1. Purpose

The purpose of this Validation Master Plan is to define the scope of necessary activities to successfully validate the NEW facilities, utilities, equipment, and processes used in the manufacture of PRODUCT at COMPANY in CITY, ST.

Company is building additional production and warehouse Buildings B and C to support manufacturing Product A, B, C at the existing production facility in City, ST.

2. Scope

The scope of this Validation Master Plan is limited to the following:
Company
New Buildings B, C
Product A, B, C
Existing Building A.

The following topics will be discussed in this Validation Master Plan:

- The scope and intended use of the facility
- A description of critical utilities, process equipment, and support equipment.
- The qualification / validation overview and approach

3. Responsible Functions

Manufacturing
Facilities
Engineering
Validation
Quality Control
Quality Assurance

Table 1 below provides an overview of the Validation Lifecycle documents and activities and the departmental responsibilities related to each. Specific roles and responsibilities will be included in the corresponding qualification or validation protocols.

Table 1: Qualification Documents and Activities

Document or Activity / Role	Validation	System User/Owner	Engineering	QA
System Impact Assessment	A	A	R	A
Specifications (URS[1], FS[2] and DS[2])	A	R/A	R/A	A
Validation Master Plan	R	A	A	A
Qualification Protocols & Reports[1]	R	A	A	A
Qualification Protocol Execution[1]	R	A	A	A

Notes: [1] Required for equipment and automated systems. [2] FS and DS documents are required for Computerized Systems only (such as LIMS, MCS, and BMS). For other equipment and Commercial Off The Shelf (COTS) units, design documents consist of, but are not limited to, P&IDs, Drawings, Schematics, and Equipment Manuals. R= Responsible/ Creator/ Author. A= Reviewer/Approver.

4. Supporting Standard Operating Procedures

The following is a list of SOPs that will describe, guide, or support the validation program.

Validation SOPs

Validation Policy
Validation & Engineering Documents Numbering Procedure
Protocol Preparation and Execution
Computer System/Software Validation Program
Analytical Methods Validation Program
Process Validation Program

Metrology, Facilities, and Engineering SOPs

Removal from service procedure
Facility Shutdown Procedure
Out Of Service Procedure
Site Maintenance Program
Site Calibration Program
P&ID Review and Revisions Procedure

Quality Control SOPs

LIMS
Facilities Environmental Monitoring Program
Critical Utilities Sampling Program
Personnel Monitoring Program
Out Of Specification Results

Quality Assurance SOPs

Training Program
Change Management Program
Deviations
CAPA program
Equipment Release and Return to Service

5. Validation Overview

Validation is an integral part of the overall product quality assurance program. The main purpose of validation is to demonstrate through documented evidence that the entire manufacturing system (critical utilities, process, support, and testing equipment and manufacturing processes) performs consistently and reliably.

The following types of validation will be implemented to achieve a Validated state of the entire manufacturing process and facility:

- Equipment, Utilities, Facilities, Computer Systems
- Cleaning, Sterilization
- Methods, Process

5.1. Installation Qualification

The purpose of installation qualification is to verify that (a) the installed system or equipment is acceptable with respect to the approved specifications or equipment manuals.

5.2. Operation Qualification

The purpose of the operational qualification is to evaluate the performance of the system or equipment, in accordance with the manufacturer's operating parameters and design specifications.

5.3. Computerized System Validation

Qualification of computerized systems and the associated software is performed for the purpose of demonstrating that systems and equipment, which are controlled by computer system(s) or programmable logic controller(s), are capable of performing the range of automated functions, within the limits of predetermined specifications.

5.4. Performance Qualification

The Performance Qualification is used to test those systems where performance or process parameters are known and would affect the product. The purpose of the performance qualification testing is to establish the ability of the system or equipment to perform within the production process criteria. Generally, performance qualification testing will involve challenging systems or equipment within a predetermined range of operation. PQ studies are performed to qualify cleaning procedures, steam sterilization, water quality, steam quality, air quality, etc, under normal operations.

5.5. Method Validation

Analytical test methods, in-process control testing methods and Analytical Equipment will be validated. Analytical parameters for analytical methods validation are determined, where

applicable, for:

- Accuracy
- Precision
- Specificity
- Limits of Detection
- Limits of Quantitation
- Linearity
- Range

The analytical methods requiring validation and the status of these validations are documented on appendix B.

6. Product Validation

After facility, utility, and equipment qualifications are completed, each manufacturing process will be validated. A protocol will be developed to demonstrate that the manufacturing process consistently produces product meeting all in-process/final product specifications. The study will consist of performing all process manipulations, according to the manufacturing batch record. In-process testing will involve sampling product at appropriate manufacturing steps. Other parameters, such as manufacturing time, product temperature, room temperature, volume, weights, equipment settings, and filter integrity testing, will also be recorded as in-process data. The Process Validation in this Master plan consists of two categories: aseptic processing and product processing.

