Includes CD-ROM

Pharmaceutical Master Validation Plan

The Ultimate Guide to FDA, GMP, and GLP Compliance

Syed Imtiaz Haider

St. Lucie Press

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Syed Imtiaz Haider, Ph.D.

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Every effort has been made to ensure that the contents of this generic validation master plan are accurate and that recommendations are appropriate and made in good faith. The author accepts no responsibility for inaccuracies or actions taken by companies subsequent to these recommendations.

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DEDICATION

This book is dedicated to the loving memory of my mother, Khursheedun-nissa, whose encouragement and love have added substantial value to my career.

PREFACE

The regulatory guidelines such as those of the FDA, Current Good Manufacturing Practices (cGMP) for Pharmaceuticals, and Good Laboratory Practices (GLP) require comprehensively documented systems. The guidelines mentioned above provide only a set of rules to be followed and leave the specificity of the working documents to the individual companies.

The purpose of this book is to provide a generic format for a Master Validation Plan, also often called a Validation Master Plan (VMP), using a pharmaceutical manufacturing site with both sterile and non-sterile operations as the case facility. The intent is to show basic format and samples of contents for all the sections of the plan, because it provides a road map for validation to establish FDA requirements master validation procedures, validation programmes, execution protocols, and resources planning and scheduling.

The pharmaceutical, medical device, and biotech industries are regulated worldwide to be in compliance with cGMP and GLP principles. Each company is required to create a VMP to qualify its equipment, utilities, buildings, and personnel. The template VMP available enables the end users to understand the principles and elements of a VMP and provides documentation language that is generic to very specific depending on the depth of the requirements.

Compliance with FDA regulations by the health care industry over the past decade has been a major goal, especially for those companies intending to export their product to the U.S. market. As a result, the FDA inspects nearly 300 companies throughout the world every year for cGMP and GLP compliance, but only five or six are able to seek approval for exportation. One reason for this is the absence or inadequacy of a VMP. The key benefits of a VMP include, but are not limited to:

- Minimize noncompliance
- Reduce reworks

- Reduce rejected lots
- Avoid recalled lots
- Helps in new drug approval
- Satisfactory inspections
- Corporate image
- Financial gain
- Secure third-party contracts
- Corporate legal protection
- Utility cost reduction
- Minimize capital expenditures
- Fewer complaints
- Reduced testing
- Improved employee awareness

The Validation Master Plan on CD-ROM is a valuable tool for those companies that are in a process of developing or revising a VMP to achieve FDA, GMP, and GLP compliance. The documentation package is especially relevant to quality assurance (QA) personnel, engineers, utilities engineers, computer engineers, validation designers, internal and external auditors, and to anyone interested in developing a qualification documentation matrix. The VMP provides administrative solutions for management, both in text and software.

The author believes that following the broadly based example of a Validation Master Plan, both new and experienced companies can benefit and enhance their existing documentation of a Validation Master Plan to meet FDA and other regulatory requirements worldwide.

Syed Imtiaz Haider, Ph.D.
September 2001

ACKNOWLEDGMENTS

I would like to thank friends and colleagues, especially Javed Zamir, for their help and encouragement in this endeavor and for creating the professional environment that demanded that this book be developed. I would like to thank the staff of CRC Press, particularly Drew Gierman and Gail Renard for their patience and diligence in the production of this work.

ABOUT THE AUTHOR

Syed Imtiaz Haider has a Ph.D. in chemistry and is a quality assurance specialist with more than 12 years of experience in pharmaceutical validation, in-process control, and auditing. He has more than 40 research publications in international refereed journals dealing with compounds of pharmaceutical interest, their isolation, purification, and structure development. Dr. Haider is a professional consultant, technical writer, and author of more than 2000 Standard Operating Procedures based on FDA regulations, ISO 9001, and ISO 14000; a Standard Certified Lead Auditor of IRCA; and registered provisional auditor of EARA. He has written more than ten manuals for multidisciplinary industries. Dr. Haider has also written *ISO 9001:2000 Document Development Compliance Manual: A Complete Guide* and CD-ROM, published by CRC Press, Boca Raton, FL, and holds a copyright certificate of registration on an electronic documentation package on ISO 14001 from the Canadian Intellectual Property Office.

PROLOGUE

The purpose of this book is to provide a generic template for a Validation Master Plan (VMP), using a broadly based pharmaceutical facility as an example. The contents of the VMP are based on a hypothetical, newly constructed ABC Pharmaceutical facility. The facility is comprised of three buildings: A, B, and C.

- Building A is dedicated to the manufacture of dry oral products.
- Building B is designed to manufacture liquid and semisolid oral products.
- Building C is constructed to manufacture injectables in ampoules, vials, and disposable ready-to-use syringes, and lyophilized products in vials.

The information provided in this introduction is intended to help those who use this book and its CD-ROM understand the basic elements of a VMP; download the electronic files provided on the CD-ROM on a personal computer; and execute the desired changes or directly adopt the contents for the development of a VMP in accordance with the operational requirements of their companies.

VALIDATION MASTER PLAN

What is a Validation Master Plan? There is no official definition; however, based on the interpretation of FDA regulatory guidelines on current Good Manufacturing Practice (cGMP), Good Laboratory Practice, and process validation, a suitable definition may be described as:

> A comprehensive document describing the applicable validation requirements for a given facility, and providing a plan for meeting those requirements. The VMP provides a "road map" for validation, to establish a sequence of events followed by facilities audits and inspections.

The benefits of a VMP are not limited to proactive regulatory compliance but help in the prevention of omissions and inappropriate or laborious testing, scheduling and tracking of tasks, identification of personnel qualifications, and human resource optimization. The overall program gains regulatory and management credibility and helps to avoid unforeseen delays in facility start-up operations for commercial production. The key benefits involved are:

- Minimize noncompliance costs
- Reduce rework
- Reduce rejected lots
- Avoid recalled lots
- Helps in new drug approval
- Satisfactory inspections
- Corporate image
- Financial gain
- Secure third-party contracts
- Corporate legal protection

The observations made during the execution of the VMP provide strength to significantly reduce the regulatory risks related to the systems and initiation of the proactive corrective actions required. The plan provides visibility for the completion of individual tasks and assures system evaluation, process validation, equipment validation, facility and utilities qualification, documentation, environmental control, and monitoring; implementation and execution of the VMP assures process reproducibility control over the applicable changes and modifications as a result in facilities, equipment, personnel, and materials.

WRITING A VALIDATION MASTER PLAN

The VMP can be written for a new or existing facility. The following unique information should be established as a minimal requirement.

For a new facility, this information is readily available and the scope of the work is easily defined. However, an existing facility may have to be assessed for vulnerability prior to planning.

Information	*New Facility*	*Existing Facility*
Facility specifications	*	*
Utilities specification	*	*
HVAC specifications	*	*
Major equipment list/specs.	*	*
List of major SOPs	*	*
Descriptions of processes	*	*
Personnel resumes	*	*
Design review documents	*	*
Major purchase orders	*	*
Equipment manuals	*	*
Review of audit citations	—	*
Review of past validation	—	*
Physical inspection of facility/equipment	—	*

Note: — = Not applicable.

Vulnerability Assessments

The vulnerability assessment is an organized review of validation-related vulnerabilities concerning the facility. The above objective is best achieved by an organizational multidisciplinary task force. The internal audits and past 483s should be reviewed. The existing validation documentation should focus, in addition, on the inspection of the physical facility and critical equipment.

DECISION MAKING

The development of a VMP requires several decisions. If the facility is new, due consideration is given to determine, on time, the target dates for routine production to ensure completion of validation for facility approval; otherwise manufacturing at risk is the alternative choice. The deadline determination provides ample opportunity to perform validation of utilities, critical equipment installation, and qualification prior to construction work. In addition, it provides a sufficient time frame to identify the critical processes and steps involved. The parameters critical for each step shall be established. The critical equipment required shall be determined. Critical processes, steps involved, parameters, and equipment are identified. For existing facilities, establish the criteria for revalidation based on known vulnerabilities and engineering projects in progress.

In general, a key decision should be taken regarding development of the multidisciplinary team supporting the quality matrix of the VMP (i.e., adequacy of in-house personnel or is contract help necessary). The availability of validation supporting procedures is also essential. Responsibility and authority for the generation of protocols and their pre- and post-approval should be clear. The mechanism for reviewing and routing protocols shall be clear, including types of protocols and formats; where possible, equipment may be grouped under specific systems. The group responsible for the execution of protocols shall be identified. Above all, the final acceptance of the facility should be after the formal review by the quality function responsible. The validation of utilities should ideally commence prior to that of support process equipment, and installation qualification prior to the operational qualification.

Define whether the facility is a new or existing one. Identify types of products or materials to be produced. Establish if any outside facility is involved as part of plan.

RESOURCE REQUIREMENT ESTIMATES

The effective execution of the VMP is based on how precisely the man-hour requirements are calculated for each task. Use input from experienced validation and engineering personnel. Consideration should be given to the time frame for protocol preparation, review, correction, and approval. Consider the analysis involved, the test equipment, and the time frame for procurement.

ELEMENTS OF VALIDATION MASTER PLAN

The elements described in the VMP are not the policy requirements. However, they can be manipulated according to individual needs.

PLAN APPROVAL

Formal approval of the plan, indicating the top-level management for each function, is essential to share the responsibility. The VMP shall be supported with approval signatures from multidisciplinary functions, including Engineering, Manufacturing, Quality Control, Quality Assurance, and Validation at a minimum.

REASONS FOR REVISION

At the end of approvals, indicate reasons for revisions with dates for the circumstances requiring revision and reapproval.

1. Introduction. The VMP should have well-defined limits pertaining to the facility. The context of the plan should include a description of the project, definitions, validation team members, and their responsibilities.
2. Concept of qualification/validation. This takes into consideration the concept of validation life cycle for the company's facilities, equipment and processes, documentation format, and numbering system.
3. Revalidation. Revalidation criteria shall be established and defined for facilities, equipment, processes, and utilities.
4. Facility description. The facility description addresses locations, numbers of employees covered and uncovered in area, specificity of processes and line capacities, etc.
5. Description of building. The facility description considers:
   a. Facility size
   b. Details of physical construction
   c. Critical design criteria
   d. Defined activity
   e. Defined personnel flow (where applicable)
6. Equipment description. The major or critical equipment shall be identified by equipment name or asset control number. There should be a brief summary of the most relevant equipment attributes, including a brief summary of process applications if possible.
7. HVAC description. The points to be considered for utilities and HVAC descriptions should include identification sources for all product contact utilities and all product contact utilities applications. The air handling system supporting controlled areas should be identified with air classification for all applicable areas, including diagrams or descriptions of air flow directions, design, etc.
8. Utilities description. The description of utilities shall be defined for their final quality and, where necessary, the surface quality, particularly where the product is in direct contact with the surface. The following utilities are the most pertinent but the list is not limited to:

Deionized water	Compressed air
Purified water	Nitrogen
Water for injection	Carbon dioxide
Chilled water	Electric power
Pure steam	Potable water

9. Validation program overview. Describe the validation group organization to establish the responsibilities of each group and/or individual. The organization of the system documents should be defined. Define project management responsibility, design review responsibility, classification of equipment, and general understanding of overall certification package (i.e., IQ, OQ, and PQ). Define contents of validation reports. Briefly describe the required protocols and their contents.
10. Calibration program summary. The instrument calibration program should describe calibration policy for validation of test equipment, pre- and post-calibration, and NIST traceability of calibration standards. The responsibility of calibration shall be defined.
11. Preventive maintenance program summary. The preventive maintenance program should be summarized for the facility with responsibility for tracking.
12. Key SOPs. The list of key standard operation procedures (SOPs) shall be included with a remark to be updated. Key procedures such as internal audit should be highlighted. Identify applicable process-related documents.
13. Validation of building. Define test functions and acceptance criteria for building finishes.
14. Validation of utility systems. Define test functions and acceptance criteria for the utilities, including workmanship.
15. Process description: dry products. The description of the processes should include a brief summary and flow diagrams for the steps involved, and describe control variables and measured responses as follows:

Process Flow Tablets
1. Addition of raw materials (actives and excepients)
2. Pre-blending
3. Granulation
4. Drying
5. Sizing
6. Addition of lubricants and disintegrates
7. Blending
8. Tableting
9. Coating
10. Blistering
11. Boxing
12. Cartoning

Identify the product characteristics impacted at each process step and the parameters requiring validation.

16. Process description: liquid and semisolid products. Apply a similar approach as defined in Step 15 and as appropriate to the process requirement.
17. Process description: parenterals. Apply a similar approach as defined in Step 15 and as appropriate to the process requirement.
18. Qualification of process equipment. Define test functions and acceptance criteria for major equipment. A comprehensive list identifying the protocols required shall be finalized, or alternatively, shall be provided by the validation program overview in Step 9.
19. Validation of support processes. Define test functions and acceptance criteria for critical validation support processes such as washing of components, sterilization of components, depyrogenation, etc.
20. Quality assurance/control laboratory validation. Describe the validation approach for the laboratory equipment and test methods. Define test functions and acceptance criteria.
21. cGMP procedures and programs. Define the following programs: engineering change control, calibration, preventive maintenance, personal training, facility cleaning and sanitization, environmental monitoring, HEPA filter integrity testing, etc.
22. Validation schedule. Provide time line chart for the on-time completion of validation tasks of equipment, utilities, processes, cleaning etc., to ensure compliance with government regulations, quality, and cost reduction.
23. Drawings. Identify all key drawings related to the civil layout, utilities, personnel flow, materials flow, etc. Assign a number to each drawing.

CD-ROM

An electronic copy of the generic Validation Master Plan is provided. See the inside back cover of this book for the CD-ROM.

VALIDATION MASTER PLAN APPROVAL PAGE

Issued on: mm/dd/yyyy Supersedes: mm/dd/yyyy

Written By	***Signature & Date***

Name
Designation
Department

Checked & Agreed By	***Signature & Date***

Name
Designation
Department

Reviewed By	***Signature & Date***

Name
Designation
Department

Approved By	***Signature & Date***

Name
Designation
Department

Reasons for Revision

mm/dd/yyyy First time issued for ABC Pharmaceutical

ABOUT THE BOOK

This book and CD-ROM take into account all major international regulations, such as FDA, cGMP, GLP, GCP and industry standard ISO 9000, to be in compliance with documentation guidelines. No other book in print deals exclusively with the key elements of a Validation Master Plan for a pharmaceutical plant and provides a hands-on template to be tailor made to achieve documentation compliance for FDA inspection.

The Validation Master Plan (VMP) is written to provide explicit instructions on how to achieve it for anyone responsible for writing and executing a VMP for drug, drug-device combination, diagnostic, pharmaceutical, biotechnology, and bulk pharmaceutical chemicals products. Included is the ready-to-use template that one can immediately use as one's own without reinventing the wheel, thus saving time and money without missing any critical element.

This book provides instant answers to validation engineers, validation specialists, quality professionals, quality assurance auditors, and protocol writers regarding what should be made part of the VMP and how to enhance productivity.

Introduction

- Validation Master Plan
- Writing a Validation Master Plan
- Vulnerability assessments
- Decision making
- Disclaimer
- Resource requirement estimates
- Elements of Validation Master Plan
- CD-ROM
- Acknowledgment

Master Validation Plan

CONTENTS

1

INTRODUCTION

1.1 PROJECT DESCRIPTION

This Validation Master Plan (VMP) specifies and coordinates all qualification/validation activities to ensure the production of pharmaceutical products according to accepted international standards. It also specifies the responsibilities for validation procedures and helps to plan the necessary activities.

The plant is designed to produce oral solid dosage forms as well as liquid dosage forms, ointments, creams, suppositories, and sterile injectable products.

The production of each product group is divided into the processing stages listed below. The general production stages for all products are:

- Receipt of raw materials and sampling
- Interim storage of raw materials
- Weighing
- Manufacturing
- Packaging
- Storage of finished product
- Dispatch

To ensure the manufacturing of pharmaceutical products in ABC Pharmaceutical according to international standards, there are several guidelines that are considered for the planning, construction, start-up, and validation of the buildings, equipment, and processes.

1.2 WHAT IS A VALIDATION MASTER PLAN?

A Validation Master Plan (VMP) is a comprehensive document describing the applicable validation requirements for the facility, and providing a plan for meeting those requirements.

1.3 SCOPE OF A VALIDATION MASTER PLAN

The Validation Master Plan (VMP) includes all relevant aspects relating to the production of pharmaceuticals in the production facility at ABC Pharmaceutical. The principles of validation, the organization of qualification and validation, and the design and nomenclature of the documentation and equipment are also described. The VMP covers all facilities used in the production of tablets, liquids, ointments, creams, suppositories, and sterile products; the facilities for storing raw materials, interim and finished products, storage, services, and the rooms for staff.

1.4 DEFINITION OF THE TERM VALIDATION

Validation is documented evidence that provides a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes.

After the requirement for each aspect is determined, the responsible engineers complete the design and it is again reviewed by the validation team. After the approved designs are constructed and/or installed, the validation cycle continues with the preparation and execution of the validation documents.

Validation is a systematic approach to gathering and analyzing sufficient data that will give reasonable assurance (documented evidence), based on scientific judgment, that a process, when operating within specified parameters, will consistently produce results within predetermined specifications.

1.5 VALIDATION TEAM MEMBERS

Members	*Qualification*[a]
Validation Manager, Quality Assurance Department	Note: Qualification must be in accordance with the job requirement in combination with experience.
Member from Production	
Member from Engineering (Utilities)	
Member from Calibration Laboratory	
Member from Quality Control Laboratory	
Member from Maintenance	
Member from HVAC Department	
Member from Product Development Laboratory	

[a] The resumes of validation team members are presented in a separate folder, including contract help.

1.6 VALIDATION TEAM RESPONSIBILITIES

Validation is a team effort that generally requires the involvement and close interaction of Quality Assurance, Production, Packaging, and Maintenance with other appropriate support such as Product Development and Quality Control. The validation team should include representatives from the above-mentioned departments to provide the necessary expertise and guidance.

