VALIDATION MASTER PLAN

PHARMA DEVILS

(Oral Solid Dosage & Injectable Facility)

APPROVAL:

Approval of this Validation Master Plan indicates agreement with the strategies and principles as outlined, and commitment to support the validation activities of the **Tablets, Capsules, Liquid Injectable, Dry Syrup & Dry Injectable** at ……...

Following signatures signify review, approval and authorization of this plan.

PREPARED BY:

Functional Areas	Name	Signature	Date
Quality Assurance			

REVIEWED BY:

Functional Areas	Name	Signature	Date
Engineering			
Production			
Quality Control			
Quality Assurance			

APPROVED BY:

Functional Areas	Name	Signature	Date
DGM Quality Assurance			

AUTHORIZED BY:

Functional Areas	Name	Signature	Date
General Manager (QA)			

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1.0 INTRODUCTION

……..is a professionally engaged Pharmaceutical company, manufacturing various dosage forms and has emerged as a reputed pharmaceutical formulation manufacturer .The company enjoys a rich manufacturing experience of over 28 years. The company has another two units in the nearby vicinity manufacturing pharmaceutical formulation in various dosage forms. The site manufactures Tablets, Capsules, liquid Injectable, dry Syrup & Dry Injectable General category. The formulations manufactured are generic and patent and proprietary medicine and for HUMAN USE ONLY.

2.0 OBJECTIVE

The objective of the Validation Master Plan (VMP) is to summarize the philosophy, intentions and approach to perform validation activities in accordance with current good manufacturing practices (cGMP)/current good laboratory practices (cGLP). Thus presents an overview of the entire validation operation, its organizational structure, its content and planning. Approval of the validation master plan signifies agreement with the validation strategy as outlined and support for the ongoing control and maintenance of manufacturing, testing and storage of Drug Products.

3.0 SCOPE

This validation master plan shall apply to all the validation activities done in Tablets, Capsules, liquid Injectable, Dry Syrup & Dry Injectable in General block at …….. The validation activities apply to the following:

1) Manufacturing

Critical Manufacturing Equipment / Instrument Qualification,
Facility Qualification,
Process Validation (PV),
Cleaning Validation (CV)
Revalidation/Re-qualification (RQ)

2) Storage

Critical equipment/Instrument qualification,
Storage area qualification

3) Testing

Critical sampling and testing equipment/Instrument qualification
Analytical method validations
Analyst Qualification.

4) Critical Utilities

Air handling unit qualification
Purified water system qualification
Compressed air system
Nitrogen Generation System
Water for injection
Pure steam generation system.

5) Critical Software/Computerized System Qualification
Programmable logic controls (PLCs) of all critical equipment's/instruments
Inventory Software Qualification
Excel Sheet Validation

4.0 VALIDATION RESPONSIBILITIES

The validation activity is joint responsibility of personnel from various functional groups (Quality assurance, Quality control, Production, Warehouse and Engineering) in the plant. The functional group and their responsibilities are as follows:

4.1 Production

The Production personnel are responsible for ensuring the validation of equipment and processes used within the department. The responsibilities include:
Review of validation master plan.
Preparation of validation plans.
Preparation, review and execution of validation protocols as required.
Providing all necessary resources during validation/ qualifications.
Develop, review departmental SOP's as appropriate.
protocol execution.

4.2 Engineering

The responsibilities of the engineering department include:
Review validation master plan.
Preparation, review and execution of validation protocols, as required.
Supply all supporting documents for equipment / utility qualification.
Provide technical assistance in protocol execution as appropriate.
Provide required utility support during validation execution.
Preparation of validation reports after protocol execution.
Maintenance and timely calibration of equipment, instruments and utilities.
Develop, review departmental SOP's as appropriate.

4.3 Quality Assurance

The responsibilities of the Quality Assurance department include:
Responsible for preparation of validation master plan
Approval validation Master Plan and Validation schedules.
Responsible for the co-ordination of all the validation activities at the site as per schedule.
Review and approval of validation protocols & reports.
Approve the departmental SOP's as appropriate.
Maintain the completed, approved validation documentation.

4.4 Quality Control

The responsibilities of the Quality Control department include:
Responsible for qualification activities of laboratory equipment.
Responsible for managing validation of analytical methods.

Responsible for Analyst validations.
Preparation, review relevant validation protocols and reports.
Manage the laboratory testing necessary for protocol execution.
Develop; review departmental SOP's as appropriate.

5.0 MANUFACTURING FACILITY DESCRIPTION

5.1 Premises

Site is situated at Plot No. 12 & 12A, Industrial Park -2, of Haridwar, Uttarakhand State. The site is 12 Km. away from the Haridwar railway Station and well connected by road on Delhi-Haridwar National Highway No-58. The site is 55 Km. away from Jolly Grant airport Dehradun. Haridwar is well connected to all major cities of the country by air, road and railway. Shipment facilities are available from Delhi airport about 200 Km. from the manufacturing site and regular rack movement is also available from Kandla and Mumbai ports.
Surrounding area of the site is a green belt and pollution free. The site is surrounded by on the east side by Meenakshi Polymer units, on the west side by Park, on the north Road 20 mtrs. & South side by Village Road. There are no units nearby which generate smoke or hazardous waste.

Manufacturing unit is separated for General block & Cephalosporin Block.

The facility also has administration office, Canteen, Utility area and effluent treatment area.