7. Process Description

Describe your process here.

7.1. Product Processing

The Product Processing portion of the Process Validation will demonstrate that the actual manufacturing process consistently produces product meeting all in-process and final product specifications.

The study will consist of performing all process functions and manipulations according to the manufacturing batch record, and sampling the in-process and final product at appropriate steps. All pertinent data will be documented.

Three batches each of the pre-determined product formulations and filling/packaging configurations will be manufactured and placed on stability. Initial process validation will consist of performing three studies of each product formulation and filling/packaging configuration to ensure that all pre-determined in-process and final product specifications are met and provide an accurate measure of variability among successive runs.

All documentation associated with manufacturing activities will be retained for review and used as criteria to determine acceptability of product release.

8. Validation Scheduling and Control

The sequential approach first requires that equipment, services, and systems scheduled for qualification/validation are mechanically complete, and that process parameters are defined. System/Equipment construction or installation must be complete and have been commissioned. Once this is complete, adequate documentation and change control systems are established. Implementation of these systems allow establishment of programs to generate documentation for

Standard Operating Procedures, calibration, qualification/validation protocols, batch records, training, preventive maintenance, etc. This documentation facilitates the validation program and is generated in a sequential manner that is compatible with the execution of the validation program.

In order to achieve the final goal of facility control and successful process validation, all qualifications/validations must be performed and all compliance programs and documentation systems must be developed and implemented. Some tasks may be performed simultaneously while others must be performed prior to undertaking subsequent tasks. Process validation, which is the integration of all other facility activities and processes, is the final task to be performed. This sequential approach ensures that conclusive, accurate data is generated to demonstrate and prove a reproducible process.

Initially, a change control program is established and implemented to ensure that once a piece of equipment, utility or process has been validated, it will remain in that state. Once the change control program is established and implemented, the Installation Qualification (IQ) studies may be started.

During the initial IQ phase, the Drawing and Equipment History Files for each system or piece of equipment to be validated is established. Critical Instrument Calibration verification is confirmed within this phase.
Existence of approved SOPs is confirmed during the OQ Phase.
During the subsequent PQ activities, the approved Standard Operating Procedures are field verified for content and accuracy.

Programs for routine preventive maintenance and calibration are established and necessary equipment use logs instituted prior to closing the change management record, before releasing the systems for GMP use.

Upon successful completion of the IQ, OQ, and CSV phases, PQ, as applicable, is conducted. The data obtained is used to develop routine sampling, cleaning, environmental monitoring, and revalidation schedules. Data collected is evaluated to determine the effectiveness of the facility cleaning program, and is used to determine the on-going strategy, schedule, and alert, action, and state-of-control levels.

9. Facility Validation

The manufacturing facility is located in City, ST. This building is comprised of approximately BIG square feet of manufacturing, laboratory, and office space.

9.1. Warehousing

Procedures for receiving, identifying, storing, and dispositioning incoming raw material and compounds as well as the operation of the warehouse storage area can be found on SOP. All climate control units storing materials are validated. The room-temperature areas are monitor and temperature control.

9.2. Facility Cleaning Validation

A Facility Sanitation Program is in place for non-product contact surfaces. Room cleaning utilizes at least two different disinfectants that are rotated monthly. The program was developed to maintain the quality of the environment, thereby reducing the potential for microbial (aerobic and anaerobic) and particulate contamination of the product. The program was implemented and is periodically evaluated in conjunction with the environmental monitoring program. The data collected is to be used to evaluate on-going

effectiveness of the cleaning procedures.

9.2.1. Procedures are in place to evaluate the following criteria:

- Testing the sanitizing agents' ability to adequately control the indigenous microbial flora
- Sanitizing schedule for specific areas
- Rotation of cleaning agents
- Storage and preparation of sanitizing agents and disposal of cleaning wastes
- Specific sanitizing procedures
- Removal and use of status tags and use of area logbooks
- Inspection of area for cleanliness prior to use
- Revalidation studies when significant changes to sanitizing agents, methods, etc., are implemented

9.3. Microbial Contamination Prevention and Control

Microbial contamination of the production areas is controlled through the implementation of standardized cleaning techniques for critical processing equipment and production areas. Appropriate process steps take place in controlled production areas. Process steps are carried out, wherever feasible, in closed systems designed to minimize exposure to the controlled areas. During critical processing steps and sampling, environmental exposure of the intermediates and bulk drug solution is minimized.

9.4. Environmental Monitoring

An environmental monitoring program was developed and implemented to manage and evaluate environmental control. Routine monitoring activities are performed to determine total particle counts, bioburden, differential pressure, etc.