The validation activities within the validation life cycle should be carried out according to the scheme shown in Figure 1.1. The documentation of the validation process is carried out in the form of programs that must be developed by the qualification/validation teams. These programs must be approved by the review team. After approval, the validation activities can start and a report of the activities must be produced. The approval of this report must be given by the same people who approved the program.

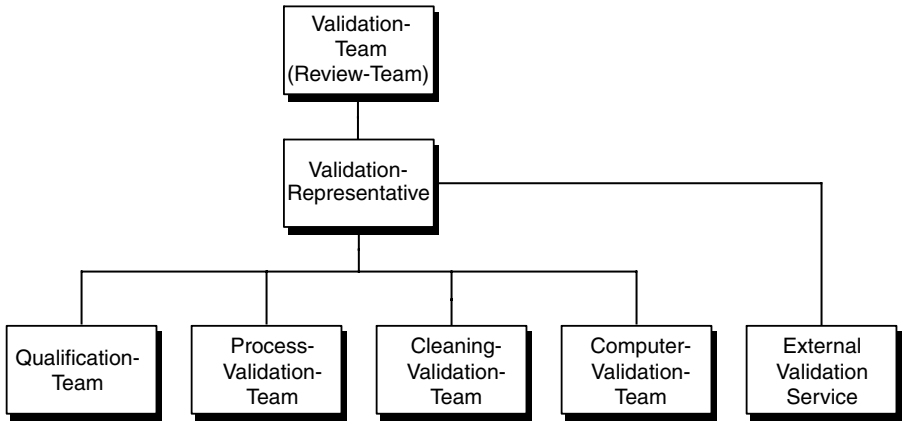

Figure 1.1 Organization chart.

If test procedures do not fulfill acceptance criteria, the review team must decide whether or not tests must be repeated or test specifications must be edited. The review team can decide whether or not test results, even if they will not fulfill acceptance criteria, should be accepted as "within specification." (See Figure 1.2.)

The teams shown in the organization chart (Figure 1.1) should consist of personnel in the following positions:

Validation team (Review team):
- Head of validation
- Head of quality assurance
- Validation representatives

Validation representative:
- Person appointed by the validation team

Qualification/validation teams:
- Personnel from different manufacturing areas. The size of the teams varies with the scope of the activities necessary. Personnel from external validation services may be included.

External validation service:
- External qualified personnel who support the qualification/validation teams if necessary.

Control of Validation Documents

The person identified for overall validation activities during the validation process is responsible for validation documents. Other departments have

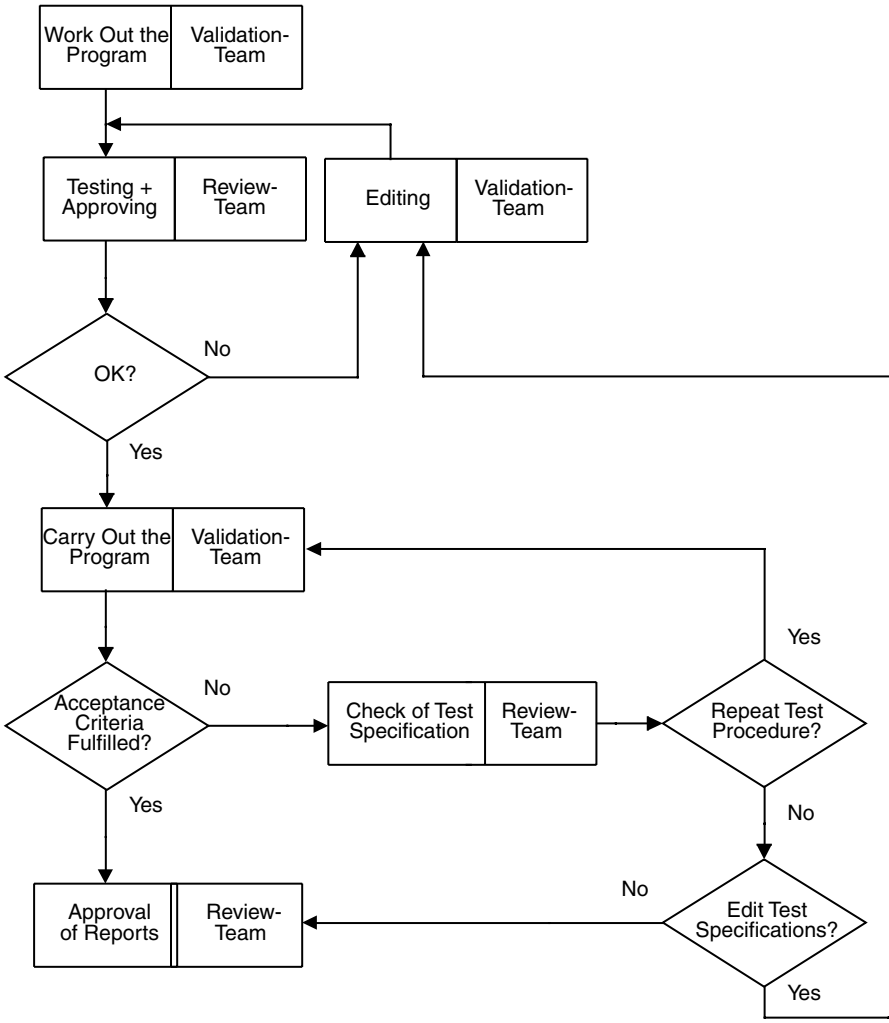

Figure 1.2 Testing and approving procedures.

access to these documents during the validation process so that they can further develop validation documentation. At the end of all validation activities, the documents are stored and controlled by the validation responsible. The updating of documentation is done during the Change or Revalidation procedure. This is also valid for documents from external validation services. The validation responsible is responsible for the distribution of updated documents.

The Engineering department is responsible for the technical documentation, for example, manuals, inspection reports, maintenance reports, specification sheets, etc. These documents are stored and updated by personnel from this department.

Quality Assurance

Validation officers from Quality Assurance (QA) coordinate the entire validation process by scheduling meetings and discussions with the validation team, preparing the validation protocols, monitoring the validation process, compiling and analyzing validation data and test results, and preparing the Final Report. All documentation associated with validation should be reviewed by the QA Manager for completeness and compliance with cGMP requirements.

Production

A validation team member from the Production department is responsible to participate in performing the validation steps during manufacturing processes and equipment qualification. This department should prepare the necessary SOPs for the new process or equipment and assist in the collection of validation data.

Packaging

A validation team member from the Packaging department is responsible to participate in performing the validation steps during packaging processes and equipment qualification. The Packaging department should prepare the necessary SOPs for the new packaging process or equipment and assist in the collection of validation data.

Utilities/Calibration/HVAC

A validation team member from the Maintenance department participates in performing the validation; defining the necessary equipment specifications, limitations, capacity, calibration, and maintenance requirements; and providing the necessary training on the proper operation and maintenance of the equipment. The Maintenance department should be responsible for providing the necessary utilities and equipment accessories.

In some cases, the Maintenance department is required to participate in equipment installation and operational qualification and provide technical support to ensure proper and efficient function during the validation process.

Quality Control

A validation team member from the Quality Control department is responsible for providing the necessary support for sampling, testing, and reporting of test results for validation. A support group in Quality Control should also perform the microbiological testing and environmental monitoring during the validation process.

Product Development Laboratory

A validation team member from Product Development Laboratories is responsible for defining the process (new product or process) to be validated and for providing technical assistance to the validation team by defining specifications, limits, and manufacturing methods.

2

CONCEPT OF QUALIFICATION/VALIDATION

2.1 FUNDAMENTALS

The aim of production facilities and processes qualification/validation in the ABC Pharmaceutical facility is to establish and provide documentary evidence that:

- The facilities, equipment, and processes have been designed in accordance with the requirements of current GMP.
- The facilities and the equipment have been built and installed in compliance with their design specifications.
- The facilities and equipment operate in accordance with their design specifications to repeatedly and reliably produce a finished product of the required quality.

To fulfill these requirements, a complete program for validation has been developed for ABC Pharmaceutical Company to ensure that all processes and equipment affecting the quality, integrity, safety, and efficacy of the pharmaceutical product are qualified and validated.

With the successful conclusion of validation, the ABC Pharmaceutical Company management can prove that all pharmaceutical products produced in the validated plant are unobjectionable, suitable for use, and correspond to the requirements of the product licence.

The concept of validation in this master plan covers the following fields of activity.

- Qualification of buildings, rooms, and supply systems
- Qualification of equipment and service units
- Validation of computer systems

- Validation of production processes
- Validation of cleaning processes
- Periodic revalidation within the scope of a change control plan

All necessary activities and responsibilities for the qualification and validation are controlled and specified in this Validation Master Plan. Every step of the described validation program for facilities, equipment, processes, process controls, and cleaning is in accordance with the current European Community Guidelines for GMP and FDA, and the cGMP guideline for finished pharmaceutical manufacturers. All requirements in these directives are fulfilled in this validation process.

In manufacturing facilities, validation test procedures are used to validate equipment and processes that may influence product quality. The tests for validation are used in accordance with approved written qualification procedures. The approval for these procedures is given by representatives from Quality Management, Production, and Engineering. During realization of this program, all activities will be documented so that the plant operates in accordance with the requirements of cGMP and within design specifications. At the end of the program, a review team will verify and approve the documented results.

The Validation Report will be the final document of all validation activities. The Validation Report includes the reports for:

- Qualification
- Computer validation
- Process validation
- Cleaning validation

To ensure a continuous validation status of facilities, processes, and process controls, continuous monitoring of the normal production conditions is necessary — as is the maintenance, calibration, and revalidation of the validated systems.

2.2 CONCEPT OF A VALIDATION LIFE CYCLE

2.2.1 Prospective Validation Life Cycle

Establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols.

The life cycle for prospective validation is divided into the following steps (Figure 2.1):

1. Validation Master Plan (VMP)
2. Design Qualification (DQ)

3. Risk Analysis (RA)
4. Installation Qualification (IQ)
5. Operational Qualification (OQ)
6. Performance Qualification (PQ)
7. Process Validation (PV)
8. Cleaning Validation (CLV)
9. Computer Validation (CV)
10. Validation Report (VR)
11. Revalidation (ReV)

Each prospective validation step will be described in Qualification/Validation documents. In these documents, except for the Validation Master Plan and the Validation Report, the test methods for validation and acceptance criteria for the results are specified. Also described are whether the equipment has to be prepared for the test method and whether the original status of the equipment has to be restored after testing.

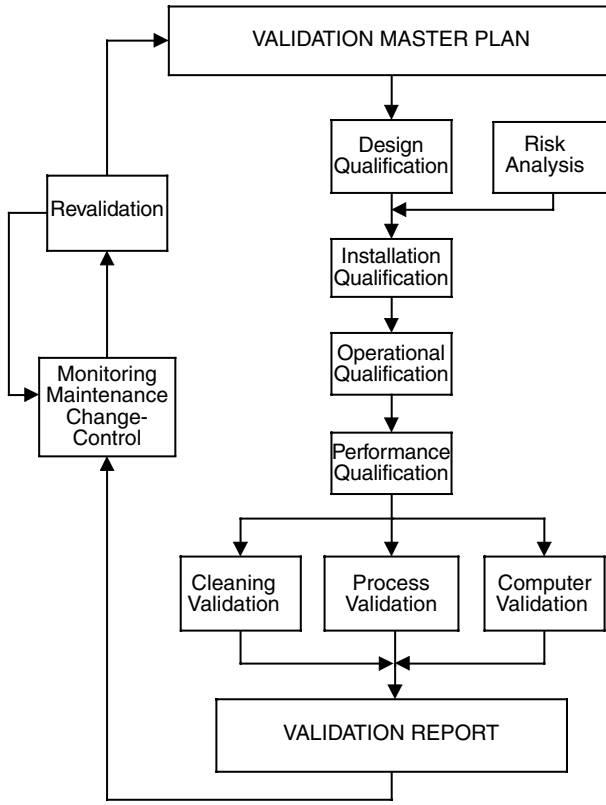

Figure 2.1 Prospective validation life cycle.

2.2.2 Retrospective Validation Life Cycle

The retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation of these facilities, processes, and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. Therefore, this type of validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment. In each case of retrospective validation it must be decided which elements of the validation life cycle (Figure 2.2) should be used. In general, the design qualification is left out of the retrospective life cycle.

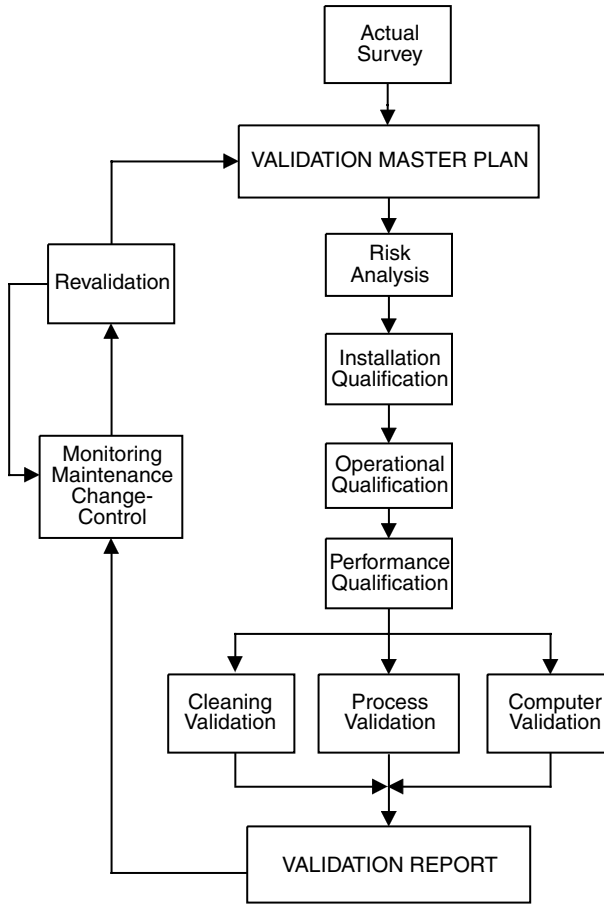

Figure 2.2 Retrospective validation life cycle.

The life cycle for retrospective validation is divided into the following steps:

1. Actual survey of facilities, processes, and process controls
2. Validation Master Plan (VMP)
3. Design Qualification (DQ)
4. Risk Analysis (RA)
5. Installation Qualification (IQ)
6. Operational Qualification (OQ)
7. Performance Qualification (PQ)
8. Process Validation (PV)
9. Cleaning Validation (CLV)
10. Computer Validation (CV)
11. Validation Report (VR)
12. Revalidation (ReV)

2.2.3 Concurrent Validation Life Cycle

Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process.

The life cycle for concurrent validation is divided into the following steps (Figure 2.3):

1. Validation Master Plan (VMP)
2. Design Qualification (DQ)
3. Risk Analysis (RA)
4. Installation Qualification (IQ)
5. Operational Qualification (OQ)
6. Performance Qualification (PQ)
7. Process Validation (PV)
8. Cleaning Validation (CLV)
9. Computer Validation (CV)
10. Validation Report (VR)
11. Revalidation (ReV)

Each concurrent validation step will be described in Qualification/Validation documents. In these documents, except for the Validation Master Plan and the Validation Report, the test methods for validation and acceptance criteria for the results are specified. Also described are whether the equipment has to be prepared for the test method and whether the original status of the equipment has to be restored after testing.

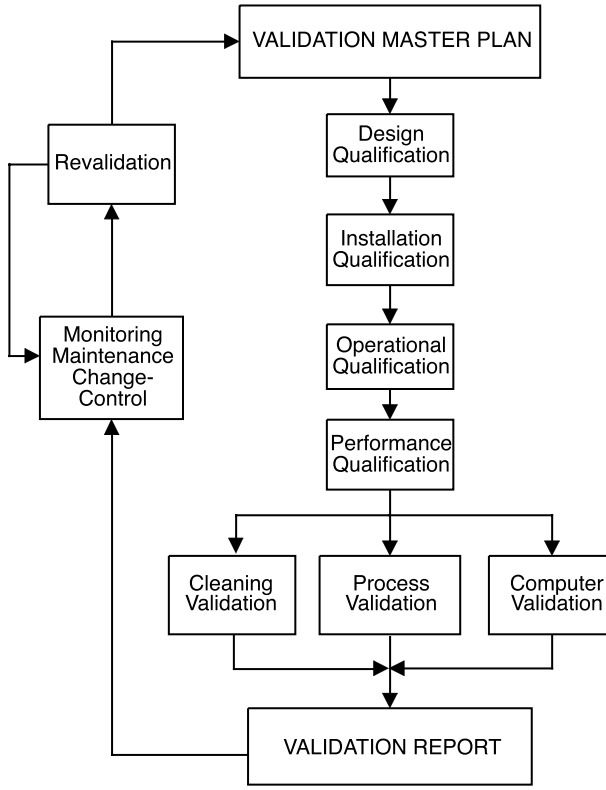

Figure 2.3 Concurrent validation life cycle.

2.3 ELEMENTS OF QUALIFICATION/VALIDATION

2.3.1 Design Qualification (DQ)

2.3.1.1 Definition

During design qualification (DQ), it is documented that the design aspects of the ABC Pharmaceutical plant have been checked and approved. The design qualification contains a plant description and shows that the plant design agrees with the design specifications of the customer. Design aspects that were not defined during design specification and that are not yet defined (i.e., when design qualification begins) must be listed and evaluated with respect to their influence on product quality.

Within the design qualification process, the design is checked to ensure that the important aspects of GMP are fulfilled and compliance with these important GMP aspects is documented. In the definition of the design qualification as well as in the further stages of the DQ process, all qualified personnel from various departments of the company must be involved. The involvement of qualified personnel is important in the process of design qualification as well as in the definition of tests that must be performed; for example, checking the technical and pharmaceutical demands. In subsequent stages of the validation process, the involvement of these qualified personnel will not be required to such a large extent. In this Validation Master Plan, Chapter 9 shows the qualification matrix. This matrix indicates the facilities for which a design qualification must be produced. Normally, when not otherwise specified, a design qualification is produced for all buildings, rooms, and process plants. However, when plants are to be validated retrospectively, no design qualification process occurs.