The formulation facility consists of the following:

- Administration Office
- Production Department
- Quality Assurance Department
- Quality Control Laboratory
- Raw Material Warehouse
- Packaging Material Warehouse
- Engineering Department
- Finished Goods Store

In General Block - Solid oral dosage and parental dosage building are separate for pharmaceutical product manufacturing: - Parental block two storied building constructed in 2010 comprising of separate processing area & packing area for parental. Basement comprises of Ware house for packing material Parental, Secondary/Tertiary Packing Material for solid oral and Finished Goods Store. Ground floor comprises of Separate Quality Control, Warehouse for Parental raw material & solid oral raw material store/ Primary Packing Material Store. First floor comprises of Parental manufacturing. The second floor comprises of Quality assurance, Administrative and water system. The top floor comprises of stability section.

Separate two stories Building is there for Solid Oral Dosage for Manufacturing and Packing area.

5.2 Nature of construction and finishes

The building is constructed of brick walls cement masonry, powder coated composite G.I. sheets and reinforced cement concrete. Walls are of modular panels and bricks, made smooth, free from pinholes

are painted with synthetic enamel color to enable proper washing. Floors are of epoxy & Kota Stone. The joints are filled with epoxy. The sanitary fitting are concealed and drainage system is under ground and provided with trapped gullies to prevent back flow. Insect killers and air curtains are provided at various points. There is a pest and rodent control for the facility. All doors and windows are flushed to the wall and have a smooth finish. Each processing area is provided with an independent flush door. The foundation of the facility has been given anti termite treatment. The corridors are designed to enhance viewing of the manufacturing operations without physically entering the processing areas. Fire extinguisher is located throughout the facility. There are emergency exit at suitable positions. Door interlocking systems are installed at relevant points. Fire alarm control system is installed at relevant points. Entire aseptic processing area for Liquid injection & Dry powder are made of SS-316L.

5.3 Purified water plant, Water for injection:

Source of water supply is from 2 bore wells with depth 160 feet. Freshly drawn water from the bore well is collected into underground RCC tank (60KL) by pump with online dosing of 2-3ppm chlorine with the solution of Sodium Hypochlorite. The water then passed through multigrade filter to remove suspended matter if any. Raw water then transferred through softener to reduce the hardness to below 5 ppm. The soft water is then stored in soft water storage tank (capacity 5KL).The water then treated with Sodium Metabisulphite solution with a online dosing to oxidize excess of chlorine and monitored through ORP meter oxidation up to less than 400 mv. The ORP meter (oxidation Reduction Potential) is installed in the feed line to RO to check for chlorine free water. Chlorine free water is supplied along with anti scaling dosing to RO- 1 & RO- 2 then to Mixed bed & UV for making Purified Water. The capacity of the RO System is 3000 Ltr./hr. To check the conductivity, the conductivity sensor is installed in the supply and return loop of the distribution system. The conductivity of the purified water is continuously monitored through Programmable Logic Control panel and in the event of variation in the conductivity; it automatically drains the water instead of going into the storage tanks with help of online dumping valve. Finally conductivity passed purified water is stored in Purified water storage tank. The capacity of the Purified water storage SS316L tank is 3KL. This water system is installed in general block and distributed through a closed recirculation loop inside the plant for appropriate user points at ambient temperature. One point of loop is going to cephalosporin block with proper slope and controlled manner to fill the purified water storage tank of cephalosporin block. Purified water storage tank capacity is also 3KL for cephalosporin block. Stored Purified water recirculated in closed loop and distributed through loop with appropriate user point at ambient temperature in cephalosporin block separately. The conductivity monitoring sensor is installed at the return loop. The conductivity of the purified water is continuously monitored through Programmable Logic Control panel and in the event of variation in the conductivity; it automatically drains the water instead of going into the storage tanks with help of online dumping valve.

Purified water is used to produce Water For Injection. To get high quality Water For Injection, installed 1 Multi Column Distillation Plant at general block. The capacity of the Multi Column Distillation Plant is 1000Ltr./hr. This unit is fully automatic and Micro processor based. Water for injection stored in water for injection tank (Capacity 3KL). This water for injection system is installed in general block and distributed through a closed recirculation loop inside the plant for appropriate user points at temperature 80-90°C. One point of loop is going to cephalosporin block with proper slope and controlled manner to fill the water for injection storage tank of cephalosporin block. Water for injection storage tank capacity is 1KL for cephalosporin block. Stored water for

injection recirculated in closed loop and distributed through loop with appropriate user point at temperature 80-90°C in cephalosporin block separately.
Vent filters provided to Purified water storage tanks and Water for Injection storage tanks. Storage tank temperatures are continuously monitored through temperature thermograph. Fresh WFI is always taken for final rinsing of Vials/Ampoules and rubber stoppers for dry injections.

5.4 Pure Steam Generation and Distribution:

For General Block: Units are having an outlet of water vapor (i.e. Pure Steam). This pure steam (i.e. generated from Pure Steam Generator) is used for flushing and cleaning and in sterilization of our process pipe lines and machines in production areas. Capacity – 300kg /Hr. Make - Pharmalab.
For Cephalosporin Block: Units are having an outlet of water vapor (i.e. Pure Steam). This pure steam (i.e. generated from Pure Steam Generator) is used for flushing and cleaning and in sterilization of our process pipe lines and machines in production areas. Capacity – 150kg/Hr. Make -Pharmalab.

5.5 Manufacturing area for Injection, tablets and capsules. General Block:
An area of 1058 square meters is provided for Basement, Ground & First floor for general Injection, Second floor is for Quality assurance, administrative office, Utility and stability. In the General second building, Ground Floor is for Tablet Section, First floor for Tablet & capsule section and second floor is for utility Section.

The flooring is done with Epoxy coating. Conduit wiring & ceiling flush electrical fixtures are provided. Aluminum Doors are powder coated. Door interlocking system is provided as applicable, Fire alarm control system and CCTV camera is installed as applicable. Separate Air handling Unit with 0.3 micron filtration is provided.