10. Utilities Validation

10.1. Heating Ventilation & Air Conditioning System

The purpose of the Air Handling System is to control environmental conditions within the production facility. The Air Handling System provides clean, conditioned air to the controlled environments within the facility. Conditioning of the air includes temperature, humidity, and particulate control. Particulate control is accomplished by passing air through pre-filters within the air handling units and terminal HEPA filters in the room ceilings. Maintenance of differential pressure between adjacent areas and room air change rates are accomplished by balancing the supply air flow from each air handler and the supply air flow to each room or area.

Major components of the Air Handling System servicing the cGMP manufacturing areas include air handler units, chiller, exhaust fans, distribution ductwork and HEPA filters.

Refer to the Plant drawing and Clean Room Classifications drawing.

10.2. WFI Generation and Distribution System

Water For Injection is used throughout the facility as process ingredients, for cleaning. Sterilization, etc. The system will require Commissioning, IOQ, and PQ testing.

10.3. Clean Steam Generation and Distribution System

Clean Steam is used sterilization. The system will require Commissioning, IOQ, and PQ

testing.

10.4. Nitrogen Gas System

The Nitrogen is supplied by a vendor. A distribution system supplies N_2 gas throughout the facility. The system will require Commissioning, IOQ, and PQ testing.

10.5. Clean Compressed Air (CCA)

CCA is generated in house. A distribution system supplies CCA throughout the facility. The system will require Commissioning, IOQ, and PQ testing.
The PQ will provide ≥ 6 days of monitoring in a 32 day period for air quality (Hydrocarbon content, dew point, particulate counts, and bioburden) at all points of use.

10.6. Plant Steam

The Plant Steam System produces saturated steam and distributes the steam through valves and regulators to various components throughout the facility. The plant steam is mainly utilized in the Heating Hot Water System at other designated utilities and process systems for temperature regulation and control. This system will require commissioning.

10.7. Chilled Water System (CHW)

The Chill Water system produces and distributes chilled water, to non-product contact use points. The chilled water is mainly utilized in the HVAC system for cooling and dehumidification. It is also utilized at other designated utility and process systems for temperature regulation and control. This system will require commissioning.

10.8. Heating Hot Water System (HHW)

The Heating Hot Water System is designed to provide heating hot water in a closed loop system to use points in the HVAC systems in the production building, including manufacturing, research, laboratory, and office spaces. This system will require commissioning.

11. Equipment Validation

See attachment A for a completed list of equipment validations. Detail for an individual piece of equipment can be found in that equipment validation file.

11.1. Tanks, Vessels, and Skids

Various tanks, vessels, and skids are used throughout the facility for various steps of the production process. All tanks are stainless steel, carbon steel, or polymer, as appropriate, and are equipped with appropriate nozzles, penetrations, utility connections, and monitoring devices necessary to maintain process control. Individual IOQ protocols are written and executed for each system or skid. PQ studies will be performed on all Tanks, Vessels, and production skids.

11.2. Temperature Controlled Chambers and Rooms (CTUs and CTRs)

The various cold rooms and freezers are utilized for in-process and finished product and samples storage. They are designed to maintain the specified temperature appropriate for that stage of the process. They are generally located in the appropriate path of materials and product flow. Each cold room or freezer typically is constructed of pre-manufactured insulated walls and doors with a galvanized aluminum finish, and contains self-contained air cooling equipment (fans, compressors, controls). CTUs will require

commissioning and IOQs: empty chamber studies. For-Information-Only studies such as Open Door and Power failure studies can be performed either within the Engineering phase or within the IOQ phase.

11.3. Equipment Cleaning & Sterilization Validation

11.3.1. Glassware Washer

The Glassware Washer is operated through an HMI, which contains 3 fixed programs and four “variants” (optional added steps). The system will require Commissioning, IOQ, and Cleaning Validation.

11.3.2. Autoclave

The Autoclave is operated through an HMI, which contains four fixed programs:

- Dry Goods cycle
- Liquid Goods cycle
- Vacuum Test cycle
- Bowie-Dick Test cycle

The system will require Commissioning, IOQ, and PQ testing. Any cycle development will take place within the Engineering testing phase (SAT or CMG).

12. Additional Programs

12.1. Training

Training on applicable SOPs is required prior to PQ execution.

12.2. Calibration

Critical Instrument Calibration is required prior to OQ execution. Approval of the calibration requirements takes place before the equipment is released for GMP use.

12.3. Change Control

A change control program is in place to ensure that existing documents, utilities, equipment, and processes including software remain in a state of control.

12.4. Maintenance & Spare Parts

Approval of the spare parts list and the maintenance requirements takes place before the equipment is released for GMP use.

12.5. Logbooks, Status Tagging, and Checklists

A system for determining the day-to-day status of critical utilities, equipment, controlled areas and activities is in place. Activities such as batch production, cleaning, preventive maintenance, and calibration are documented in logbooks. Status tags are utilized to indicate the status such as dirty, in-process, clean, quarantine, out-of-service, released, etc.