2.3.1.2 Contents

The Design Qualification should be divided into the following sections:

- History of DQ
- Fundamentals
- Purpose
- Implementation procedure
- Acceptance criteria
- Tests specification
- Summary of DQ evaluation
- Additional design aspects

The basis of the DQ is the design specification of ABC Pharmaceutical. The DQ is done by the personnel responsible from the ABC Pharmaceutical Company and the plant designers. The design specifications demanded by the customer are compared with the actual design of the plant. Written evidence of this comparison is produced which confirms whether or not the actual design agreed with the customer's design specifications.

Once the DQ is approved, the status of the design specifications is frozen. From this point on, the DQ and the specifications are under the control of change management.

2.3.2 Risk Analysis (RA)

2.3.2.1 Definition

The purpose of validation is to obtain written evidence that processes and equipment work within their specifications to produce products of the demanded quality. However, when working with processes and equipment, there are always risks that may or may not be acceptable. To prove whether or not possible risks are acceptable for the product quality, a risk analysis (RA) must be done. The purpose of the RA is to identify critical and noncritical parts of processes and equipment. This risk analysis also identifies the activities necessary for validation, maintenance, and calibration.

The RA must be done for prospective as well as retrospective validation processes. For a realistic opinion of possible risks to be obtained and to cover the most relevant aspects, it is necessary to involve qualified personnel with different specialist knowledge in the process of RA. For example, Quality Control personnel, Production personnel, Engineering personnel, etc.

In this Validation Master Plan, Chapter 9 shows the qualification matrix. This matrix indicates the processes and parts of the plant for which an RA must be produced.

2.3.2.2 Contents

The risk analysis should be divided into the following sections:

- History of RA
- Fundamentals
- Purpose
- Implementation procedure
- Participants
- Risk analysis

2.3.2.3 Risk Analysis Procedure

The RA is systematically carried out by personnel/departments specified in Section 1.5 of this master plan. Documents used for the analysis of processes and equipment might include:

- P&I diagrams
- System descriptions
- Manufacturer's documentation
- Recordings from logbooks, batch documents, etc. (for plants in use)
- Literature

The RA procedure is divided into the following steps:

1. List of all parts of the plant and their functions
2. Classification (critical or noncritical)
3. Reason for classification
4. Possible influence on quality parameters
5. Estimation of failure probability
6. List of measurements taken

2.3.3 Installation Qualification (IQ)

2.3.3.1 Definition

In the installation qualification (IQ) process, written evidence is given that all parts of the equipment are installed according to the equipment supplier's and purchase specifications. For complicated or large pieces of equipment, it may be decided to undertake a predelivery check of the equipment at the supplier's assembly facility. This predelivery check will also be part of the IQ. It is documented that the operating criteria for the equipment, as installed, are in compliance with the P&I diagrams, plant functional specifications, and process flow diagrams.

The IQ represents the status of the plant where the completeness and correctness of all required documents are checked. At this point, if necessary, documents must be completed and corrected.

In the case of retrospective validation, processes and purchase specifications as well as manuals from the manufacturer of equipment are rarely available. Therefore, the IQ is, for many parts, equivalent to the actual survey of the plant and uncompleted documentation can be replaced by the IQ documentation.

The IQ refers as often as possible to engineering documents (e.g., P&I diagrams, plant functional specifications, process flow diagrams, inventory lists, etc.) to avoid redundant documentation and to minimize the expenditure of updating.

2.3.3.2 Contents

The IQ procedure is divided into the following steps:

1. History of the IQ
2. Fundamentals
3. Purpose
4. Implementation procedure
5. Identification of signatures
6. Acceptance criteria

7. Description of the systems
8. Specification of tests
9. Results of the tests

The specifications of the test procedures should be divided into the following sections:

- Check completeness and current status of documentation
- Check delivered equipment from manufacturer
- Check if all parts of the plant are according to their specifications
- Check the identity of all parts of the plant
- Visual check of complete and craftsmanship installation of all parts of the plant
- Check if materials used are within their specifications

2.3.3.3 IQ Process and Documentation

In the IQ process, the first documents to be written are the IQ programs. Persons responsible for the release of IQ programs are identified in Chapter 9. An auditor and a witness carry out the test procedures given in the approved IQ programs. During the test procedures, the auditor will decide whether or not the tests' acceptance criteria are fulfilled. The witness certifies by signature that the test procedures are carried out by the auditor in accordance with their test specifications. If the IQ programs are filled in with all results of the test procedures, they become the IQ report. The persons named in Section 1.5 will approve the IQ reports again, and they become the final IQ documents.

2.3.4 Operational Qualification (OQ)

2.3.4.1 Definition

During the OQ process, documented evidence is given that all parts of the plant and equipment work within their specifications and process parameters are within the acceptance criteria. Process controls that are part of the equipment (e.g., PLC [programmable logic controller]) will be qualified during the OQ process. Computerized process controls (i.e., for complex processes) should be qualified in the Computer Validation (CV) process. To ensure that the systems tested during OQ are doing what they are believed to do, a simulation of normal production conditions must be done.

The given definition of OQ is valid for retrospective validation as well as for prospective validation.

SOPs for use, maintenance, calibration, and cleaning of the plant must be developed during the OQ process, as well as schedules for maintenance and calibration. Each OQ document contains a list of required SOPs for the use of the plant. At this point, training of the technical staff of the plant should take place. The training must be documented and checked using prepared forms. Within the OQ process, the calibration of measuring and controlling devices must be checked. Critical parameters and circumstances identified in the risk analysis (RA) must be checked for conformity to the acceptance criteria.

The OQ refers as often as possible to start-up protocols and engineering documents (e.g., P&I diagrams, plant functional specifications, process flow diagrams, inventory lists, etc.) to avoid redundant documentation and to minimize the expenditure of updating.

2.3.4.2 Contents

The OQ procedure is divided into the following steps:

1. History of the OQ
2. Fundamentals
3. Purpose
4. Implementation procedure
5. Description of the systems
6. Measuring instruments
7. Services of the processes
8. Consumables
9. Specification of tests
10. Results of the tests
11. Malfunction protocol

To avoid extensive documentation, the specifications of the test procedures in OQ should be divided into sub-sections as in the IQ procedure. An example of some essential sections is given below.

- Purpose of test specification
- Required equipment
- Preparative measures
- Testing procedures
- Acceptance criteria
- Data to be recorded
- Additional measures

2.3.4.3 OQ Process and Documentation

To start the OQ process for a given part of the plant, it is necessary that the IQ process for this part has been completed. As in the IQ process, the first documents that must be written in the OQ process are the OQ programs. The persons named in Section 1.5 and Chapter 9 give the approval/release of these OQ programs. The test procedures given in the approved OQ programs are carried out by an auditor and a witness. During test procedures, the auditor will decide whether or not the tests acceptance criteria are fulfilled. The witness certifies by signature that the test procedures are carried out by the auditor in accordance with their test specifications. If the OQ programs are filled in with all results of the test procedures, they become the OQ report. The OQ reports will be approved again by the persons named in Section 1.5 and Chapter 9 and they become the final OQ document.

2.3.5 Performance Qualification (PQ)

2.3.5.1 Definition

The PQ process provides documented evidence that all parts of the plant and the processes validated produce products of the specified quality under conditions of normal production for a longer period of time. It is shown that product quality is within the specifications as long as the quality of raw materials stays within specification. The PQ includes critical variable studies, for example, by simulating conditions of upper and lower processing, processing at the operating limits of the equipment, or circumstances like worst-case conditions. It is shown that such conditions should not necessarily induce process or product failure.

In contrast to the OQ procedures where all parts of the plant and equipment are qualified separately, the PQ procedures qualify the entire plant with respect to the production process. The definition given for PQ is valid for retrospective validation as well as for prospective validation. While carrying out PQ processes, all necessary SOPs (e.g., for the use or cleaning of the plant) should be approved. Values of critical and noncritical process parameters recorded during PQ must be collected to evaluate the efficiency and performance of the plant.

In this Validation Master Plan, the qualification matrix is presented in Chapter 9. This matrix indicates processes and parts of the plant for which a PQ must be produced.

2.3.5.2 Contents

The PQ procedure is divided into the following steps:

1. History of the PQ
2. Fundamentals
3. Purpose
4. Implementation procedure
5. Description of the systems
6. Measuring instruments
7. Services of the processes
8. Consumables
9. Specification of tests
10. Results of the tests
11. Malfunction protocol

For the same reasons as in the OQ, the specifications of the PQ test procedures should be divided into sub-sections. Some essential sections are listed below.

- Purpose of test specification
- Required equipment
- Preparative measures
- Testing procedures
- Acceptance criteria
- Data to be recorded
- Additional measures

2.3.5.3 PQ Process and Documentation

The OQ procedures must be completed before starting the PQ process. The PQ process and documentation are carried out in a similar manner to the OQ process. As in OQ documentation, the PQ documents are the PQ programs, the PQ report, and the approved final PQ document. With this, document qualification of the plant is completed.

At this point, a summary of the activities during DQ, RA, IQ, OQ, and PQ must be written and qualification activities remaining open should be listed.

2.3.6 Process Validation (PV)

2.3.6.1 Definition

Process Validation (PV) ensures and provides documented evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of predetermined quality.

The PV process is divided into the steps shown in Figure 2.4. First, a plan for the process validation must be developed. This process validation plan (PV plan) regulates the validation procedures for the manufacturing processes for each product. The process validation program is a single document and contains the specifications and test procedures for each single product. The process validation report contains the results of each validation program. In contrast to PQ documentation, where the program and report are together in one document, the validation program and report of PV are stated in two different documents. A summary of all PV activities is given in the final PV document at the end of the PV process.

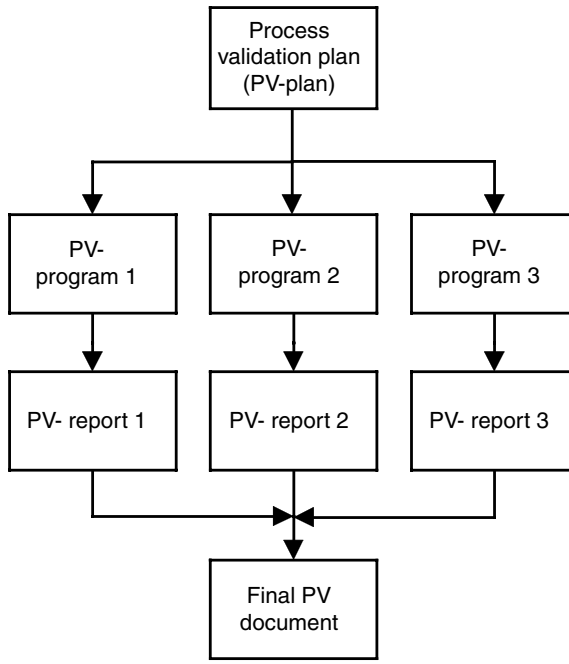

Figure 2.4 The PV process.

2.3.6.2 Contents of PV Plan

The PV plan contains several essential sections, for example, the points listed below:

- Which manufacturing processes must be validated (product matrix)
- Which kind of validation (prospective, retrospective, or concurrent) must be done
- Schedule of the validation of product processes
- Number of batches that must be used for validation (normally 3 to 10 batches of the quantity assigned for production)
- Responsibilities

2.3.6.3 Contents of PV Program

The following points should be included in the Process Validation program:

- History of development and a description of the product (if available, the development report would be useful)
- A manufacturing procedure and flowchart of the manufacturing process
- A list of all equipment required for production
- A list of production stages that may be critical for product quality
- A schedule for PV test procedures
- A detailed description for all test procedures, including:
  - Sampling procedure
  - Labeling of the samples
  - Test procedure
  - Evaluation procedure
  - Specifications for the intermediate and finished products
  - Acceptance criteria
- Responsibilities

2.3.6.4 PV Process and Documentation

All qualification procedures for equipment and services of the manufacturing process must be completed before starting the PV process. A manufacturing process achieves the status of "validated" if all batches defined in the PV plan fulfill the specifications for the intermediate and finished products.

Schedules and other requirements for the PV process and documentation are stated in the PV plan document.

2.3.7 Cleaning Validation (CLV)

2.3.7.1 Definition

During the CLV process, written evidence is given that specified cleaning procedures will lead to reliable and repeatable results in the cleaning of surfaces with and without contact with the product. It is shown that the following criteria will be fulfilled if cleaning procedures are used as specified in cleaning SOPs:

- The concentration of active substances on product contact surfaces will not exceed specified limits.
- The concentration of highly active substances (e.g., hormones or cytostatics) on surfaces without contact with the product will not exceed specified limits.
- The concentration of other pharmacologically active substances (e.g., process and cleaning materials or disinfectants) in the product to follow will not exceed specified limits
- The number of germs on product contact surfaces will not exceed specified limits.

The procedures within the CLV process must be specified in a CLV plan. Cleaning procedures for products and processes that are very similar do not need to be individually validated. It is acceptable to select a representative range of similar products and processes and then to justify a validation program that addresses the critical issues relating to the selected products and processes. A single validation study can be carried out that takes into account the relevant criteria. This practice is termed "bracketing." The criteria for the bracketing of products and processes must be given in the CLV plan.

For nondedicated multi-purpose equipment (i.e., equipment for the production of products from different defined product groups), the cleaning procedures must be validated for each and every product group. For single-purpose equipment (i.e., equipment for the production of one single product), it is acceptable to visually confirm that the equipment is clean after batch-to-batch cleaning procedures. The validation of these procedures is not necessary, but it must be established that the equipment is microbiologically clean after these cleaning procedures and the stability of the product due to the reduced cleaning. For products that decompose into intermediate or final products, acceptance criteria for the concentration of degradation product on the equipment inside surface must be given to ensure that all validation requirements are fulfilled. The development and

validation of cleaning procedures are usually part of product development and therefore should be validated prospectively.

Figure 2.5 illustrates the steps of the CLV process. The different programs represent the selected brackets of products.

2.3.7.2 Contents of CLV Plan

The CLV plan should contain essential sections for example the points listed below:

- Which manufacturing processes must be validated (product matrix)
- Which kind of validation (prospective, retrospective or concurrent) must be done
- Schedule of the validation of product processes
- Number of batches that must be used for validation (normally three to ten batches of the quantity assigned for production)
- Responsibilities

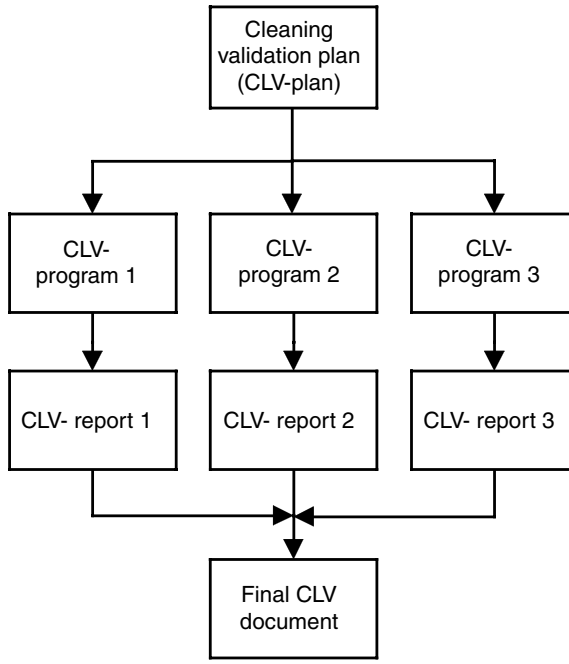

Figure 2.5 The CLV process.

2.3.7.3 Contents of CLV Program

The following points should be included in the Cleaning Validation program:

- Purpose of validation
- Responsibilities
- Composition of the product (formulation)
- A short master formula
- A description of:
  - Substance that should be detected
  - Cleaning procedure
  - Sampling method
  - Analytical method used
  - Evaluation method used for the result
  - Acceptance criteria
- Description of the plant to be cleaned and of the sampling locations
- Description of the sampling procedure
- Time between end of production and sampling
- Number of test runs (test runs must be performed by qualified personnel only)
- Description of procedures necessary in the case of exceeded acceptance criteria

As in the PV process, the CLV program and CLV report are two separate documents. A final CLV document summarizes the results of all CLV activities.

2.3.7.4 Bracketing of Products and Equipment

As shown above, similar products can be validated together on the same equipment by selecting representative products for the validation procedure ("bracketing"). The Cleaning Validation procedures must be carried out according to the critical parameters of these products.

Criteria for the selection of a representative range of similar products include:

- Identical dosage form
- Identical manufacturing process
- Similar formulation
- Properties of active substances
- Similar therapeutical efficacy
- Toxicity

As with similar products, the production plants should be divided into similar plants. Plants with similar layouts and functionalities should be selected, and representative plants should be used to carry out the Cleaning Validation procedures. Essential for this type of bracketing is that the selected plants will be cleaned in exactly the same way, that is, according to the same cleaning SOP.

2.3.8 Computer Validation (CV)

Validation of computerized systems differs from the validation processes previously described because of the complexity and key-function in the process controls of such systems. Therefore, computer validation has a special life cycle (system development life cycle [SDLC]) that contains the hardware and the software. The sub-sections of the SDLC are similar to the subsections of the life cycles for prospective/retrospective validation processes.

2.3.8.1 Definition

The CV provides documented evidence that processes controlled by computerized systems are checkable and produce the specified product quality repeatedly and reliably.

The life cycle for computer validation (SDLC) contains planning, specification, programming, testing, start-up, documentation, operation, checking, and changing. To validate the software according to the requirements given above, the following activities should be part of the SDLC:

- Documentation
  - Project plan/application
  - Quality plan
  - User requirements
  - Functional specifications
  - User manual
  - System operator manual
- SDLC document standards
- Risk analysis
- Coding modules/setting of parameters/configuration
- Planning and performing module and integration tests
- Software installation
- Planning and performing acceptance tests
- Validation report/release
- Putting out of action

The comprehensive activities that must be considered for the points listed above include:

- Management of configuration
- Failure investigation and corrective activities
- Change control
- Training
- Responsibilities
- Planning and performing of audits
- Planning and performing of reviews

The life cycle for the hardware is divided into the following steps:

1. Obtaining and Installation
2. Operation
3. Putting out of action

The physical conditions in the computer systems' surroundings could have an effect on the operation. Therefore, these conditions must be controlled or protective measures must be taken. The physical quantities that must be controlled include:

- Temperature
- Humidity
- Voltage stability
- Smoke

Controls and protective measures must be considered during planning or modification of all rooms with computerized systems for the following factors:

- Aggressive gases
- Voltage fluctuation
- Flash of lightning
- Fire
- Water
- Vibration
- Electrostatic charge

The range of controls and protective measures should be specified for each system separately according to the sensitivity of the system and the associated risk.