5.6 Manufacturing area for Cephalosporin Block:
The covered area of 813 square meters is provided for Ground floor Tablets & Dry Syrup section, First floor QC & Dry Injection section & Second floor Utility section.
This area is constructed in RCC structure and composite panels. The flooring is done with epoxy with coving; conduit wiring and flush electrical fixtures are provided. Doors are of Aluminum powder coated**.** Separate Air handling Unit with 0.3 micron filtration is provided.

6.0 FUNCTIONAL DESCRIPTION OF UTILITIES

6.1 Air Handling System

Air Handling system is designed as per the GMP requirement in each area of the plant. Separate air handling units are provided for the critical production and support areas.
An environment monitoring program is in place to monitor the critical manufacturing areas.
The area for handling sterile products meets Grade-A requirements. The background of the Grade- A area meets the requirement of Grade-B.

For oral dosage forms the class of air in core processing area meets the requirement of Grade-D. Other area is also controlled but not classified. Pressure differentials are maintained as per the specified guidelines for the respective dosage forms. Temperature & Relative humidity in the different sections is as mentioned below:

Section	Temperature	Relative Humidity

Sterile Filling & sealing Liquid Injection	25 ± 2°C	55 ± 5%
Sterile Filling & sealing dry powder injection(General Block)	25 ± 2°C	20 ± 5%
Tablet Block	25 ± 2°C	50 ± 5%
Capsule Block	25 ± 2°C	40 ± 5%
All other controlled areas	25 ± 2°C	55 ± 5%

For Cephalosporin block manufacturing & Sampling/Dispensing of oral dosage forms the class of air in core processing area meets the requirement of Grade-D. Other area is also controlled but not classified. Pressure differentials are maintained as per the specified guidelines for the respective dosage forms. Temperature & Relative humidity in the different sections is as mentioned below:

Section	Temperature	Relative Humidity
Manufacturing, Filling & Sealing of Dry Powder Injection	23 ± 2°C	20 ± 3%
Dispensing, Mixing, Compression, Manufacturing & Filling for Tablets & Dry Syrup	25 ± 2°C	50 ± 5%
All other controlled areas	NMT 27°C	50 ± 5%

The ventilation system design is based on re-circulation of air. 80-85% of the air is re-circulated and 10-20% fresh air is taken from outer atmosphere. The air changes in the Grade-B area is not less than 60 Air Change/Hr and for Grade-C & D area is not less than 40 & 20/Hr. respectively.

Filtration system for different grade of area:

Grade of area	Pre filter	Return air filter	Fine filter	Final filter
GRADE-A	Not applicable	Not applicable	3µ (EU-7)	0.3µ (EU-13)
GRADE-B	10µ (EU-4)	10µ (EU-4)	3µ (EU-7)	0.3µ (EU-13)
GRADE-C	10µ (EU-4)	10µ (EU-4)	3µ (EU-7)	0.3µ (EU-13)
GRADE-D	10µ (EU-4)	10µ (EU-4)	3µ (EU-7)	0.3µ (EU-13)
Controlled but not Classified	10µ (EU-4)	10µ (EU-4)	Not applicable	3µ (EU-7)

6.2 Water System

The following types of water are available in the plant:

6.2.1 POTABLE WATER- For drinking, canteen and toilets.

6.2.2 PURIFIED WATER- For formulation and washing of equipment/components.

Source of water supply is from 2 bore wells with depth 160 feet. Freshly drawn water from the bore well is collected into underground RCC tank (60KL) by pump with online dosing of 2-3ppm chlorine with the solution of Sodium Hypochlorite. The water then passed through multigrade filter to remove suspended matter if any. Raw water then transferred through softener to reduce the hardness to below 5 ppm. The soft water is then stored in soft water storage tank (capacity 5KL).The water then treated with Sodium Metabisulphite solution with a online dosing to oxidize excess of chlorine and monitored through ORP meter oxidation up to less than 400 mv. The ORP meter (oxidation Reduction Potential) is installed in the feed line to RO to check for chlorine free water. Chlorine free

water is supplied along with anti scaling dosing to RO- 1 & RO- 2 then to Mixed bed & UV for making Purified Water. The capacity of the RO System is 3000 Ltr./hr. To check the conductivity, the conductivity sensor is installed in the supply and return loop of the distribution system. The conductivity of the purified water is continuously monitored through Programmable Logic Control panel and in the event of variation in the conductivity; it automatically drains the water instead of going into the storage tanks with help of online dumping valve. Finally conductivity passed purified water is stored in Purified water storage tank. The capacity of the Purified water storage SS316L tank is 3KL. This water system is installed in general block and distributed through a closed recirculation loop inside the plant for appropriate user points at ambient temperature. One point of loop is going to cephalosporin block with proper slope and controlled manner to fill the purified water storage tank of cephalosporin block. Purified water storage tank capacity is also 3KL for cephalosporin block. Stored Purified water recirculated in closed loop and distributed through loop with appropriate user point at ambient temperature in cephalosporin block separately. The conductivity monitoring sensor is installed at the return loop. The conductivity of the purified water is continuously monitored through Programmable Logic Control panel and in the event of variation in the conductivity; it automatically drains the water instead of going into the storage tanks with help of online dumping valve.

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Vent filters provided to Purified water storage tanks and Water for Injection storage tanks. Storage tank temperatures are continuously monitored through temperature thermograph. Fresh WFI is always taken for final rinsing of Vials/Ampoules and rubber stoppers for dry injections.

6.3 Compressed Air System

Five Oil free air compressors, with 94 CFM, each with drier provided to supply Process air & Instrument air. The compressed air is stored in a Air receiver, filtered by 2 micron filter at the header and dried to (-20°C dew point) by heat supplied from compression type air drier prior to distribution network @ 7.5 bar pressure. The header and distribution legs are kept under pressure. Where sterile air is required for product contact the air is sterile filtered by 0.2 micron filter local to the user point. Sampling provisions are ensured at appropriate locations.

