taken and Training.

### Self Inspection Report:

A report should be made after completion of Self Inspection.
The report includes:

- Self Inspection Results
- Evaluation and Conclusion
- Recommended and Corrective Actions

### Follow up Action:

Self Inspection Team evaluates Self Inspection Report and Corrective & Preventive Action (CAPA) Report.

### REFERENCES:


- PIC/S Guidelines “Explanatory Notes for Pharmaceutical Manufactures on the Preparation of a Site Master File” PE 008-04 (1 Annex) -1 January 2011.

- WHO Technical Report Series, No.961, 2011; Annex14 “WHO guidelines for drafting a Site Master File”.