The Validation Report is the final document of all validation activities. It summarizes the essential parts of the activities and marks the end of the validation process. Separate reports for the validation sub-sections listed below must be written.

2.3.9 Validation Report

2.3.9.1 Definition

- Qualification — Includes: DQ, RA, IQ, OQ, PQ
- Process validation — PV
- Cleaning validation — CLV
- Computer validation — CV

The Validation Report refers to these sub-sections.

2.3.9.2 Contents

A detailed discussion of the following points should be included in the Validation Report:

1. Changes and deviations of the qualification/validation activities from the documentation must be listed. The measures taken instead must be justified and incomplete measures must be listed.
2. Critical points found during qualification/validation that are not included in the risk analysis must be listed and the measures taken described.
3. The Validation Report must include an overview of all documentation, including appendices.
4. At the end of the Validation Report, a statement must be given as to whether or not the equipment and the processes have the status "qualified/validated."

2.3.10 General Acceptance Criteria

The general acceptance criteria for the tests during IQ, OQ, and PQ processes are listed in subsequent chapters. Specific acceptance criteria that belong to individual test procedures are listed in each separate qualification document.

2.3.10.1 Installation Qualification

1. All parts of the plant must be produced and installed according to approved documents from the manufacturer. These could be:
   a. Process and service flow sheets
   b. Construction/P&I diagrams
   c. Layout and installation specifications
   d. Manufacturer's manuals and statements
2. All documents listed must be available.
3. All critical parameters, equipment models, capacity, and material must be checked and proved against approved construction and order specifications.
4. The performance of electrical devices must be checked.
5. Manuals and lists of spare parts must be available.
6. Results of equipment test runs by the manufacturer must be satisfactory.

2.3.10.2 Operational Qualification

1. Tests must be done according to approved plans for testing and using suitable test procedures.
2. Automatic systems (e.g., locks, alarms, or timers) that are connected to systems to be validated must work according to their approved design specifications.
3. All systems and equipment parts must work reliably under normal plant operating conditions.
4. The operating status of systems that contain programmable process controls as part of the equipment must be equivalent to the status defined in the program.
5. Indicating and recording instruments used in test procedures and normal operation must be calibrated by qualified personnel.
6. The first draft of SOPs for normal operation, control, and maintenance must be available.
7. The first calibration of measurement and control devices must be checked.
8. Operational staff must be trained in their areas of responsibility.

2.3.10.3 Performance Qualification

1. The system must operate within the specifications for a longer period of time.
2. Samples must have the specified quality.

2.4 DOCUMENTATION FORMAT OF QUALIFICATION PROGRAM

2.4.1 The Coversheet

The coversheets of the different qualification programs should be designed as follows.

The header contains the name of the pharmaceutical manufacturer, the specific plant name, and the document number.

ABC	ABC Pharmaceutical Company	Doc.-No.:

Each coversheet should contain the following points below the header:

- Title
- Area of application
- Number of pages
- Version number

The author as well as the person approving the document should be named in the next section of the coversheet. The position of these persons should also be given. All following pages should contain the number of pages and the current page number within the header.

2.4.2 Document Structure

The documentation of each qualification procedure is divided into two sections. The first section is a general section that includes, for example, the coversheet, the history, the table of contents, and all other points except for the test specifications and the results of the tests. The second section includes the test specifications and the results of the tests. Each test specification should be listed in the table of contents.

2.4.2.1 Header Test Specification

The structure of the test specification header is the same as the header of the general section except for the number of pages. The pages of each test specification should be counted separately so that the page number Z represents the pages of a single test specification.

2.4.3 Change of Documents

If it is necessary to edit or remove test specifications from the documentation, this should be done according to the following procedure.

1. The version number of the test specification should be increased by one after the specification is edited (i.e., version V01 becomes version V02).
2. The results of the test should be updated.
3. The version number of the general section should be increased by one.
4. The history should be updated.
5. The table of contents should be updated.
6. The changes should be approved by qualified personnel by signature on a new coversheet. (The approval is valid for the changes only.)

Each qualification document could contain sections/specifications with different version numbers.

2.5 NUMBERING SYSTEM

2.5.1 Numbering System for Equipment

To identify the main parts of the plant and equipment, a numbering system is used based on the ABC Pharmaceutical Equipment Code.

2.5.2 Numbering System for Validation/Qualification Documentation

The purpose of a numbering system for the documentation is to ensure an unambiguous identification of each validation/qualification document produced within the field of application of the Validation Master Plan. The document number is a combination of letters and numbers with a length of 10 or 11 characters. An example of such a document number might be:

MM001IQ.V01 or RO001CLP.D01

The letters in the first and second positions represent the area that is covered by the document (e.g., qualification of rooms or validation of liquids). A legend for the first two letters is given below:

Rooms	=	RO
Manufacturing machines	=	MM

Liquid dosage forms	=	LI
Creams/ointments/suppositories	=	CR/OT/ST
Solid dosage forms	=	SO
Cleaning	=	CL
Computer systems	=	CS
Service units	=	SU

The next three positions represent a serial number for the document. This number should be assigned according to the chronological order of documentation development.

The sixth through eighth positions represent the type of document (e.g., a specification or a performance qualification). A legend is given below:

Validation master plan	=	VMP
Specification	=	SP
Risk analysis	=	RA
Design qualification	=	DQ
Installation qualification	=	IQ
Operational qualification	=	OQ
Performance qualification	=	PQ
Validation report	=	VR
Process validation plan	=	PVP
Process validation program	=	PPG
Cleaning validation plan	=	CLP
Cleaning validation program	=	CPG
Computer validation plan	=	CVP

The first place to the right of the dot shows whether it is a version or a draft version of the document:

Version	=	V
Draft version	=	D

The subsequent two characters identify the serial number of the version or draft version.

3

REVALIDATION

The revalidation process is essential to maintain the validated status of the plant, equipment, manufacturing processes, and computer systems. It should be as important as calibration and maintenance.

Possible reasons for starting the revalidation process include:

1. The transfer of a product from one plant to another
2. Changes to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality
3. The necessity of periodic checking of the validation results

Note to point 1: For the transfer of a product from one plant to another qualified production plant, it is essential to revalidate the entire manufacturing process in the new plant. It is possible that several new critical or noncritical parameters must be determined.

Note to point 2: In the case of the following changes, revalidation might be necessary:

- Changes in the plant
- Changes in product composition
- Changes in manufacturing processes
- Changes in the packaging materials
- Changes to computer systems
- Changes in the cleaning processes or agents
- Changes which may affect the quality and efficacy of product

The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.

Note to point 3: Periodic revalidation must be done to ensure that no unintentional changes were made and to prove that the results of the previous validation procedures are still valid.

The period of time between the revalidation activities is fixed by the review team. The members of this team should consider the following questions:

1. Are the manufacturing processes sterile, or not?
2. Are the results of the plant (product, performance) expected?
3. Are maintenance and calibrating procedures carried out regularly?
4. What are the critical stages of the processes?

4

FACILITY DESCRIPTION

ABC Pharmaceutical is a medium-sized pharmaceutical industry in New York state and employs approximately 500 employees. The plant intends to produce millions of units annually. The annual sales of the plant are above U.S. $200 million. The total covered area is 50,000 square feet. ABC Pharmaceutical places basic emphasis on the concept of quality and on strict compliance with the rules of current Good Manufacturing Practice (cGMP) in all steps of manufacturing, shipping, and marketing.

The Head Office of ABC Pharmaceutical is located at Kennedy Airport Road, approximately 60 km east of New York City, New York, U.S.A.

Building "A" of ABC Pharmaceutical is designed to manufacture dry oral products. The conventional pharmaceutical dosage forms include tablets, capsules, and powders for suspension.

Building "B" of ABC Pharmaceutical is designed to manufacture liquids and semisolid products. The conventional pharmaceutical dosage forms include drops, syrups, suspensions, creams/ointments, and suppositories.

Building "C" is designed to manufacture injectables in ampoules, vials, and disposable ready-to-use syringes, and lyophilized products in vials.

The products manufactured are shipped in market packages to customers worldwide.

The plant operations are administered through the Administration Division, Quality Affairs Division, and Technical Affairs Division as below:

Quality Affairs Division
- Quality Assurance
- Quality Control
- Product Development Laboratory
- Registration

Technical Affairs Division
- Production
- Packaging

- Materials Planning
- Maintenance
- Shipping
- Purchasing

Administration Division

- Marketing
- Personnel
- Accounts
- Management Information System

4.1 LINE CAPACITIES

Production line capacities for ABC Pharmaceutical would be as follows in the different dosage forms:

- The capsule line, with an annual production capacity of about 50 million capsules.
- The tablets line, with an annual production capacity of about 1 billion tablets.
- The powder for suspension line, with an annual production capacity of about 3 million bottles.
- The syrup and suspension line, with an annual production capacity of about 60 million bottles.
- The drops line, with an annual production capacity of about 10 million bottles.
- The cream and ointment line, with an annual production capacity of about 15 million tubes.
- The suppositories line, with an annual production capacity of about 20 million suppositories.
- The injectable line, with the following annual production capacity of
  - Ampoules 12 million
  - Disposable syringes 5 million
  - Lyophilized vials 3 million
  - Vials 10 million

The following is a detailed description of ABC Pharmaceutical, which in addition to the warehouse, reception, and cafeteria, consists of three buildings A, B, and C:

A: Dry products
B: Liquids and semisolid products
C: Parenteral products

The buildings can be divided into three sections:

1. Description of building
2. Description of equipment
3. Description of process

4.1.1 Building Description

The design and material selection will be done according to cGMP regulations. All walls and ceilings inside the production area are designed as recommended by cGMP, and cleanroom walls and ceilings are designed as cleanroom sandwich steel panels with a chemical-resistant coating and nonporous surfaces. The panel joints are sealed with silicon or acrylic sealants. The wall bases as well as the floor are covered with seamless epoxy coating. For room specifications, climate, and utilities, refer to Chapter 5:

1. Building for dry production
2. Building for liquid and semisolid production
3. Building for parenterals production

4.1.2 Equipment Description

This section provides facility, HVAC, and major equipment descriptions for the following areas of all three manufacturing buildings.

1. Equipment for dry production
2. Equipment for liquid and semisolid production
3. Equipment for parenterals production
4. HVAC of dry production area
5. HVAC of liquid and semisolid production area
6. HVAC of parenterals production area
7. Raw material stores and weighing area
8. Over-printing
9. Quality Control
10. Quality Assurance (in-process)
11. Product Development Laboratory

4.1.3 Process Description

This description provides a summary of process steps and control parameters for the following dosage forms:

1. Tablets
2. Capsules
3. Powder for suspensions
4. Drops
5. Syrups
6. Suspensions
7. Creams/ointments
8. Suppositories
9. Injectables
   a. Aseptic fill (ampoules/vials/syringes)
   b. Terminally sterilized (ampoules/vials)
   c. Lyophilized (vials)

The pharmaceutical products of ABC Pharmaceutical include the following dosage forms and processes.

4.1.3.1 Dry Oral Production

The conventional pharmaceutical products include the following dosage forms and processes.

Tablets	*Capsules*	*Powder for Suspensions*
Milling	Milling	Mixing
Blending	Blending	Filling
Compression	Capsulation	Packing
Blistering	Blistering	
Packing	Packing	

4.1.3.2 Liquids and Semisolid Oral Production

The conventional pharmaceutical products include the following dosage forms and processes.

Syrups	*Drops*	*Suppositories*	*Creams/Ointments*
Mixing	Mixing	Compounding	Compounding
Filling	Filling	Filling	Filling
Packing	Packing	Packing	Packing

4.1.3.3 Injectables

Aseptic Fill Amp./Vials	*Terminally Sterilized Amp./Vials*	*Lyophilized Vials*	*Ready-to-Use Disposable Syringes*
Solution preparation	Solution preparation	Solution preparation	Solution preparation
Sterile filtration	Filtration	Sterile filtration	Sterile filtration
Aseptic filling/sealing	Filling/sealing	Aseptic filling	Aseptic filling
Leak test	Steam sterilization	Pre-stoppering	Stoppering
Optical checking	Leak test	Shelf chamber loading	Inspection
Labeling/packing	Optical checking	Lyophilization	Plunger rod assembly
	Labeling/packing	Freezing Sublimation Desorption	Blister packing
		Full stoppering	
		Chamber unloading	
		Container sealing	
		Optical checking	
		Labeling/packing	

5

DESCRIPTION OF BUILDING

5.1 DRY PRODUCTION FACILITY: BUILDING A

Civil

Room No.	Area	Activity	Floor		Wall		Ceiling	
			Construction	Covering	Construction	Covering	Construction	Covering

Area Requirement

Room No.	Area	Activity	RH	Temp.	Lux	Sound Level	Gases	Water	Steam

5.2 LIQUID AND SEMISOLID PRODUCTION FACILITY: BUILDING B

Civil

Room No.	Area	Activity	Floor		Wall		Ceiling	
			Construction	Covering	Construction	Covering	Construction	Covering

Area Requirement

Room No.	Area	Activity	RH	Temp.	Lux	Sound Level	Gases	Water	Steam

5.3 PARENTERALS PRODUCTION FACILITY: BUILDING C

Civil

Room No.	Area	Activity	Floor		Wall		Ceiling	
			Construction	Covering	Construction	Covering	Construction	Covering

Area Requirement

Room No.	Area	Activity	RH	Temp.	Lux	Sound Level	Gases	Water	Steam

6

EQUIPMENT DESCRIPTION

6.1 DRY PRODUCTION: BUILDING A

Stores and Weighing Area

Location	*Equipment Name*	*Capacity*	*Manufacturer*
	Weighing scale		
	Weighing station (LF)		

Mixing/Blending/Sieving

Location Room No.	*Equipment Name*	*Manufacturer*
	Granulation machine	
	Milling machine	
	Sieving machine	
	Blender	

Encapsulation

Location Room No.	*Equipment Name*	*Manufacturer*
	Capsule filling machine	
	Capsule sorting machine	
	Hard gelatin capsule polisher	

Capsule Blistering

Location Room No.	*Equipment Name*	*Manufacturer*
	Thermoform blister machine	

Tablets Compression

Location Room No.	*Equipment Name*	*Manufacturer*
	Compression machine	

Sugar/Film Coating

Location Room No.	*Equipment Name*	*Manufacturer*
	Air pressure pump	
	Cota 60″	
	Coating pan	

Powder Filling

Location Room No.	*Equipment Name*	*Manufacturer*
	Powder filling machine	
	Capping machine	

Labeling and Cartoning Area

Location Room No.	*Equipment Name*	*Manufacturer*
	Labeling machine	
	Cartoning machine	

6.2 LIQUID AND SEMISOLID PRODUCTION: BUILDING B

Stores and Weighing Area

Location Room No.	*Equipment Name*	*Manufacturer*
	Weighing cabinet (balance)	
	Weighing station	

Syrups/Suspensions/Drops Manufacturing

Location Room No.	*Equipment Name*	*Manufacturer*
	Syrup manufacturing tank	
	Filter press	
	Suspension manufacturing tank	
	Drops manufacturing vessel	

Syrups/Suspensions/Drops Fill and Pack

Location Room No.	*Equipment Name*	*Manufacturer*
	Syrup filling machine	
	Capping machine	
	Labeling machine	
	Cartonator	
	Shrink-wrapping machine	
	Suspension filling machine	
	Capping machine	
	Labeling machine	
	Cartonator	
	Shrink-wrapping machine	
	Drops filling machine	
	Capping machine	
	Labeling machine	
	Cartonator	

Creams/Ointments and Suppository Manufacturing

Location Room No.	*Equipment Name*	*Manufacturer*
	Manufacturing vessel	
	Homogenizing machine	
	Transfer pump	

Creams/Ointments and Suppository Fill and Pack

Location Room No.	*Equipment Name*	*Manufacturer*
	Cream filling and packing machine	
	Cartonator	
	Ointment filling and packing machine	
	Cartonator	
	Suppository filling and packing machine	

6.3 PARENTERALS PRODUCTION: BUILDING C

Solution Preparation

Location Room No.	*Equipment Name*	*Manufacturer*
	Mobile vessel - 500 liter	
	Integrity testing	

Ampoule/Vial Washing and Dry Heat Sterilization

Location Room No.	*Equipment Name*	*Manufacturer*
	Washing machine for amp./vials	
	Hot sterilization tunnel	

Aseptic Filling for Ampoules and Vials

Location Room No.	*Equipment Name*	*Manufacturer*
	Vial filling and closing machine	
	Ampoule filling and sealing machine	
	Laminar flow unit	

Steam Sterilization (Autoclave)

Location Room No.	*Equipment Name*	*Manufacturer*
	Steam sterilizer (autoclave)	

Syringe Preparation and Filling

Location Room No.	*Equipment Name*	*Manufacturer*
	Laminar flow unit	
	Filling and closing machine for syringes	

Freeze Drying

Location Room No.	*Equipment Name*	*Manufacturer*
	Freeze dryer	
	Rotary table	
	Automatic loading/unloading system	
	Automatic vial closing machine	
	Buffer and feeding equip. for bottles	
	Control panel for freeze dryer	

Ampoule Coding

Location Room No.	*Equipment Name*	*Manufacturer*
	Automatic ampoule coding machine	

Packing

Location Room No.	*Equipment Name*	*Manufacturer*
	Labeling machine for amp./vials	
	Rotary infeed table	
	Inspection machine for amp./vials	

6.4 OVER-PRINTING AREA

Location Room No.	*Equipment Name*	*Manufacturer*
	Labels/Box printing machine	
	Leaflet folding machine	
	Aluminum foil and PVC printing machine	