6.4 Dust Extraction System

Tablet section is provided by Dust Extraction System. This system enhances filter cleaning / replacement time, reduces operators exposure to various process ingredients, provides clean working environment and meets GMP requirements.

6.5 Pure Steam Generation and Distribution:

For General Block: Pharmalab units are having an outlet of water vapor (i.e. Pure Steam). This pure steam (i.e. generated from Pure Steam Generator) is used for flushing and cleaning and in sterilization of our process pipe lines and machines in production areas. Capacity – 300kg/Hr. Make - Pharmalab.

Steam System:
For General Block: Steam is to be provided to the facility as a utility and is non-product contacting. The plant steam is generated by two oil fired boilers capacity 600 kg\hr – Make Thermax.
For Cephalosporin Block: Steam is to be provided to the facility as a utility and is non-product contacting. The plant steam is generated by one oil fired boilers capacity 400 kg\hr -Make Thermax.

6.6 Nitrogen Generation System:

For General Block: Nitrogen is to be provided to the facility as a utility. The Nitrogen is generated by PSA Based Nitrogen Gas Generation Plant Capacity: 15 Nm^3/hr. Make: Mass Gas, Delhi.

6.7 Electricity Supply:

……..has a electricity connection of - 1000 KVA, electricity supply from Electricity Board U.K. Apart from Govt. Supply ……has its own electricity generation by following generators:

1. 500 KVA - Make Jackson Ltd. - 2 Nos
2. 380 KVA - Make Jackson Ltd. - 1 No.
3. 250 KVA - Make Jackson Ltd. - 1 No.
4. 40 KVA - Make Jackson Ltd. - 1 No.

7.0 PROCESS/PRODUCT DESCRIPTION AND REQUIREMENTS

7.1 Process/Product Description

The plant is designed to manufacture and pack oral solid dosage (, un-coated tablets, Bilayered Tablets, Coated Tablets & Capsule,) and Parental (Dry & Liquid Injection) Dry Syrup formulations. As per the production schedule, QC released raw materials are brought to dispensing room where materials are dispensed for the respective batch. All the raw materials are weighed, dispensed and staged batch-wise. Dispensed materials are taken to the processing rooms for the product manufacturing.

7.2 Process / Product Requirements

The major functional departments like Manufacturing, Quality Assurance, Quality Control and Engineering are involved in the manufacturing of product. Minimum facilities with responsibilities of each department for product manufacturing are listed below-

7.3 Manufacturing (Production): engaged in manufacturing and all related activities. Facilities provided are

Granulation (Mixing, granulation, drying, sifting, milling, blending and lubrication)
Compression
Coating of Tablets
Capsule blending & Filling.
Packaging of tablets/Capsules in blister, Alu.-Alu. & strips.

Injection (Manufacturing, Filling & sealing of Vial/Ampoule/Bottles).
Packaging of Filled Vial/Ampoule/Bottles.

7.4 Quality Assurance - Engaged In,
In - Process monitoring of the manufacturing and packaging operations
Release of area, equipment for manufacturing or packaging operations
Release of finished products for distribution
Handling of change control, deviation and complaints
Maintaining the records/documents & control samples
Monitoring validation of process, facilities, equipment, systems
Document control etc.

7.5 Quality Control: Engaged in:

Analysis of Raw Material
Analysis of Packing Material
Analysis of Finished Product
Analysis of other samples (In-process, Validation, Stability)
Environmental monitoring
Water Analysis.

7.6 Warehouse: Engaged in

Receipt**,** Handling, Dispensing, Issuance/Distribution & storage of Raw, Packing Materials and Finished goods.

7.7 Engineering: Engaged In
Engineering department is engaged and maintain all the equipment, utilities and other facilities routinely on need basis and as per schedule to facilitate smooth manufacturing operation and all time compliance with cGMP. Also the department holds responsibility of producing and supplying purified water, compressed air and other utilities required for the manufacturing activities.

8.0 QUALIFICATION/VALIDATION OVERVIEW

Validation is a significant part of the ……..quality program. The purpose of the validation program is to establish documented evidence that provides a high degree of assurance that a specific Process, System or equipment consistently produces material meeting its predetermined quality characteristics.

Qualification and Validation documentation will consist of a predetermined selection from the following:

- Design Qualification (DQ)
- Installation Qualification (IQ) protocols and reports
- Operational Qualification (OQ) protocols and reports
- Performance Qualification (PQ) protocols and reports

- Process Validation (PV) protocols and reports
- Cleaning Validation (CV) protocols and reports
- Water validation
- HVAC validation
- Compressed Air Validation/Nitrogen gas generation validation
- Analytical Method validation
- Temperature Mapping
- Transport Validation

8.1 Design Qualification (DQ)

Where appropriate, a review of the developed design to ensure that cGMP compliance has been addressed at the design stage:
Compliance to user's requirements
Compliance with cGMP requirement
Practical validation tests are possible
The above requirements are ensured through following documentation where appropriate:
Vendor's Manuals and other technical documentation

The findings of the design qualification are documented and reviewed.

8.2 Installation Qualification (IQ)

IQ is the documented verification that the Critical Facilities, Systems, Equipment's and Utilities, as installed or modified, complies with specification & Design Qualification. IQ is inspection of System, Equipment, Instrument or Utility along with their supporting systems:

for conformance to design, purchasing and construction specifications and for verification of proper installation.