13. Attachments

13.1.	Attachment 1	Systems Commissioning and Validation Checklist (Included)
13.2.	Attachment 2	Required Documents Process Flow (Included)
13.3.	Attachment 3	Laboratory Equipment Qualification List
13.4.	Attachment 4	Process Flowcharts
13.5.	Attachment 5	Facilities drawings: Personnel Flow, Raw Material Flows, Product Flows, Sample Flow. And Waste Flow
13.6.	Attachment 6	Pressurization Plan drawing and Clean Room Classifications drawing.
13.7.	Attachment 7	Validation schedule

Attachment 1 – Systems Commissioning and Validation List

System	Commissioning	Equipment	CSV	Cleaning	Sterilization	Process
Main Production Line						
Portable Bioreactors	X	X	N/A	X	X	X
Production Bioreactors	X	X	N/A	X	X	X
Media Vessels	X	X	N/A	X	X	X
Centrifuge	X	X	N/A	X	N/A	X
Pool Vessels	X	X	N/A	X	X	X
Chromatography Skids	X	X	X	X	N/A	X
Viral Filtration Skid	X	X	X	X	N/A	X
Production Vessels	X	X	N/A	X	X	X
Buffer Vessels	X	X	N/A	X	X	X
UF/DF Skid	X	X	X	X	N/A	X
Supporting Systems						
Parts Washers	X	X	N/A	X	N/A	N/A
Autoclaves	X	X	N/A	N/A	X	N/A
Laminar Flow Hoods	X	X	N/A	N/A	N/A	X
Biosafety Cabinets	X	X	N/A	N/A	N/A	X
CTUs	X	X	N/A	N/A	N/A	N/A
Facilities,						
HVAC	X	X	N/A	N/A	N/A	N/A
ISO 8 Rooms	X	X	N/A	N/A	N/A	X
ISO 7 Rooms	X	X	N/A	N/A	N/A	X
ISO 5 Rooms and Skids	X	X	N/A	N/A	N/A	X
Utilities						
Clean Steam	X	X	N/A	N/A	N/A	X
AWFI	X	X	N/A	N/A	X (1)	X
HWFI	X	X	N/A	N/A	N/A	X
CCA	X	X	N/A	N/A	N/A	X
N_2	X	X	N/A	N/A	N/A	X
CO_2	X	X	N/A	N/A	N/A	X
O_2	X	X	N/A	N/A	N/A	X
Plant Steam	X	N/A	N/A	N/A	N/A	N/A
Plant CA	X	N/A	N/A	N/A	N/A	N/A
Vacuum	X	N/A	N/A	N/A	N/A	N/A
Computerized Systems						
LIMS	X	N/A	X	X	X	X
MCS	X	N/A	X	X	X	X
BMS	X	N/A	X	X	X	X

Notes: (1) The AWFI requires Sanitization verification.

Attachment 2 – Required Documents Process Flow

Item #	Document	Input	Output	Responsible Group
1	User Requirements Specification (URS)	-	5, 12	System Owner
2	System Impact Assessment (SIA)	- [1]	3	All
3	Site Master Validation Plan	2	12	Validation
4	Change Management record(s)	3	12	System Owner
5	Functional Specification (FS)	1	6	Engineering
6	Design Specification (DS)	5	12 [2]	Engineering
7	Factory Acceptance Test (FAT)	-	-	Engineering
8	Site Acceptance Test (SAT)	-	-	Engineering
9	Turn Over Package (TOP)	-	12	Engineering
10	Commissioning Qualification Protocols	9	12	Engineering
11	Requirements Traceability Matrix (RTM)	6[3]	12	Engineering/Validation [5]
12	Installation qualification (IQ)	1, 3, 4, 6 [2], 9[3], 11[4]	13	Validation
13	Operational qualification (OQ)	12	16, 17	Validation
14	SOPs	6 [2]	15	User, Facilities, Engineering [6]
15	SOP Training	14	16	User
16	Performance qualification (PQ)	13	17	Validation
17	Equipment Release	Per individual CM	18	System Owner
18	CM Record(s) closure	Per individual CM	-	System Owner

Notes: [1] A list of utilities and major equipment list is needed. [2] A DS is required only for Automated Systems. Equipment Manuals are sufficient for COTS units. [3] A TOP is not required for Commercial Off The Shelf units. [4] An RTM is required for Computerized Systems only. [5] Engineering is responsible for updating the RTM once the DS is approved. Validation is responsible for updating the RTM once the qualification is complete. [6] The user is responsible for Operations SOPs, Engineering may be responsible for Maintenance and Metrology SOPs, Facilities may be responsible for Cleaning SOPs.