6.5 QUALITY CONTROL

Location Room No.	*Equipment Name*	*Manufacturer*
	Autoclave	
	Hot air sterilizer	
	Laminar air flow	
	Incubator	
	Refrigerator	
	pH meter	
	Microscope	
	Water bath	
	Compact sterility tester	
	Analytical balance; Min. 0.5 g, Max. 3100 g	
	Analytical balance	
	Distillation unit	
	Hot plate	
	Vortex mixer	
	UV-VIS spectrophotometer	
	UV-VIS spectrophotometer w/auto sampler	
	IR spectrophotometer	
	Luminescence spectrometer	
	Dissolution apparatus	
	Potentiometer	
	Moisture analyzer	

Location Room No.	*Equipment Name*	*Manufacturer*
	HPLC	
	HPLC	
	Refractometer	
	Conductivity meter	
	pH meter	
	Polarimeter	
	Friability tester	
	Viscometer	
	Suppository hardness tester	
	Suppository melting tester	
	Antibiotic zone reader	
	Air sampler	
	Centrifuge	
	Muffle furnace	

6.6 QUALITY ASSURANCE (IN-PROCESS)

Location Room No.	*Equipment Name*	*Manufacturer*
	Analytical balance	
	Torque tester	
	Leak test chamber	
	Tablet/capsule testing system	
	Friabilater	
	Disintegration unit	
	Analytical balance	
	Moisture analyzer	
	pH meter	

6.7 PRODUCT DEVELOPMENT LABORATORIES

Location Room No.	*Equipment Name*	*Manufacturer*
	Granulator	
	Oven	
	Granulator	
	Compression machine	
	Sugar coating pan	
	Blister machine	
	Digital pH meter	
	Granulate flow tester	
	Particle size analyzer	
	Hardness tester	

7

HVAC DESCRIPTION

7.1 DRY PRODUCTION FACILITY: BUILDING A

Stores and Weighing Area

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Weighing scale	A:BLU 30	20	1440
	Weighing station (LF)			

Blending/Sieving

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Granulation machine	A:BLU 30	20	4160
	Mill/Sieve			
	Pneumatic conveyor			
	Bin weighing station			
	Tumbler			
	Drum emptying station			

Encapsulation

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Capsule filling machine	A:BLU 30	20	2880
	Capsule sorting machine			
	Hard gelatin capsule polisher			

Capsules Blistering

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Thermoform machine	A:BLU 30	20	6720
	Cartonator			

Tablet Compression

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Compression machine	A:BLU 20	20	1920
	Compression machine	A:BLU 30	20	2880
	Compression machine	A:BLU 30	20	2880

Sugar/Film Coating

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Air pressure	A:BLU 40	20	2520
	Cota 60"	A:BLU 40	20	2520

Powder Filling

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Powder filling	A:BLU 30	20	2880
	Capping machine			

Labeling and Cartoning Area

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Labeling machine	A:BLU 40	20	3840
	Rotary table			

7.2 LIQUID AND SEMISOLID PRODUCTION FACILITY: BUILDING B

Stores and Weighing Area

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Weighing cabinet (balance)	B:BLU 30	20	1440
	Weighing station			

Syrups/Suspensions/Drops Manufacturing

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Syrup manufacturing tank	B:BLU 30	20	2880
	Filter press	B:BLU 30	20	2880
	Suspension manufacturing tank	B:BLU 10	20	2680
	Drops manufacturing vessel	B:BLU 20	20	2550

Syrups/Suspensions/Drops Fill and Pack

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Syrup filling machine	B:BLU 40	20	3360
	Capping machine			
	Labeling machine			
	Cartonator			
	Shrink wrapping machine			

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Suspension filling machine	B:BLU 30	20	3210
	Capping machine			
	Labeling machine			
	Cartonator			
	Shrink wrapping machine			
	Drops filling machine	B:BLU 30	20	2880
	Capping machine			
	Labeling machine			
	Cartonator			

Cream/Ointment and Suppository Manufacturing

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Manufacturing vessel	B:BLU 20	20	2520
	Homogenizing machine			
	Flux pump			

Cream/Ointment and Suppository Fill and Pack

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Cream filling and packing machine	B:BLU 10	20	2960
	Cartonator			
	Ointment filling and packing machine			
	Cartonator			
	Suppository filling and packing machine	B:BLU 10	20	2210

7.3 PARENTERALS PRODUCTION FACILITY: BUILDING C

Solution Preparation

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Mobile vessel, 300 liter	C:BLU 50	20	2120
	Integrity testing			

Ampoule/Vial Washing and Dry Heat Sterilization

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Washing machine for amp./vial	C:BLU 50	20	5880
	Hot sterilization tunnel			

Aseptic Filling for Ampoules and Vials

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Vial filling and closing machine	C:BLU 50	30	2970
	Ampoule filling and sealing machine			
	Laminar flow unit			

Steam Sterilization (Autoclave)

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Steam sterilizer (autoclave)	C:BLU 50	30	2070

Syringe Preparation and Filling

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Laminar flow unit	C:BLU 50	20	840
	Conveyors			
	Filling and closing machine for syringes	C:BLU 50	30	1620

Freeze Drying

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Freeze dryer technical area	C:BLU 10	20	990
	Rotary table	C:BLU 50	30	2700
	Conveyor			
	Automatic loading/unloading system			
	Automatic vial closing machine	C:BLU 50	20	720
	Buffer and feeding equipment for bottles			
	Control panel for freeze dryer	C:BLU 10	20	1210

Ampoule Coding

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Automatic ampoule coding machine	C:BLU 50	20	550

Packing

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Conveyor belt	C:BLU 40	20	4500
	Labeling machine for amp./vial	C:BLU 40	20	4020
	Rotary infeed table			
	Inspection machine for amp./vial			

7.4 OVER-PRINTING AREA

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Labels/box printing machine	B:BLU 10	20	3210
	Leaflet folding machine			
	Aluminum foil and PVC printing machine			

7.5 QUALITY CONTROL

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Autoclave	B:BLU 10	20	5040
	Hot air sterilizer			
	Laminar air flow			
	Incubator			
	Refrigerator			
	pH meter			
	Microscope			
	Water bath			
	Compact sterility tester			
	Analytical balance, min. 0.5 g, max. 3100 g			
	Analytical balance, min. 0.1 mg, max. 210 g			
	Distillation unit			
	Hot plate			
	Vortex mixer			
	UV-VIS spectrophotometer			
	IR spectrophotometer			
	Luminescence spectrometer			
	Dissolution apparatus			
	Potentiometer			
	Moisture analyzer			
	HPLC			

7.6 QUALITY ASSURANCE, IN-PROCESS

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Analytical balance	B:BLU 10	20	2210
	Torque tester			
	Leak test chamber			
	Tablet/capsule testing system	A:BLU 10	20	2210
	Friabilater			
	Disintegration unit			
	Analytical balance			
	Moisture analyzer			
	pH Meter			

7.7 PRODUCT DEVELOPMENT LABORATORIES

The HVAC system covering this area is controlled by air handling unit (AHU) No.

Location	*Equipment Name*	*AHU No.*	*Min. Air Change*	*Air Flow (m^3/h)*
	Granulator	BLU 15	20	4410
	Oven			
	Granulator			
	Compression machine			
	Fette (single station)			
	Sugar coating pan			
	Blister machine			
	Krieger			
	Digital pH meter			
	Granulate flow tester			
	Particle size analyzer			
	Hardness tester			

8

UTILITIES DESCRIPTIONS

The major utilities involved in the routine operation of the plant are as follows:

8.1 DEIONIZED WATER (DI WATER)

DI water is produced using an XYZ rapid, high-performance, twin-bed deionizer. The plant consists of two glass-reinforced plastic pressure vessels that hold the ion exchange resins together with a process pump, pipe work, valves, flowmeters, and controls to enable the plant to produce high-quality deionized water and automatically regenerate the resins.

8.2 PURIFIED WATER

The water treatment plant produces Purified Water. The unit that fills the 1000-liter storage tank is located in building C first floor from where a loop will start to distribute water in building C. A separate distribution loop starts in building C and allows filling of tanks in buildings A and B.

8.3 WATER FOR INJECTION

The Water for Injection (WFI) is produced by an XYZ multi-effect water still (type 300-S), which is intended to produce pure, pyrogen-free distilled water from pretreated feed water by evaporating and condensing the feed water (i.e., DI Water). The water still consists of pressure vessels, five columns, and a condenser. The piping between the pressure vessels is stainless steel (S.S.) 316L.

The WFI distribution system (storage tanks, circulation pumps, pipework) is steam sterilized. The sterilization cycle is controlled and monitored by temperature indicators located at critical points.

8.4 CHILLED WATER

Two chillers (300-ton capacity each) provide Chilled Water for various air handling units and all machinery in need of chilled water. Another chiller (15-ton capacity) provides chilled water to boiler, compressor, and deionized water plant.

8.5 PURE STEAM

Pure Steam is produced by an XYZ 1500-S pure steam generator. The generator is fed with deionized water that descends the inside tubes where it is converted into steam. The steam generator is located in building C first floor, from where the loop diverts to different use points; steam traps are installed to collect condensate when necessary. The quality of pure steam condensate is the same as for Water for Injection.

8.6 COMPRESSED AIR

The plant has two reciprocating oil-free compressors, with a total capacity of 20 m^3/h. The oil-free Compressed Air is supplied to a stainless steel air receiver. The air then passes through the air filter along with the oil and water separator system and passes through the air dryer and is distributed through S.S. use points in the three buildings. Terminal sterile filtration (0.01 μm) is used at critical use points.

8.7 NITROGEN (N_2)

Nitrogen is supplied by a membrane generator with a capacity of 20 m^3/h and a minimum purity of 97%. Nitrogen is distributed by an S.S. 316L pipe network with TIG welding to all required use points. Nitrogen is utilized for the following:

- Purging during solution preparation
- Pressurizing process vessels for product transfer and filtration
- Purging during filling of oxygen-sensitive products
- Vacuum break during freeze drying
- Removal of air during filling of liquids

8.8 CARBON DIOXIDE (CO_2)

Carbon Dioxide is supplied in cylinders and distributed by stores from the gas cylinders storage area. Carbon dioxide is utilized during manufacturing of liquids for blanketing oxygen-sensitive products.

8.9 ELECTRIC POWER

ABC Pharmaceutical's total peak power consumption is about 4000 kWh, and is obtained from Water and Electricity Supply Corporation, New York. ABC Pharmaceutical also has three (2) standby generators totalling 4500 KVA, which are to be used during main power failure.

8.10 SANITARY WATER

ABC Pharmaceutical's average water consumption (based on 3 months, i.e., June, July, and August) is about 80,000 gal/day; the water obtained from Water and Electricity Supply Corporation, New York.

The water is stored in an underground tank having a capacity of 200,000 gal.

8.11 HVAC (HEATING, VENTILATION, AND AIR-CONDITIONING) SYSTEM

Buildings A, B, and C of ABC Pharmaceutical have a total of 35 Air Handling Units (AHUs). Each building has its own HVAC system with absolutely separate air handling units.

Building A	Dry production
Building B	Liquids and semisolid production
Building C	Parenterals production

No contamination is allowed between the three buildings. They are completely segregated.

All air handling units (AHUs) are intended to be in continuous operation. The AHU fans are equipped with built-in air flow measuring devices of the direct-read type (Q-nozzles). This will facilitate monitoring of the delivered air at remote locations. All exhaust fans are also provided with air flow measuring devices. Some of the parameters will be continuously monitored in the critical areas, as shown in the monitoring document. Table 8.1, a monitoring document for buildings A, B, and C, respectively, provides the following information:

Room number
Activity
Cleanliness class
Pressure (Pascal)
Temperature (°C)
Relative humidity (%)
Number of air changes
AHU number

Table 8.1 Monitoring Document for HVAC System

Building A

Room No.	*Activity*	*Cleanness Class*	*Pressure (Pascal)*	*Temperature (°C)*	*Relative Humidity (%)*	*No. of Air Changes*	*AHU No.*

Building B

Room No.	*Activity*	*Cleanness Class*	*Pressure (Pascal)*	*Temperature (°C)*	*Relative Humidity (%)*	*No. of Air Changes*	*AHU No.*

Building C

Room No.	*Activity*	*Cleanness Class*	*Pressure (Pascal)*	*Temperature (°C)*	*Relative Humidity (%)*	*No. of Air Changes*	*AHU No.*

9

VALIDATION PROGRAM OVERVIEW

9.1 VALIDATION PROJECT MANAGEMENT: ORGANIZATION

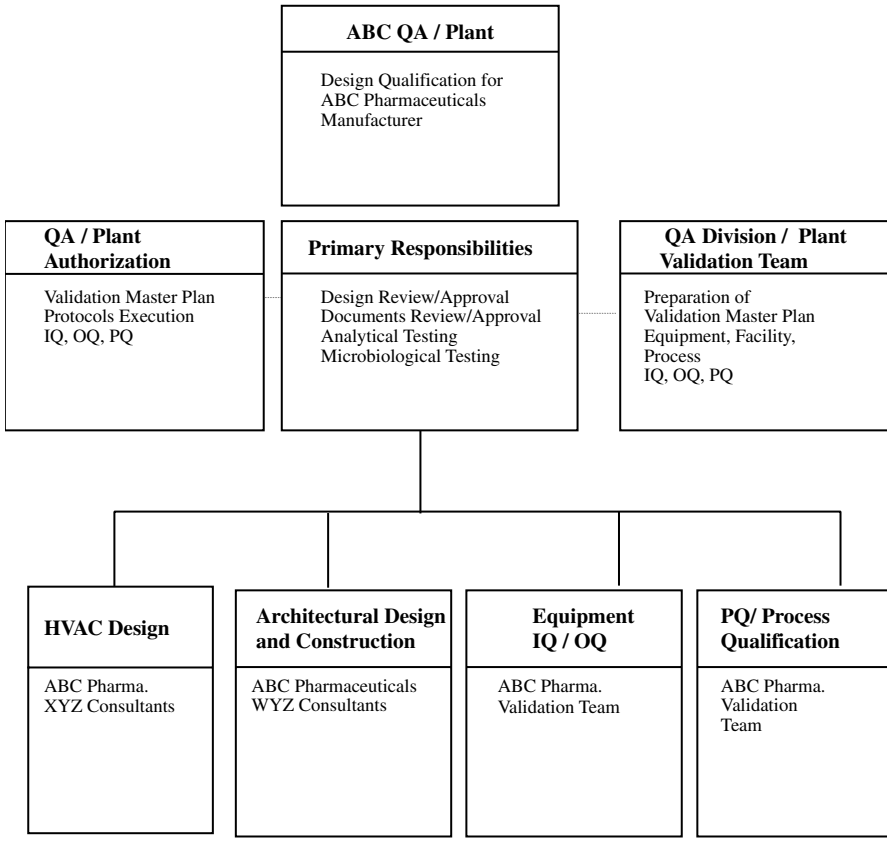

Figure 9.1 The organization and responsibilities of the ABC Pharmaceutical validation.

9.2 VALIDATION RESPONSIBILITIES

The Validation Team has overall responsibility for validating the facility. The Quality Assurance Manager has responsibility for approval of all validation protocols, final reports, standard operating procedures, chemical and microbiological testing, as well as other critical cGMP documentation.

9.3 DESIGN AND VALIDABILITY REVIEW

The validation of the ABC Pharmaceutical facility is to be started simultaneously with the initial conceptual design. At key stages throughout the

design process, design review meetings are to be held to review and make key cGMP design decisions.

Through these design review meetings, cGMP and functionality requirements have and continue to be determined for each aspect of the facility, including:

- Architectural layout
- Civil work execution
- HVAC and cleanroom
- Water for Injection/Purified water
- Steam
- Oil-free compressed air
- Personnel and material flow
- Mechanical equipment
- Material receipt, storage, and shipping
- Quality Assurance/Control testing and inspection
- Drainage system
- Process equipment design
- Maintenance and calibration access
- Emergency power
- Safety engineering
- Waste disposal

Class Equipment and Systems

1. Class I Equipment and Systems: systems representing processes, equipment, and areas with the highest degree of product quality and regulatory impact. For example:
   a. Product/commodity sterilization and depyrogenation
   b. Utilities utilized during manufacturing (e.g., distilled/deionized water facilities, compressed air, etc.)
   c. HVAC system
2. Class II Equipment and Systems: systems representing processes, equipment, and areas with a high degree of product quality and impact, but which are established processes generally recognized as prevalent throughout the drug industry. For example:
   a. Equipment used in product processing (e.g., manufacturing tanks, mixers, blenders, dryers, etc.)
   b. Product fill/seal machines
   c. Commodity washers
   d. Granulators.

3. Class III Equipment and Systems: systems representing processes, equipment, and areas with a low regulatory and product impact. For example:
   a. Cap assemblers, cleaners, and washers
   b. Drying equipment
   c. Incubators

9.4 VALIDATION DOCUMENTS

Enhanced Turn-Over Package (ETOP)

The Enhanced Turn-Over Package (ETOP) consists of documentation binders or files that contain all relative design, installation, and testing documentation generated during the design and construction of a particular engineered system such as HVAC or Pure Steam. ETOPs serve to capture all engineering documentation generated throughout the design construction process.

This information is compiled into single-source packages, which then provide the foundation for Installation and Operational Qualification.

The Enhanced Turn-Over Package (ETOP) for each system contains all information relating to the following areas:

- General
- Equipment
- Piping
- Instrumentation
- Controls and automation
- Electrical
- Operating procedures
- Maintenance procedures and schedules
- Calibration procedures and schedules
- Calibration specifications (accuracy requirements)

An Enhanced Turn-Over Package (ETOP) is prepared for each of the following systems:

- Water for Injection (WFI) system
- Pure steam
- Plant steam
- Drainage and waste decontamination system
- Compressed gas system
- Electrical system

- Building automation system
- HVAC system
- Civil work execution

Certification Package Requirements

The following table summarizes the documentation package requirements for each equipment system classification.