The IQ protocol contains a description of the system, including a discussion of intended use and major components. The execution of the protocol verifies the system's static attributes against the user and manufacturer's specifications. The system is examined for proper installation and connection of supporting utilities like compressed air and electricity. Physical condition of equipment, Model, serial numbers and identification number of equipment and major subsystems of each piece of equipment is recorded. Material of construction is verified for product contact surfaces through certificates provided by manufacturer. Critical supporting documentation, such as manufacturer's manuals, vendor test results/ certificates, purchase orders, specifications, drawings and any other required documentation are verified as available and are annexed or location is recorded. All instruments are identified for calibration during IQ and calibration completed prior to the start of OQ. Logbooks and Standard Operating Procedures (SOP) for Operation and cleaning, Preventative Maintenance schedule are identified. Variances from specifications encountered during IQ execution are identified and documented in a variance sheet, investigated and an appropriate course of action taken is documented.

A summary of IQ is written in IQ protocol after completion of IQ for review and approval, before proceeding to OQ. Certification of IQ document and summary indicates equipment is ready for OQ.

8.3 Operational Qualification (OQ)

The OQ is the documented evidence that the Critical Facilities, systems, Equipment's, Instruments and Utilities operate as specified throughout the entire range. The exercise will involve identification and testing of all critical variables. After successful completion of the IQ. OQ protocol is executed this describes the operational tests and measurements of key parameters for proper operation of the system.

OQ protocol is executed under following headings: objectives, methodologies and acceptance criteria etc. Controls are verified to test the ability of the system to provide adequate control over variables specific to each piece of equipment. Alarm / Safety features testing, wherever required, are conducted as part of the OQ. OQ includes calibration of instruments attached to the equipment / system and development & finalization of Standard Operating Procedures for Operation, Cleaning and Maintenance. All the calibrations are performed with calibrated instruments traceable to National Standards. Variances encountered during the OQ are recorded in variance sheet. Appropriate corrective actions are taken and documented. Acceptance of system with variance is justified. Any change(s) made to the system / equipment during the OQ must be routed through change control procedure and is documented with OQ report. A summary report is written at the completion of OQ within the executed OQ protocol for review and approval before proceeding to PQ or process validation or routine use, as applicable. On successful completion of the OQ activities the equipment / system will be released for routine use. PQ will be planned wherever necessary.

8.4 Performance Qualification (PQ)

PQ is the documented verification that the Critical Facilities, Systems, Equipments, Instruments and Utilities, with their Components as connected together, can perform effectively and reproducibly, based on the approved process method and product specification. On successful completion of IQ and OQ, the tests using production materials will be carried out. PQ includes testing a condition or set of conditions encompassing upper and lower operating limits. Test, Objectives, methodologies and acceptance criteria are defined and approved prior to execution. Where appropriate, a sufficient number of replicate studies are performed to determine the ability of the equipment and supporting controls to achieve reproducible results. Utilities testing may include capacity and quality measurements under actual operating conditions. The protocol may incorporate peak load challenges to the intended operating range of the equipment / supporting controls. Performance qualification may also be clubbed with process validation and data shall be reviewed, summarized and attached to the qualification document. System challenged with worst case scenario will also be performed, if applicable. Any variance encountered during the PQ is identified for review. Exceptional conditions are investigated and the appropriate corrective actions are taken. After completion of PQ, summary report is prepared for the activity indicating the key parameters tested and results. The report is reviewed and approved by Operating department, Engineering and Quality Assurance as a part of closing of the qualification and handover of the equipment / system for routine use. For some equipment/instruments IQ, OQ and PQ protocol may be prepared separately or in conjunction.

9.0 VALIDATION REQUIREMENTS

9.1Facility Qualification

Facility qualification is done to ensure that the facility meets the product, process and cGMP requirements. The facility qualification involves verifying that each operational area is suitable for its intended use.

Following are the parameters generally considered as a part of facility qualification

Men-Material Flow
Layouts / Dimensions of area
Construction / finish of the area
Civil accessories like doors, drains, wall railings etc.
Electrical accessories like tube light fixtures, electrical points etc.
Utilities in the area like water, compressed gases etc.
Heating Ventilation and Air conditioning system connected
Environmental Monitoring
Luminance Level
Facility/Area re-qualification is undertaken when major modification to the facility is carried out.

9.2Equipment/Instrument/Utilities Qualification

Qualification is a subset of validation and is documented evidence that provides confidence that equipment, instruments, facilities, or utility systems have been selected, designed, installed, constructed and/or operated, as intended, and meets pre-determined specifications.

All the equipment/Instrument/Utilities newly received, installed, or after major modification shall be qualified before taking into actual use. All critical equipment/Instruments/utility will go through all the steps defined i.e. DQ/IQ/OQ/PQ, wherever applicable.

Utilities, services and equipment scheduled for qualification must be mechanically completed at the commencement of qualification. The documentation is generated in a sequential manner that is compatible with the execution of the qualification programme. IQ is performed before OQ, followed by PQ, process validation and cleaning validation as required by the specific piece of equipment or utility.IQ, OQ and PQ can be combined into a single study, depending on the complexity of the equipment. Although when combined it is a single document, it is composed of IQ section and OQ section and as appropriate a PQ section which are completed sequentially. At the judgement of the QA head, combined IQ and OQ or combined IQ, OQ and PQ protocols will be prepared for less complex equipment and systems. PQ of the process equipments may be done using production material or can be clubbed with process validations and data shall be compiled, reviewed and documented.

For Non-critical or ancillary equipments, qualification may be completed with IQ and OQ. DQ may not be essential for Standard models available in market like Dissolution test Apparatus. Upon completion of the equipment qualification, these are placed on calibration and preventive maintenance schedules. For the equipments which are transferred from other plants to the facility, IQ/OQ/PQ shall be performed. The old equipments, for which qualification had not been performed during installation, shall be re-qualified and verified for its static, operational and performance attributes.