Equipment Class	*Certification Package Requirements*[a]
Class I	IQ, OQ, and PQ
Class II	IQ and PQ

[a] IQ = Installation Qualification; OQ = Operational Qualification; PQ = Performance Qualification

9.5 INSTALLATION QUALIFICATION PROTOCOLS

The Installation Qualification (IQ) verifies that the equipment or system and/or corresponding utilities are installed in accordance with design specifications, manufacturer recommendations, and cGMPs. In addition, the IQ will confirm that critical instruments are calibrated and that system components are properly identified. Any exceptions will be documented, corrected, and/or justified.

Where possible and applicable, pre-shipment inspection of equipment and documentation is included as part of the Installation Qualification.

Pre-shipment inspection can be performed along with vendor audits to address issues such as software development and quality assurance plans, operational reports, and specific vendor/purchaser inspection reports.

Typical Installation Qualification test functions include, but are not limited to, the following:

- Manufacturer specifications
- Purchase order specifications
- Piping and installation drawing (P&ID)
- Construction and installation
- Test equipment calibration
- Required spare parts
- Cleaning/passivation
- Weld inspection
- System installation compliance to cGMPs

The IQ is performed in accordance with a preapproved written protocol. The specific IQ attributes to be verified during the performance of the IQ protocol will be developed from system and component design criteria, cGMP requirements, and other specifying documentation. They, along with the acceptance criteria, will be approved as part of the protocol approval process.

9.6 OPERATIONAL QUALIFICATION PROTOCOLS

The Operational Qualification (OQ) verifies that the system or equipment operates in accordance with design specifications, manufacturer recommendations, and cGMPs. OQ testing is designed to simulate the full range of operating conditions to establish a system capabilities baseline and to ensure that the system operates as intended.

Operational Qualification test functions include, but are not limited to, the following:

- General operational and control verification
- Functional testing of computer-related systems
- Specific operational testing (generation of baseline data)
- Utility system capability
- Calibration of test equipment
- Standard operating procedures (SOPs)
- Maintenance procedures
- Cleaning or sanitizing procedures

For equipment or systems controlled or monitored by a computer-related system, the functional testing cycle approach to computer validation is included and performed as part of the Operational Qualification. Functional testing verifies that the integrated hardware and software program perform in accordance with the functional specifications developed during the requirements phase.

The Operational Qualification is performed in accordance with a preapproved written protocol. The specific Operational Qualification attributes to be verified during the performance protocol will be developed from the design specifications, manufacturer documentation, cGMP requirements, and other specific documentation. They, along with the acceptance criteria, will be approved as part of the protocol approval process.

9.7 CHANGE CONTROL INITIATION

Each system/equipment/process will be covered by the Engineering Change Control program immediately following the completion of the OQ test functions. Any change(s) made to the system during OQ must be documented in the Final Report. Any engineering changes proposed after OQ (i.e., during cycle development, performance qualification, or manufacturing) must be preapproved and follow the Engineering Change Control procedure.

If changes are made prior to approval of the Final Report, the Change Control documentation must be included in the Validation Packages, and the change and its justification must be documented in the Final Report.

9.8 CYCLE DEVELOPMENT

Critical processes other than the actual product manufacturing process — such as sterilization, component washing, and equipment cleaning — require prevalidation cycle development work. This may include establishment of appropriate sterilization cycle types, cleaning agents, etc. This test work is performed during or after Operational Qualification.

Cycle Development does not have to be performed per a written procedure; however, the procedure and results of all work must be recorded in laboratory notebooks, performed in accordance with cGMP documentation practices and sound scientific methods, and retained as part of the Validation Package. At the completion of Cycle Development work, a brief Cycle Development Report will be prepared that identifies parameters having a high probability of successfully meeting the Performance Qualification requirements.

9.9 PERFORMANCE QUALIFICATION PROTOCOLS

Performance Qualification (PQ) verifies the performance of critical utility systems or processes. Critical utility systems such as WFI and Pure Steam are challenged throughout proposed operating ranges for extended periods of time, while an extensive program of quality monitoring is performed. Critical processes such as sterilization of components are challenged three (3) consecutive times under worst-case conditions.

Performance Qualification is carried out in accordance with a preapproved written protocol. The specific PQ attributes to be verified during the performance of the protocol will be developed from the finished product specifications, research and development data, cGMP requirements, and other specific documentation. They, along with the acceptance criteria, will be approved as part of the protocol approval process.

9.10 PROCESS VALIDATION PROTOCOLS

Process Validation (PV) verifies the performance of the overall product manufacturing process. PV is performed on the entire product manufacturing process, which includes all support, processes, preparation of media, components, buffers, formulation, filtration, filling, and packaging.

During Process Validation, three (3) consecutive batches are manufactured, and all in-process and finished product specifications are verified at much higher than normal inspection quantities and frequencies. Critical parameters are set at different ranges during the manufacturing process to verify that the product consistently meets its predetermined quality specification over the range of critical parameter settings. Consequently, a proven acceptable range for each critical parameter is developed.

All equipment, processes, and quality assurance test procedures must be validated (or verified if using a compendial method) prior to the start of Process Validation.

Process Validation is performed in accordance with a preapproved written protocol. The specific PV attributes and process parameters to be verified during the performance of the protocol will be developed from the finished product specifications, research and development data, the manufacturing process capability, cGMP requirements, and other specific documentation. These, along with the acceptance criteria, will be approved as part of the protocol approval process.

9.11 VALIDATION FINAL REPORTS

The Final Report summarizes the results of the validation process and provides an analysis of the test data in support of the conclusion that the equipment or system demonstrates consistent performance within the established acceptance criteria. Deviations and/or exceptions to approved protocols, along with suitable explanations and justifications, are also documented in the Final Report.

9.12 VALIDATION PACKAGE

The Final Report, completed protocols, and all supporting documentation are then gathered into a Final Report Package for review, approval, and retention.

9.13 CERTIFICATION FOR USE IN MANUFACTURING

Validation of a system/equipment/process will be considered complete when its respective protocols identified in the Validation Master Plan have been successfully implemented and the Final Report has been approved.

A system/equipment/process may be certified for use in manufacturing upon completion of the following.

- Applicable protocols identified in the Validation Master Plan have been successfully completed and the Final Report has been approved.
- Applicable SOPs identified in the Validation Master Plan have been approved.
- Validation is complete for all utility systems that support the equipment or process, and for all equipment that supports a process.
- All system/equipment/process instrumentation is still within calibration.

9.14 REQUIRED PROTOCOLS AND PROCEDURES FOR DRY PRODUCTION: BUILDING A

IQ	Installation Qualification protocol	FR	Final Report
OQ	Operational Qualification protocol	OP	Operating Procedure
PQ	Performance Qualification protocol	CL	Cleaning Procedure
PV	Process Validation protocol	CAL	Calibration Procedure
PM	Preventive Maintenance procedure	CV	Computer Validation

System/ Equipment	*Protocols*					*SOPs*				
	IQ	*OQ*	*PQ*	*CL*	*FR*	*OP*	*PM*	*CL*	*CAL*	*CV*
Compressed air	1	1	1		1	1	1			1
HVAC and monitoring system	1	1	1		1	1	1			1
Drainage system	1	1			1		1			
Civil work	1				1					
Emergency power	1	1			1	1	1			
Labeling machine	1	1		1	1	1	1	1		1
Powder filling machine	1	1	1	1	1	1	1	1	1	1

System/ Equipment	Protocols					SOPs				
	IQ	OQ	PQ	CL	FR	OP	PM	CL	CAL	CV
Capsule filling machine	1	1	1	1	1	1	1	1	1	1
Mill	1	1		1	1	1	1	1	1	
Sifter	1	1		1	1	1	1	1	1	
Granulation machine	1	1		1	1	1	1	1	1	
Blister machine	1	1	1	1	1	1	1	1	1	1

9.15 REQUIRED PROTOCOLS AND PROCEDURES FOR LIQUID AND SEMISOLID PRODUCTION: BUILDING B

IQ Installation Qualification protocol
OQ Operational Qualification protocol
PQ Performance Qualification protocol
PV Process Validation protocol
PM Preventive Maintenance procedure
FR Final Report
OP Operating Procedure
CL Cleaning Procedure
CAL Calibration Procedure
CV Computer Validation

System/ Equipment	Protocols					SOPs				
	IQ	OQ	PQ	CL	FR	OP	PM	CL	CAL	CV
Compressed air	1	1	1		1	1	1			1
HVAC and monitoring system	1	1	1		1	1	1			1
Drainage system	1	1			1		1			
Civil work	1				1					
Emergency power	1	1			1	1	1			
Labeling machine	1	1		1	1	1	1	1		1
Syrup filling machine	1	1	1	1	1	1	1	1	1	1
Capping machine	1	1		1	1	1	1	1	1	1
Labeling machine	1	1		1	1	1	1	1	1	
Susp. filling machine	1	1	1	1	1	1	1	1	1	1
Capping machine	1	1		1	1	1	1	1	1	1
Labeling machine	1	1		1	1	1	1	1	1	

System/ Equipment	Protocols					SOPs				
	IQ	OQ	PQ	CL	FR	OP	PM	CL	CAL	CV
Drops filling machine	1	1	1	1	1	1	1	1	1	1
Capping machine	1	1		1	1	1	1	1	1	1
Cream filling/ packaging machine	1	1	1	1	1	1	1	1	1	1
Ointment filling/ packaging machine	1	1		1	1	1	1	1	1	1

9.16 REQUIRED PROTOCOLS AND PROCEDURES FOR PARENTERALS PRODUCTION: BUILDING C

IQ Installation Qualification protocol
OQ Operational Qualification protocol
PQ Performance Qualification protocol
PV Process Validation protocol
PM Preventive Maintenance procedure
FR Final Report
OP Operating Procedure
CL Cleaning Procedure
CAL Calibration Procedure
CV Computer Validation

System/ Equipment	Protocols					SOPs				
	IQ	OQ	PQ	CL	FR	OP	PM	CL	CAL	CV
Pure steam generator	1	1	1		1	1	1		1	1
Water still	1	1	1		1	1	1		1	1
Compressed air	1	1	1		1	1	1		1	1
Nitrogen	1	1	1		1	1			1	1
HVAC and monitoring system	1	1	1		1	1	1		1	1
Drainage system	1	1			1	1	1		1	
Emergency power	1	1			1	1	1		1	1
Laminar flow units	1	1			1	1	1		1	1
Automatic ampoule coding machine	1	1		1	1	1	1		1	1
Filling and closing machine for syringes	1	1	1	1	1	1	1	1	1	1
Autoclave	1	1	1	1	1	1	1	1	1	1

System/ Equipment	*Protocols*					*SOPs*				
	IQ	*OQ*	*PQ*	*CL*	*FR*	*OP*	*PM*	*CL*	*CAL*	*CV*
Washing machine for ampoules and vials	1	1	1	1	1	1	1	1	1	1
Hot sterilization tunnel	1	1	1	1	1	1	1	1	1	1
Labeling machine for ampoules and vials	1	1			1	1	1		1	
Inspection machine for ampoules and vials	1	1	1		1	1	1		1	1
Freeze dryer	1	1	1	1	1	1	1	1	1	1
Automatic vial filling and closing machine	1	1	1	1	1	1	1	1	1	1
Ampoule filling and sealing machine	1	1	1	1	1	1	1	1	1	1
Manufacturing vessels	1	1	1	1	1	1	1	1	1	

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CALIBRATION PROGRAM SUMMARY

Below is a summary of ABC Pharmaceutical's Calibration Program, which is defined in related SOP(s).

1. All process and facility instruments are classified as to their calibration status into one of the three following categories:
   a. Calibration
   b. Preventive Maintenance
   c. No Calibration/No Preventive Maintenance
2. All instruments providing critical process information necessary to make a quality determination are calibrated with the available standards.
3. ABC Pharmaceutical is in the process of procuring calibration standards. The Calibration Engineer will be responsible for scheduling, tracking, and maintenance of standards, records, etc. All standards will be traceable to NIST standards.
4. Pre- and post-calibration of instruments utilized in validation studies are performed to ensure data accuracy.
5. All instruments providing critical process information should be calibrated before performing the validation studies.

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PREVENTIVE MAINTENANCE PROGRAM SUMMARY

Below is a summary of key points of ABC Pharmaceutical's Preventive Maintenance Program, which is defined in related SOP(s).

1. An appropriate Preventive Maintenance Program is defined for the equipment that will be checked at the time of validation.
2. The Supervisor of the related area and the Engineer concerned will sign the register and verify if repairs are required.

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KEY STANDARD OPERATING PROCEDURES (SOPs)

Below is a list of key procedures for process operations and maintenance for ABC Pharmaceutical.

Description	*SOPs*		
	A	*B*	*C*
Contractors qualification system	1	1	1
Raw material issuing system	1	1	1
Packaging material issuing system	1	1	1
Manufacturing procedures	1	1	1
Batch packaging record system	1	1	1
Equipment operating procedures	1	1	1
Equipment calibration procedures	1	1	1
Equipment maintenance procedures	1	1	1
Product release procedures	1	1	1
Handling of out-of-specification results	1	1	1
Complaints handling system	1	1	1
Change control system	1	1	1
Calibration procedures	1	1	1

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VALIDATION OF BUILDING

13.1 CIVIL WORK

Test Functions

1. Inspect the facility as per approved layout.
2. Inspect floors in each room.
3. Inspect painted surfaces in each room.
4. Perform dimensional testing for each room.
5. Inspect windows in each room, if any.
6. Inspect lights in each room.
7. Inspect utilities penetration into each room.
8. Inspect all drains.
9. Inspect all communicators.
10. Inspect all doors and interlocks.

Acceptance Criteria

1. The facility has been constructed in accordance with design specifications and cGMPs.
2. Doors open/close properly, and interlocks operate in accordance with design specifications.
3. Floor surfaces are smooth, and free of crevices, holes, and rough spots.
4. Painted surfaces are to have full and smooth coverage.
5. The length, width, and height of each room conform to the design specifications.
6. All windows are installed for easy cleaning, correct window type, and are sealed with smooth surfaces.
7. All lights switches operate; light is adequate at all workstations; and fixtures are flush mounted.

8. All utilities penetrations are correctly installed, labeled, and sealed.
9. All drains are located according to the design specifications.
10. All communicators are correctly installed and sealed.

13.2 DRAINAGE SYSTEM

Test Functions

1. Inspect the drainage system as per the approved layout.
2. Inspect floor drain locations as per the approved design.
3. Check that process drains are segregated from the sanitary waste.
4. Ensure that process drains are provided with deep-seal traps.

Acceptance Criteria

1. The system is constructed and installed in accordance with design specifications, manufacturer recommendations, and cGMPs.
2. No open floor drains are to be located in Aseptic Core areas: Classes 100, 10,000, and 100,000.
3. Process drains must be separated from sanitary waste drainage system.
4. Process drains must have adequate back-flow prevention devices (deep-seal traps) at tie-in to sewer line.
5. Tie-in to sewer line must be located outside immediate building, away from the production area.

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VALIDATION OF UTILITY SYSTEMS

This chapter provides a summary of the key validation test functions and acceptance criteria for each utility system. These are provided as a guideline for those involved in the validation of ABC Pharmaceutical. Approval of this Master Plan neither provides approval of these test functions and acceptance criteria nor does it limit the test functions and acceptance criteria included in any protocol. Final approval of test functions and acceptance criteria is made by approval of the Installation, Operational, and where applicable, Performance Qualification protocols.

14.1 PLANT STEAM

Test Functions

1. Perform Installation Qualification of deionizer and distillation equipment, holding tanks, clean steam generator, and distribution system.
2. Complete and document all required pre-start-up maintenance procedures (including cleaning).
3. Perform general operational controls verification testing.
4. Operate system throughout the range of operating design specifications or range of intended use.
5. Confirm that the pressure-reducing regulators in the sub-branches are set at the predetermined operating pressure ±2 psi.
6. Verify that the system has adequate steam capacity during peak hours of operation. Confirm that the steam pressure is within 5 psi of the recommended operating pressure.

7. Record the range of all process or equipment parameters (set points, pressure, timing sequences, etc.) verified during operational and performance qualification testing.
8. Test the water produced by the system to ensure adequate conductivity.
9. Check that the holding tank water quality does not change adversely during storage in holding tanks.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. System regulators must operate within ±2 psi of design levels.
5. The system capacity must be sufficient to operate all systems at peak demand periods.

14.2 PURE STEAM

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout range of operating design specifications or range of intended use.
4. Verify that clean steam is fed by a purified water system or WFI system.
5. Confirm that the pressure-reducing regulators in the sub-branches are set at the predetermined operating pressure ±2 psi.
6. Verify that the system has adequate steam capacity during peak hours of operation. Confirm that the steam pressure is within 5 psi of the recommended operating pressure.
7. Operate the system per applicable SOPs. Perform sampling as per the sampling procedure and schedule. Test steam condensate samples for conformance to current USP Water for Injection monograph (also endotoxin, sterility).

8. Record the range of all process or equipment parameters (set points, pressure, timing sequences, etc.) verified during Operational and Performance Qualification testing.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The system capacity must be sufficient to operate all systems at peak demand periods.
5. Operate the system per applicable SOPs. Perform sampling over a 1-month period as per the sampling procedure and schedule. Test samples for conformance to current USP Water for Injection monograph.
6. All samples must meet following criteria:
   a. Chemical Testing. Test samples must meet the acceptance criteria of the chemical tests as described in USP 24 Monograph on Water for Injection.
   b. Bacteriological Purity. All samples must contain no more than 10 cfu/100 ml; no pseudomonas or coliform are detected.
   c. Endotoxins. Less than 0.25 EU/ml.

14.3 WATER FOR INJECTION (WFI)

Test Functions

1. Perform Installation Qualification. Verify piping, fittings, proper dimensions, drawings, wiring, PC software, calibration, and quality of materials.
2. Check flow rates, low volume of water supply, excessive pressure drop, resistivity drops below set point, and temperature drop or increase beyond set level.
3. Perform general operational controls verification testing.
4. Operate system throughout the range of operating design specifications or range of intended use.
5. System regulators must operate within ±2 psi of design level.

6. Operate the system per applicable SOPs. Perform sampling over a 1-month period per the sampling procedure and schedule. Test samples for conformance to current USP Water for Injection monograph, microbial content, and endotoxin content. Identify all morphologically distinct colony forming units (CFUs) to at least the genus level.
7. Measure the flow rate and calculate the velocity of the water, or measure the velocity directly at a point between the last use point and the storage tank.
8. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during Operational and Performance Qualification testing.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The system flow rate must be in compliance with design specifications.
5. All samples must meet the following criteria:
   a. Chemical Testing. Test samples must meet the acceptance criteria of the chemical tests as described in USP 24 Monograph on Water for Injection.
   b. Bacteriological Purity. All samples must contain no more than 10 cfu/100 ml; no pseudomonas or coliform are detected.
   c. Endotoxins. All samples must contain no more than 0.25 EU/ml.
   d. Physical Properties. The temperature of the hot Water for Injection must be greater than 80°C.
   e. Particulate Matter. Small Volume Injection: The Small Volume Injection meets the requirements of the test if the average number of particles it contains is not more than 10,000 per container that are equal to or greater than 10 μm in effective spherical diameter and not more than 1000 per container equal to or greater than 25 μm in effective spherical diameter.

14.4 COMPRESSED AIR

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that the compressed air system is capable of supplying pressurized compressed air to all use points. Perform an operational test of the distribution system and pressure regulators by monitoring the pressure output at the respective use points.
5. Perform a capacity test to verify that the system is capable of supplying the required gas, pressure, and flow rate at each use point.
6. Verify that in-line filters are integrity tested. Confirm that all documentation clearly indicates acceptable test results.
7. Perform dew point measurement.
8. Perform hydrocarbon content measurement.
9. Perform viable particulate count, microbiological at critical use points after sterile filters (refer to Federal Standard 209E).
10. Identification of oxygen content.
11. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during Operational and Performance Qualifications testing.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls, alarms, and interlocks operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The compressed air distribution system must consistently deliver pressurized compressed air to the use points at the design pressure as specified.
5. All in-line filters are integrity tested and qualify per manufacturer's operating specifications.
6. Dew point must be <0° or lower.

7. Hydrocarbon content must be ≤1 ppm.
8. Viable particulate must be ≤1.0 cfu/10 ft^3.
9. Nonviable particulate counts must be ≤100/ft^3 of 0.5 μ or larger at all critical use points.

14.5 NITROGEN (N_2)

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that the nitrogen gas system is capable of supplying pressurized nitrogen to all use points. Perform an operational test of the distribution system and pressure regulators by monitoring the pressure output at the respective use points.
5. Perform a capacity test to verify that the system is capable of supplying the required gas, pressure, and flow rate at each use point.
6. Verify that the filters are integrity tested. Confirm that all documentation clearly indicates acceptable test results.
7. Perform dew point measurement.
8. Perform hydrocarbon content measurement.
9. Perform nitrogen gas identification (USP 24 Monograph).
10. Check bioburden if necessary.
11. Record the range of all process or equipment parameters (set points, pressure, timing sequences, etc.) verified during Operational and Performance Qualifications testing.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls, alarms, and interlocks operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The nitrogen distribution system must consistently deliver pressurized nitrogen to the use points at the design pressure specified.
5. All filters are integrity tested and qualified per manufacturer operating specifications.

6. Dew point must be –20°C or lower.
7. Hydrocarbon level must be ≤1 ppm.
8. Gas quality must conform to the USP 24 Monograph for nitrogen purity.
9. The microbiological test must meet the approved specification requirements.

14.6 CARBON DIOXIDE (CO_2)

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that the carbon dioxide gas system is capable of supplying pressurized carbon dioxide to all use points. Perform an operational test of the distribution system and pressure regulators by monitoring the pressure output at the respective use points.
5. Perform a capacity test to verify that the system is capable of supplying the required gas, pressure, and flow rate at each use point.
6. Verify that the filters are integrity tested. Confirm that all documentation clearly indicates acceptable test results.
7. Perform dew point measurement.
8. Perform hydrocarbon content measurement.
9. Perform viable particulate count (microbiological particulates).
10. Perform nonviable particulate count.
11. Perform CO_2 gas identification (USP 24 Monograph)
12. Record the range of all process or equipment parameters (set points, pressure, timing sequences, etc.) verified during operational and performance qualifications testing.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls, alarms, and interlocks operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The carbon dioxide distribution system must consistently deliver pressurized carbon dioxide to the use points at the design pressure specified.

5. All filters are integrity tested and qualified per manufacturer's operating specifications.
6. Dew point must be –20°C or lower.
7. Hydrocarbon level must be ≤1 ppm.
8. Viable particulates must be ≤1.0 cfu per 10 ft^3.
9. Nonviable particulate counts must be ≤100/ft^3 at 0.5 μ or larger.
10. Gas quality must conform to USP 24 Monograph for carbon dioxide purity.

14.7 HEATING, VENTILATION, AND AIR CONDITIONING (HVAC)

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Integrity test all HEPA filters with dioctylphthalate (DOP) smoke (0.3 μ).
5. Measure the average face velocity of each terminal HEPA filter. Measure the average velocity 1 ft above the workspace, exposed product areas, or exposed component areas in all Class 100 laminar flow rooms or areas.
6. Verify that system air flows have been balanced to within ±10% of design criteria.
7. Verify that directional air flows are consistent with design drawings by verifying relative differential air pressures.
8. Verify that each room maintains the design temperature range for three (3) consecutive days.
9. Verify that each room maintains the design relative humidity range for three (3) consecutive days.
10. Verify that air flow patterns within Class 100 laminar flow areas are nonturbulent and unidirectional by performing smoke-stick air flow studies and recording the test on videotape.
11. Verify that rooms identified with particulate classifications are certified per Federal Standard 209E for their respective classification (Class 100, 10,000, and 100,000).
12. Verify that AHUs, fans, and heat exchangers operate per design ratings.
13. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, etc.) verified during operational and performance qualifications testing.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. HEPA filters are 99.99% efficient when tested with DOP smoke (0.3 μ).
5. All terminal HEPA filter face velocity measurements are within ±30% of the average filter velocity.
6. The average face velocity of terminal HEPA filters servicing Class 100 laminar flow rooms is 90 ft/min ±20%, with no points below 75 ft/min or above 105 ft/min.
7. All room supply, exhaust, and return flow rates must be within ±10% of design flow rates.
8. Directional air flows (as determined by room differential pressure) must be consistent with design drawings.
9. Each room must maintain the design temperature range for three (3) consecutive days.
10. Each room must maintain the design relative humidity range for three (3) consecutive days.
11. Air flow in Class 100 laminar flow areas must be nonturbulent and unidirectional, as demonstrated by smoke-stick studies.
12. All classified rooms are certified to meet their particulate classification per Federal Standard 209E.
13. AHU, fan, and heat exchanger operations must meet or exceed their respective design ratings.

14.8 EMERGENCY POWER (STANDBY GENERATOR)

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that the emergency power generation system has adequate power to provide all intended users upon normal power source interruption.

5. Record the range of all process or equipment parameters (set points, etc.) verified during operational and performance qualifications testing.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. All intended users must operate under normal power source interruption conditions.

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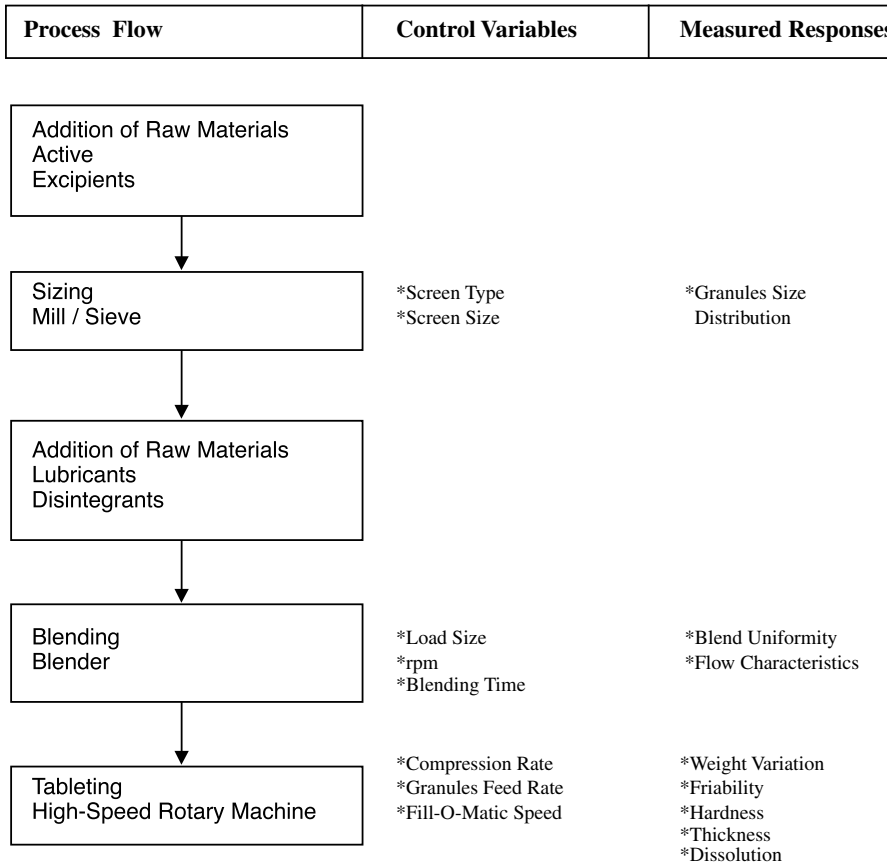
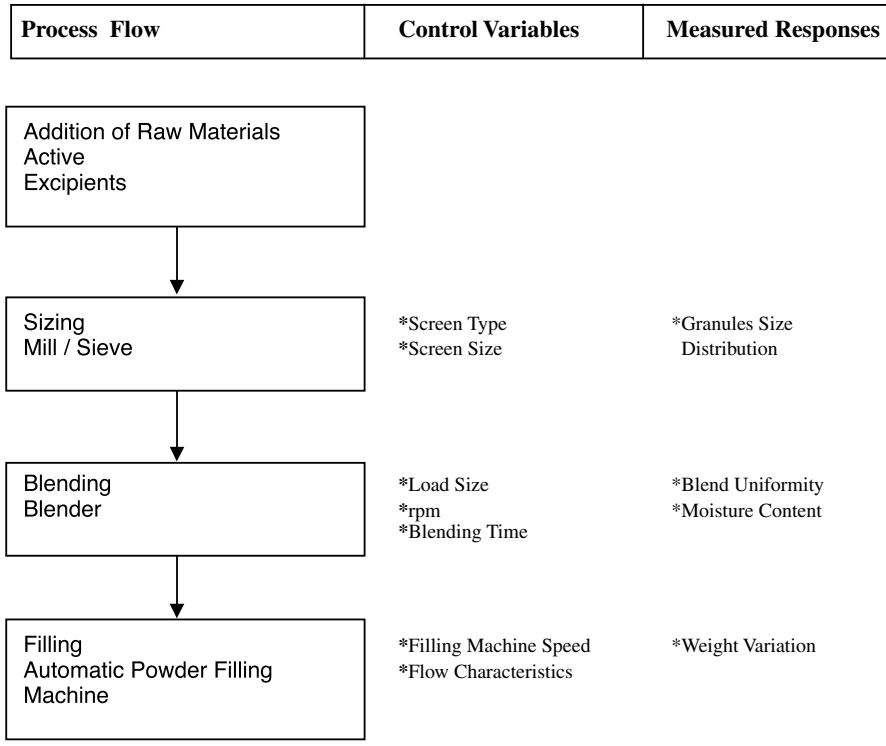
PROCESS DESCRIPTION FOR DRY PRODUCTION FACILITY: BUILDING A

15.1 PROCESS FLOW, VARIABLES, AND RESPONSES: TABLETS



15.2 PROCESS FLOW, VARIABLES, AND RESPONSES: POWDER FOR SUSPENSIONS



15.3 PROCESS FLOW, VARIABLES, AND RESPONSES: CAPSULES

Process Flow	Control Variables	Measured Responses
Addition of Raw Materials Active Excipients		
Mixing Mixer	* Load Size * rpm * Mixing Time	* Mixing Uniformity
Addition of Raw Materials Lubricants Disintegrants		
Blending Blender	*Load Size *rpm *Blending Time	*Blend Uniformity *Flow Characteristics
Capsulating High-Speed Capsulation Machine	*Capsulation Speed *Powder Feed Rate	*Weight Variation *Disintegration Time *Locking

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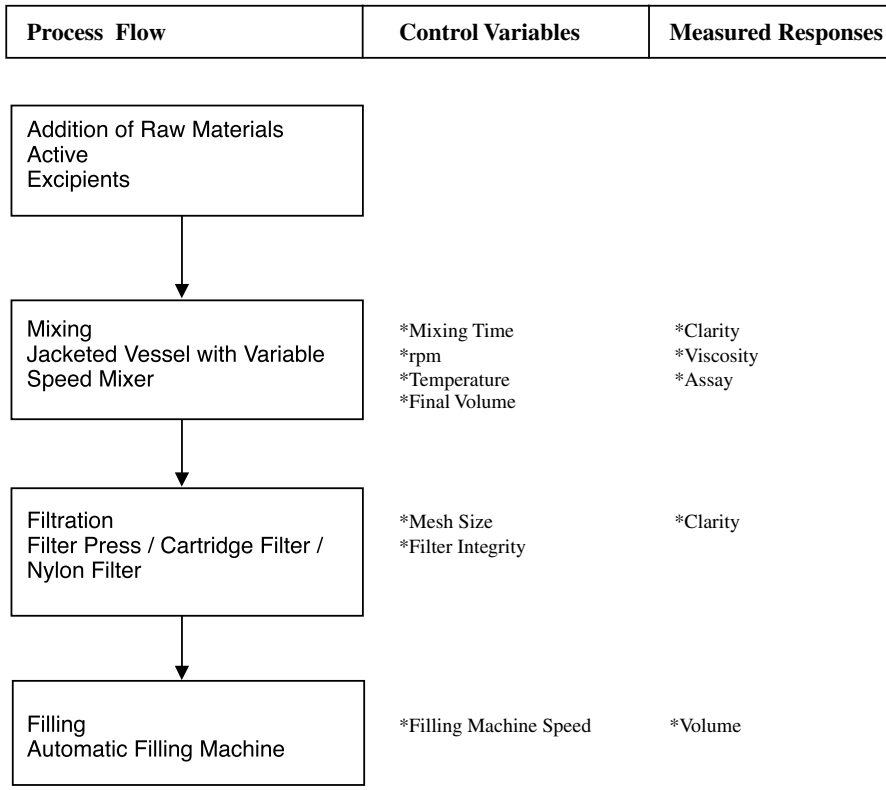
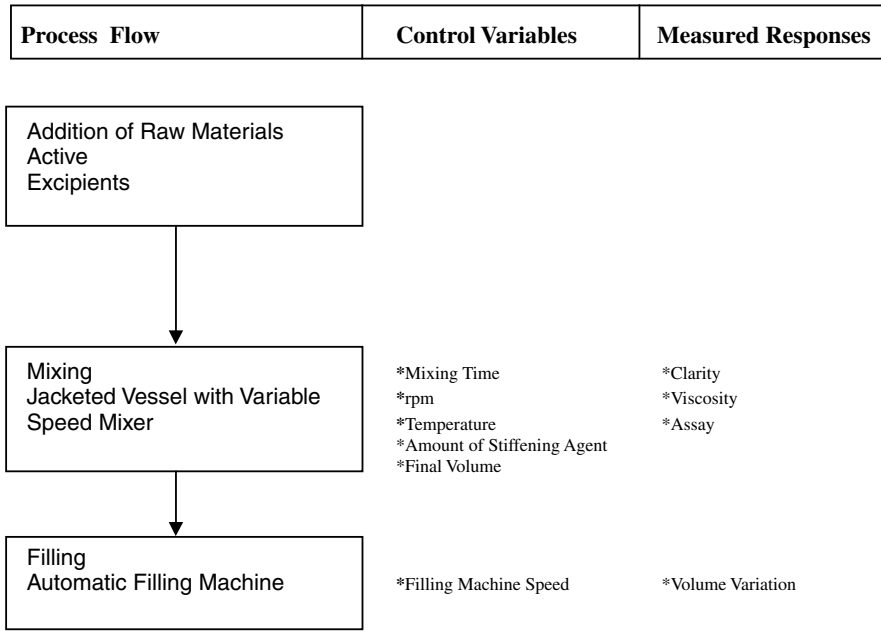
PROCESS DESCRIPTION FOR LIQUID AND SEMISOLID PRODUCTION FACILITY: BUILDING B