Any variances reported during any stage of qualification is documented in variance sheet and corrective action is taken or acceptance of equipment with variance is justified.

9.3 Heating Ventilation and Air Conditioning (HVAC) System Qualification

The HVAC system helps in maintaining the environmental conditions as required for manufacturing of pharmaceutical products. It also helps in preventing cross contamination by maintaining pressure differentials. It is one of the most critical utilities for all the processing areas where the product or its intermediates are likely to be exposed to the environment. The improper operation of HVAC systems may adversely affect the quality of the product especially in the manufacture of moisture sensitive products, as the temperature and humidity of area is controlled by HVAC system. Steps for qualification of new system is similar to the qualification of equipment's or system as defined above. In routine, the parameters related to the HVAC system which shall be verified / validated at defined frequency for a particular facility are as follows.

Temperature & relative humidity
Room air pressure differentials
Air flow Visualization
HEPA filter integrity
Airborne particle count
Air flow velocity
Air changes
Room recovery study

All the parameters may not be applicable for a particular HVAC system under consideration. The methodology for verification of the various parameters applicable to the tests shall be mentioned in the protocols designed specifically for each area.

9.4 Water System Qualification

Quality of products is heavily dependent on the quality of water used in production stage or to clean components, equipment, and other surfaces. Water quality is defined in terms of chemical and mainly microbiological purity. Steps for qualification of new system is similar to the qualification of equipment's or system as defined above. Initial qualification of water system in first stage involves operational parameters and the cleaning / sanitization / sampling procedures and frequencies development. It demonstrates that the system will consistently produce desired water quality when operated in conformance with the SOPs. This stage generally runs from 2 to 4 weeks. Second stage demonstrates that when the water system is operated in accordance with the SOPs over a long period of time it will consistently produce water of the desired quality. Any variations in the quality of the feed water that could affect the operation and ultimately the water quality will be picked up during this phase of the validation. This stage runs for 2 to 4 weeks. After successful completion of first stage, system is handed over for routine production usage. Third phase runs for 1 year study duration, wherein seasonal variance study is conducted i.e. Trends of chemical and microbial parameters shall be evaluated.

Details of water system (generation and distribution system), along with the sampling points, Frequency of sampling shall be followed in accordance to the current SOP related to Water system. For periodic qualification of the water system the trends of various parameters monitored shall be evaluated. If the data suggests, necessary changes wherever required, modification, monitoring frequency and revalidation shall be considered.

9.5 Compressed Air System:
The same approach as defined for Equipment/Instrument/Utilities Qualification shall be followed for qualification

9.6 Nitrogen Gas
The same approach as defined for Equipment/Instrument/Utilities Qualification shall be followed for qualification

9.7 Pure Steam Generator:
The same approach as defined for Equipment/Instrument/Utilities Qualification shall be followed for qualification

9.8 Water for injection:
The same approach as defined for Equipment/Instrument/Utilities Qualification shall be followed for qualification

9.9 Temperature Mapping:

The temperature Mapping shall be performed for Evaluation of Temperature and Relative Humidity in the key areas (controlled area) and related Equipments to assure the area & related Equipments is under controlled environmental condition. The temperature Mapping shall be carried out 72 Hrs. for Controlled areas and 24 Hrs. for related Equipments.

9.10 Transport Validation

Transport Validation in such a manner that transport temperatures meet local regulatory requirements at the sending and receiving sites and/or so that temperature excursions above or below the manufacturer's labeled storage temperature range do not adversely affect product quality. Product stability data must demonstrate the acceptable temperature excursion time during transport. The **three** consecutive batches/runs will be studied in validation.

10.0 PROCESS VALIDATION

Process Validation is to "establish documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes". Staff taking part in the validation work should be appropriately trained.

Process validation documentation shall include, but not limited to-

Purpose of the document
Scope of the document
Personnel responsibility
Short description of the process and flow diagram
List of the equipment/facilities to be used (including measuring / monitoring / recording equipment) together with its calibration status
Proposed in-process controls with acceptance criteria
Sampling plan

The product performance characteristics/attributes to be monitored, together with the test method;

Finished product specifications and acceptable limits for release
Methods for recording and evaluating results

The above parameters are for guidance purpose and may change as per requirement. Unless significant changes are made in the validated state of the process or product, re qualification shall not be carried out. However re qualification is considered where there are negative trend and investigation warranting the same.

The Validation of Product /Process are of different type depending upon the approach used to carry out the activity: Details of each type are given below-

Process Validation is to "establish documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."

The Validation of Product /Process shall involve following types depending upon the approach used to carry out the validation activity:

10.1Prospective Process Validation

Prospective validation is validation carried out before routine production of products. This approach is followed for all new products to be manufactured at site. Based on the requirement of the process, risks associated and identified key parameters, experimental protocol shall be generated and the parameters shall be established in the initial /optimization/experimental batches. After establishing the key process and product parameters **three** consecutive batches shall be validated for confirming the predefined parameters written in the validation protocol. These validation batches shall be kept for complete **stability study**.

For prospective process validation, minimum of **three** consecutive batches are evaluated to meet pre-determined acceptance criteria. Batch size of such batches shall be same as intended for commercial scale batches. The sampling and testing plan is defined based on an evaluation of the process to be validated. If it is intended that validation batches be sold or supplied, the same shall be done after completion of validation exercise, receipt of all data & results, its review and compliance and final approval by Quality head. As a prerequisite to process validation, all equipment, facility and analytical testing methods to be used shall be validated. Staff taking part in the validation work shall be appropriately trained.

10.2 Concurrent Process Validation

Concurrent Validation is validation carried out during routine production of products. This involves monitoring of critical processing steps and end product analysis to generate data to establish that the process is under control.

Following are the instances where it is appropriate to validate a process during routine production- Change in process or product parameters, any negative trend observed in the process or product parameters, change in manufacturing facility, on the basis of findings of annual product review, change in raw material supplier etc. In any case **three** consecutive batches/runs will be studied.

The batches may be kept on **stability study** depending upon the reason for which the validation is carried out. The completed protocols and reports should be reviewed and approved before product is released for sale or supply.

10.3 Retrospective Process Validation

This type is applicable for the well-established products and for which prospective or concurrent validation is not done. Validation of these processes is possible by using analytical and other quality data from batches manufactured during review period. The historical data from batch processing and packaging records, process control charts, maintenance logbooks, records of personnel changes, process capability studies, finished product data, including trend, market complaint and storage stability data will be used for retrospective validation. Batches selected shall be representative of all batches made during the period, including any batch that failed to meet specification. A sufficient number of batches (normally **3 and** above**)** shall be considered to demonstrate process consistency. On the basis of the findings or trend observed in review, the concurrent validation may be planned for the product.

11.0 CLEANING VALIDATION (CV)

Cleaning Validation provides a high degree of assurance that the cleaning process effectively and consistently removes product and cleaning agent residues to predetermined acceptable levels. Cleaning procedures are equipment specific. With the introduction of new product into the existing equipment train, an assessment will be made with respect to cleaning feasibility of the equipment. During this evaluation, the degree of effectiveness of the cleaning procedure for the product to be manufactured is determined. If required, cleaning procedure is revised and revalidated or effectiveness of the existing cleaning procedure is validated upon the manufacturing of new product.

A detailed approach for cleaning validation is documented in the **SOP**.

12.0 COMPUTERISED SYSTEMS VALIDATION

Computerized system validation applies to Critical Equipment's, Instruments, Systems and business systems which are controlled with a programmable computer, including programmable logic controllers (PLC). The approach to computerized system validation incorporates all of the other elements of validation discussed in this Site Validation Master Plan, including IQ, OQ and PQ. Only **GMP** related computerized systems shall be validated.

Specifications are also prepared with key areas to be verified by installation checks and functional tests. Engineering drawings and manuals where appropriate are a part of the specifications.

Where applicable, the vendor will be requested to provide or allow access to copies of validation related documentation including software test plans and results. Adequate vendor documentation may reduce the amount of validation work that needs to be performed. Conversely, when there is little or no documentation available, the system user will need to develop test procedures necessary to assure the software will consistently perform according to predetermined specifications.

13.0 SANITIZING/DISINFECTING AGENT VALIDATION

Antimicrobial agents (sanitizing/disinfecting agents) help in maintaining microbiological load in the area under control at all the times during the production. To avoid the risk of microbes developing resistance to sanitizing/disinfecting agents; they will be used in rotation as per validation data provided by quality control which also describes the procedure and concentration to be used. Any new disinfectant, before recommendation for use in facility for disinfecting or sanitizing purpose will be qualified for its efficacy to kill or minimize the bio-burden. On the basis of the study the frequency and concentration of the same will be incorporated in the relevant SOP.

14.0 REVALIDATION AND RE-QUALIFICATION (RQ)

Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. The approach for the revalidation/re-qualification shall be defined in respective protocols.

14.1 Equipment Re-qualification

After major breakdown or replacement of major component in the equipment or relocation of equipment will be considered for re-qualification of the parameters to ensure that equipment remains in the validated state. Otherwise after every **5 years**, based on the date of qualification, shall be re-qualified for operating parameters and documented. Portable equipment's, which are moved, need not to re-qualify for change of locations. Periodic re-validation of Autoclave & Tunnel shall be carried-out **twice** in a year. Washing Machine, Filling & Bunging Machine and Sealing Machine shall be carried-out in a **two** year.

14.2 Process Re-validation

The major change in process will require for revalidation of the critical parameters to show that it does not affect product quality. The process will be revalidated in case there is known changes. For example: formula, critical equipment, critical process parameters, batch size, site and change in vendor for API. The critical parameters identified in the prospective or concurrent validation will be monitored during revalidation. The number of the batches to be studied will depend on the nature of change for which study is planned. In case there is no change in process, re-validation shall be carried out once in **5 years**.

14.3 Facility / HVAC Re-qualification

Re-qualification of facility shall be carried out only when there is major modification or changes introduced. In HVAC, apart from the parameters monitored routinely like temperature, RH, pressure differential and microbial monitoring, other parameter shall be verified **once in year** for all class and Non Viable Particle count shall be **twice** in year for class B, C and class A area. Review of routine parameters and compilation of other parameters shall constitute re-qualification.

14.4 Water System Re-qualification

Any major changes in water system needs for re-qualification. Data generation will be depending on the nature of changes. Data trends for routine monitoring parameter shall be prepared periodically and reviewed.

14.5 Cleaning Re-validation

Re-qualification shall be carried out in case on change in Equipment / Cleaning process/ product and Introduction of new product in the same equipment chain.

14.6 Analytical Method Re-validation

All non- pharmacopoeial analytical methods shall be validated prior to routine use. The re-validation will be carried out in case of any change in the method or critical components like column, mobile phase etc. The introduction of new component in the product will also require re-validation of the test method. The extent of the study will depend on the type of change taken place.

14.7 Transport Re-Validation

Transport Re-Validation shall be carried out in case of change in formulation of Product and change in Storage condition of the product.

14.8 Temperature Mapping

Temperature Mapping shall be carried out once in a year and in case of change or modification of the controlled areas and any critical change in related equipments.

15.0 DOCUMENTATION

15.1 Validation Documentation

Before commencing the validation/qualification activity a protocol specifying critical steps, and acceptance criteria. Protocol also includes purpose, responsibility of personnel and detailed procedure for validation / qualification activity. If party's qualification document is available the same may be reviewed, executed, referred and attached to the in-house qualification document. During review of the party's documents, if any deficiency is observed, only the same study/tests shall be done in-house.

After completion of validation / qualification activity summary of results obtained, any deviations or variance observed, recommending and closing of variances, conclusion will be documented in protocol or report (as applicable). Any changes to the plan as defined in the protocol will be

Documented with appropriate justification. Report generated by the external contract party will be part of the qualification /validation document. After completion of satisfactory qualification, a formal release for the next step in qualification / validation will be made.

A validation package consists of final report, completed protocols, and all supporting documentation gathered. The package is reviewed and approved. Protocol & Report will be reviewed and approved by concerned department head/ designee. These documents shall be identified by unique numbers. All the approved protocols and completed validation documents are archived with QA.
After qualification, if some parameters or tests are identified to be performed, the same shall be carried out as supplementary qualification (Addendum) and attached to the existing qualification document.

15.2 Qualification/ Validation Matrix

The matrix provides summary of validation steps applicable for equipments in the facility.

15.3 Standard Operating Procedures (SOP)

To ensure that all operations are performed consistently, written and approved SOPs are developed. The procedures need to be clear, concise, and written at the anticipated user/ operator educational level to eliminate any misinterpretation of the operational instruction.

Preparation, Approval, Revision and Control of Standard Operating Procedures shall be done as per SOP. SOPs shall be written to address all activities (that may affect product quality directly or indirectly) performed in the facility, including documentation, facility cleaning and monitoring, component and semi-finished material handling, control of personnel movement, equipment and system operation, maintenance, cleaning, calibration and personnel training.

16.0 ADDITIONAL PROGRAMMES

The following programs are developed to ensure that operations relating to product manufacturing and release comply with current Good Manufacturing Practices.

16.1Change Control

A change control program and procedure ensures that equipment, systems and processes remain in a state of validation. The procedure outlines steps to follow when a change is proposed for a critical system or process that is under validation or has been validated. All these changes will be formally requested, investigated, documented and accepted by representative of production ,QA/QC, Engineering and Regulatory affairs (as applicable).

The change control program ensures that proposed changes are reviewed and approved by appropriate departmental representatives prior to initiating changes. The review also defines the required tests and documentation to be performed to verify that the system, equipment, and process remain in a validated state.

16.2 Deviation

The deviation encountered during the execution of process / cleaning validation protocols is handled and investigated through SOP. For equipment/utilities qualification, all variances/ deviations encountered during protocol execution are reported in the qualification protocol with due investigation and corrective actions taken. Deviations are results not meeting the expected results or mismatches between the protocol and the physical reality of the system or piece of equipment.

16.3 Calibration and Preventive Maintenance

A calibration program is available to maintain instrumentation within acceptable operational limits. The operational limits for calibrated instruments are based on system and processing requirements. All equipment used to perform calibrations must be calibrated to standards traceable to the recognized national/ international standards. Procedures relating to frequency of calibration, how to calibrate, and documentation of calibrations are available. A schedule for calibration is required to assure instrumentation maintains defined acceptance criteria. This calibration system apply to all calibration required at the site, including those performed by …….., third party and equipment vendors as part of routine maintenance. A preventive maintenance (PM) program is also available to maintain all manufacturing and packaging equipment and support systems in proper working condition and reduce equipment malfunctions.

16.4 Training

An induction training program is available for all the new recruits to accustom to the new work environment and systems. Job specific training is given to the employees in all activities they are required to perform, as well as in applicable cGMP. SOP training is ensured before the procedure is made effective. All the training is appropriately documented. The effectiveness of the training is ascertained by way of oral, written and practical tests. Persons engaged in specific validation related task shall be qualified on the basis of education, training imparted to them and / or experience gained by them in performing these tasks.

16.5 Annual Product Review

Annual Product Review shall be carried out for Products manufactured during the calendar year to evaluate process tolerance. Annual Product Review shall contain the following details: The annual product review shall be carried out once in a calendar year. There shall be minimum **Five** batches for annual product review.

Review of batch data.

Review of finished product analytical data.

Review of deviations and investigations.
Review of change controls.
Review of stability data.
Review of market complaints / product returns / product recall / Product Failure.
Physical observation of control samples.
Review of validations and need for revalidation/performance verification.

17.0 VALIDATION PLANNING & SCHEDULING

The new equipment validation/qualification are planned based on qualification schedule change control raised for introduction of new equipment in the facility. For existing equipment's a re-qualification is prepared based upon the equipment / instruments qualification status of various departments. The re-qualifications shall have an excursion period of 30 Days with respect to the scheduled date. In any case, new equipment / instrument / system / product / facility shall be qualified before taking into routine use and details shall be included in the schedule, whenever activity is taken.

18.0 REVISION CONTROL

The Validation Master Plan shall be reviewed and revised once in **two** years or if required to include any Critical modification to update the contents including the validation status of facilities, equipment and process. Validation/Qualification Status and Validation /Qualification Schedule shall be updated to keep the Qualification/Validation Status current.

19.0 ANNEXURE:

ANNEXURE	DESCRIPTION
Annexure-I	Equipment qualification/Validation matrix
Annexure-II	Laboratory equipment qualification/Validation matrix
Annexure-III	Validation planner for air handling unit
Annexure-IV	Validation planner for equipment's
Annexure-V	Validation planner for laboratory equipment's
Annexure-VI	Validation planner for Process Validation
Annexure-VII	Validation planner for Analytical Method Validation
Annexure-VIII	History sheet for annexure to VMP

20.0 REASON FOR REVISION:

S.No.	Supersedes No.	Review Date	Reason for Review	Change Control No.	Approved By
1.	00				