16.1 PROCESS FLOW, VARIABLES, AND RESPONSES: SYRUP, SUSPENSION, AND DROP PRODUCTS



16.2 PROCESS FLOW, VARIABLES, AND RESPONSES: CREAM, OINTMENT, AND SUPPOSITORY PRODUCTS



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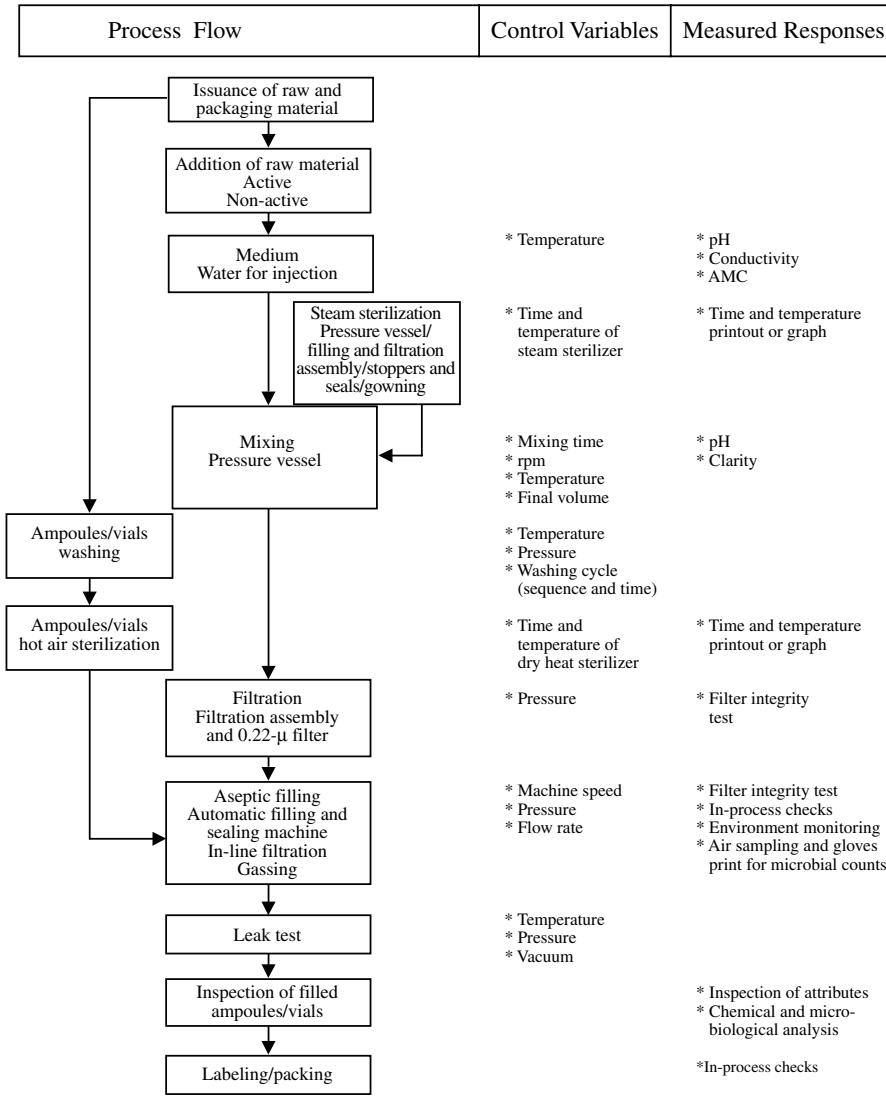
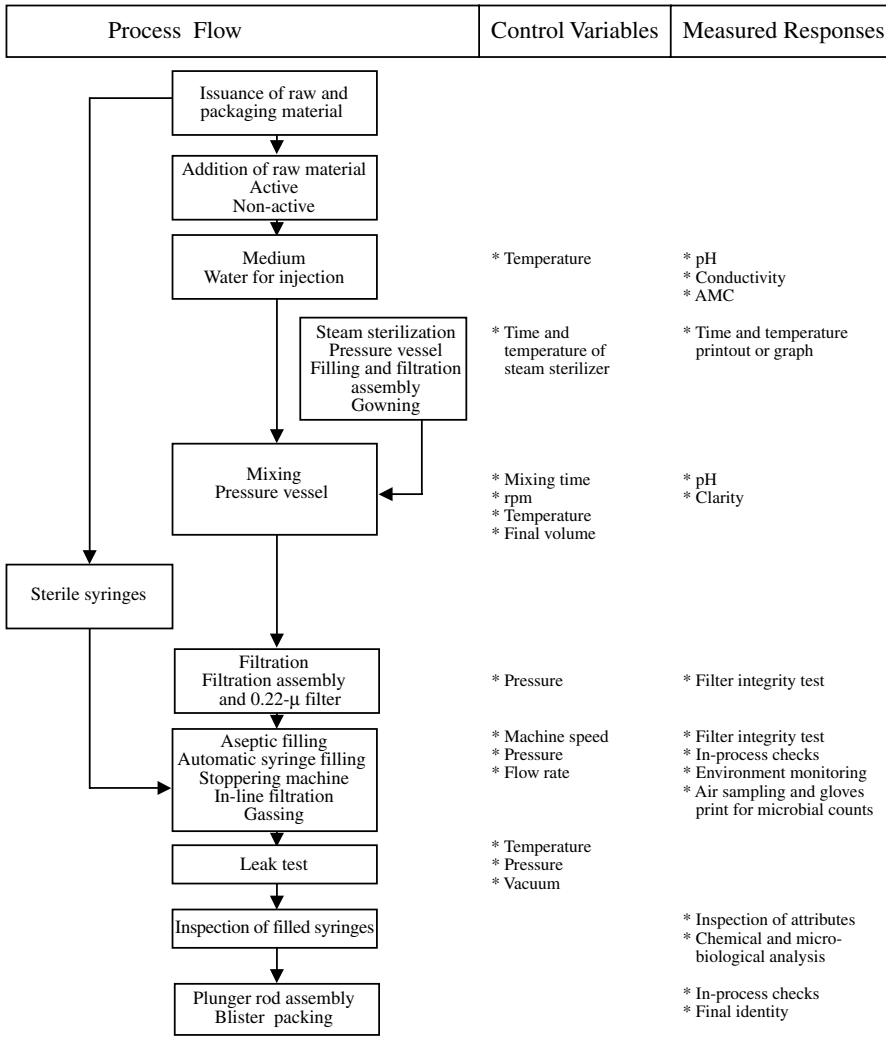
PROCESS DESCRIPTION FOR PARENTERALS PRODUCTION FACILITY: BUILDING C

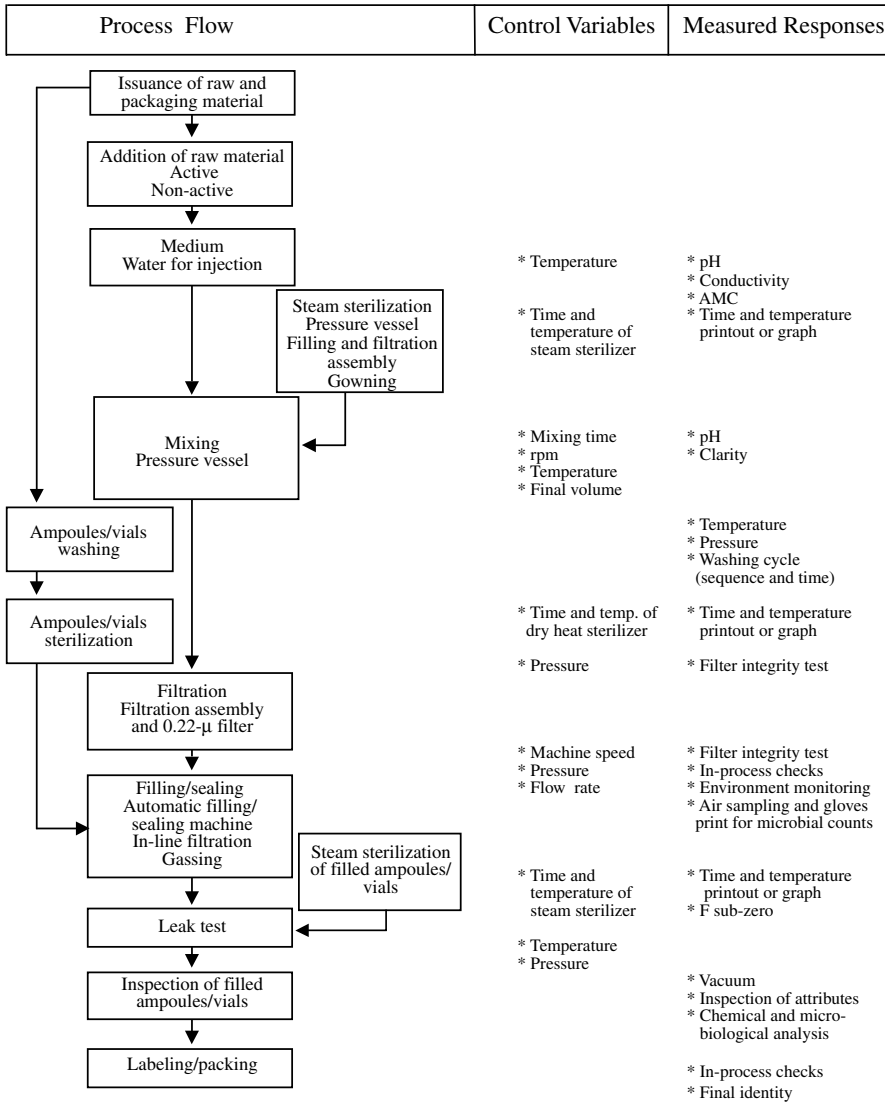
17.1 PROCESS FLOW, VARIABLES, AND RESPONSES: ASEPTIC FILL PRODUCTS



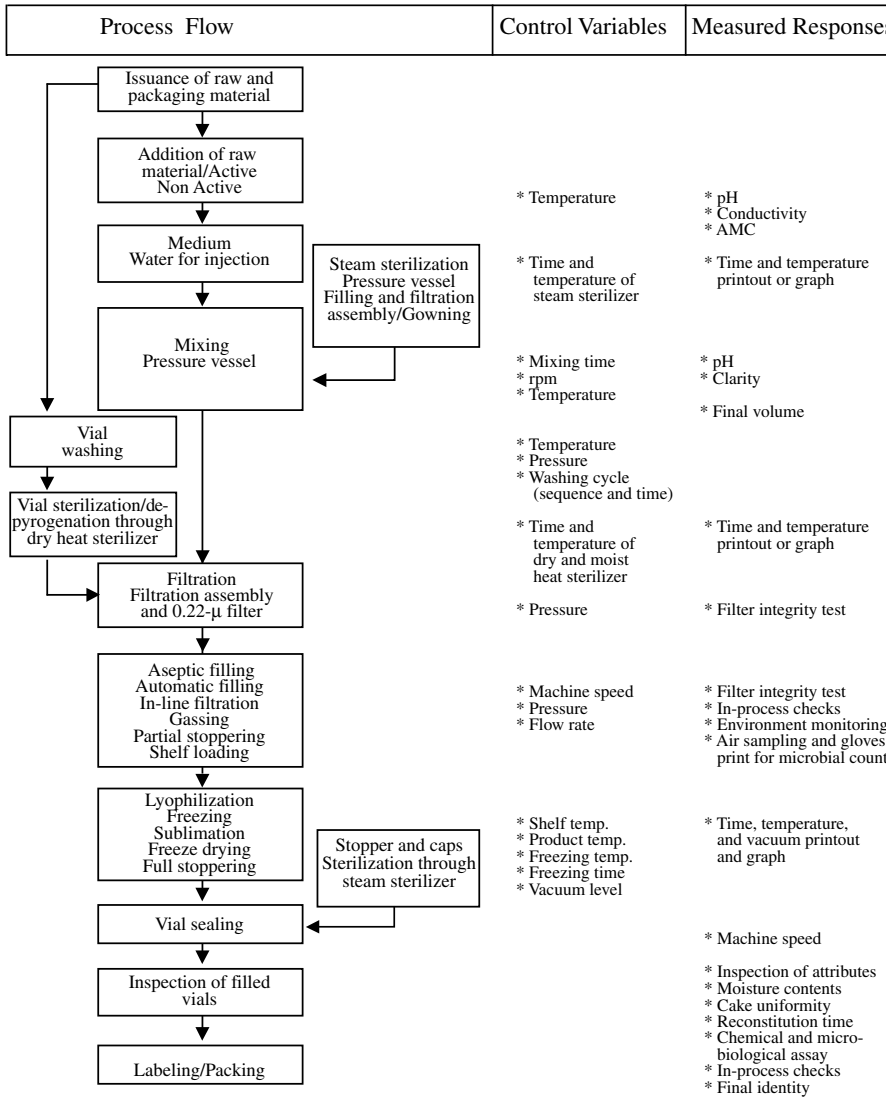
17.2 PROCESS FLOW, VARIABLES, AND RESPONSES: READY-TO-USE DISPOSABLE SYRINGES



17.3 PROCESS FLOW, VARIABLES, AND RESPONSES: TERMINAL STERILIZATION PRODUCTS



17.4 PROCESS FLOW, VARIABLES, AND RESPONSES: LYOPHILIZED PRODUCTS



18

QUALIFICATION OF PROCESS EQUIPMENT

18.1 COMMUTING MILL

Test Functions

1. Perform Installation Qualification. Verify equipment identification, required documents, utilities, manual, and drawings.
2. Perform general operational controls verification testing. Verify calibration requirements.
3. Operate system throughout the range of operating design specifications or range of intended use. Verify switches and push-buttons, motor speed, empty and loaded mill, rotor blade arrow directions, auger speed arrow direction, rotor blade rotation speeds, and auger feed speed.
4. Verify that all safety devices are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates and the oxidizing effect of the air is minimal.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform the particle size test to check the fineness of each product as per product specification.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General alarms and controls operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices operate as specified in the manual.
5. The quality of lubricants is adequate, and their storage is dry and cool.
6. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
7. The particle size of the mill granules should meet specifications.

18.2 DRYER

Test Functions

1. Perform Installation Qualification. Verify equipment identification, required documents, utilities, manual, and drawings.
2. Perform general operational controls verification testing. Verify calibration requirements.
3. Operate system throughout the range of operating design specifications or range of intended use. Verify switches and push-buttons, open-door leaks, differential pressure, timer operations, circulation air flow, exhaust air flow, high-temperature limit, and oven-door opening.
4. Verify that all safety devices of oven drying are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
7. Perform studies to check the moisture removal on each product as per SOP.
8. Perform the study for establishing the drying time as per acceptable moisture level.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General alarms and controls operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices operate as specified in the manual.
5. The quality of lubricants is adequate, and their storage is dry and cool.
6. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
7. The moisture level should meet specifications.

18.3 V-SHELL BLENDER

Test Functions

1. Perform Installation Qualification. Verify equipment identification, required documents, utilities, manual, and drawings.
2. Verify components material.
3. Verify equipment safety features.
4. Operate the blender throughout the range of operating design specifications or range of intended use.
5. Verify equipment switches, push-buttons, rotation direction, and motor fixed speed.
6. Perform the assay to check the content uniformity on blended granules at different locations.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General alarms and controls operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices operate as specified in the manual.

5. The quality of lubricants is adequate and the lubricants are properly stored.
6. Unauthorized changes to cycle parameters are not allowed without supervisory control or password.
7. Assay results should be within the specifications.

18.4 TABLET COMPRESSION

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that all safety devices of the tablet press are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
7. Perform capability and consistency studies to check the weight variation of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. The machine must be in statistical control as per capability and consistency studies.

18.5 CAPSULATION

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that all safety devices on the capsulation machine are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform capability and consistency studies to check the weight variation of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Machine must be in statistical control as per capability and consistency studies.

18.6 POWDER FILLING

Test Functions

1. Perform Installation Qualification.

2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that all safety devices of the powder filling machine are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform capability and consistency studies to check the weight variation of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to the manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Machine must be in statistical control as per capability and consistency studies.

18.7 CAPSULE POLISHER

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.

4. Verify that all safety devices of the capsule polisher are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform studies to check the capsule polishing of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General alarms and controls operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices operate as specified in the manual.
5. The quality of lubricants is adequate and as per supplier's recommendation.
6. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
7. The machine must be in statistical control as per study.

18.8 TABLET COATING

Test Functions

1. Perform Installation Qualification. Verify equipment identification, required documents, utilities, component materials, drawings, and manuals.
2. Perform general operational controls verification testing. Verify coating pan motor, supply blower, exhaust motor, and spray system.
3. Operate system throughout the range of operating design specifications or range of intended use. Verify switches and push-buttons, rotator direction, motor variable speed, supply temperature, differential pressure, and pan air flow.
4. Verify that all safety devices are operating as specified in the manual.

5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform physical attribute characteristic studies to check the uniformity of the coating on each product as per SOP and acceptance criteria.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General alarms and controls operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices operate as specified in the manual.
5. The quality of lubricants is adequate and their storage as recommended by the manufacturer.
6. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
7. Coating must be in compliance with SOP and acceptable quality levels.

18.9 SYRUP MANUFACTURING VESSEL

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications of mixing speed, temperature, and vacuum, or the range of intended use.
4. Verify that all safety devices of vessel are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.

7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Assay the final mix to check the content uniformity of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Assay results should meet specifications.

18.10 SUSPENSION MANUFACTURING VESSEL

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications of mixing speed, temperature, and vacuum and homogenization, or the range of intended use.
4. Verify that all safety devices of the vessel are operating as specified in the manual.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Assay the final mix to check the content uniformity of each product as per SOP.
9. Perform particle size distribution and re-suspendibility tests over the final blend as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Assay results and re-suspendibility should meet specifications.

18.11 DROPS MANUFACTURING VESSEL

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications of mixing speed, temperature, and vacuum, or the range of intended use.
4. Verify that all safety devices of the vessel are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Assay the final mix to check the content uniformity of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.

2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Assay results should meet specifications.

18.12 MIXER

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of mixing speed or range of intended use.
4. Verify that all safety devices of the mixer are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Assay the mixed blend to check the content uniformity of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.

5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Assay results should meet specifications.

18.13 EMULSIFYING MIXER

Test Functions

1. Perform Installation Qualification. Verify equipment identification, required documents, utilities, component materials, drawings, and manuals.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications, or range of intended use, at fixed speed. Verify switches and push-buttons, rotator direction, and motor variable speed.
4. Verify that all safety devices of the emulsifying mixer are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform globule size assay to check the uniformity of emulsification on each product blend as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General alarms and controls operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices operate as specified in the manual.
5. The quality of lubricants is adequate and their storage is according to manufacturer recommendations.

6. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
7. The machine must be in statistical control as per capability study.
8. Assay results should meet specifications.

18.14 FILTER PRESS

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of vacuum operating design specifications or range of intended use.
4. Verify that all safety devices of filter press are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform visual inspection under magnification to check the clarity of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Visual inspection results must meet product specifications.

18.15 CREAM/OINTMENT/SUPPOSITORY MANUFACTURING VESSEL

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications of mixing speed, temperature, and vacuum, or the range of intended use.
4. Verify that all safety devices of vessel are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform assay of final mix to check the content uniformity of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Assay results should meet specifications.

18.16 SYRUP, SUSPENSION, AND DROP FILLING MACHINE

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use (e.g., different packages).
4. Verify that all safety devices of vessel are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform capability studies to check the volume variation on each size of product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. The machine must be in statistical control as per capability study.

18.17 CREAM AND OINTMENT FILLING MACHINE

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that all safety devices of filling machine are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform capability studies to check the weight variation of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. The machine must be in statistical control as per capability study.

18.18 SUPPOSITORY FILLING MACHINE

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.

3. Operate system throughout the range of operating design specifications of mixing speed, temperature, fill volume/weight, or the range of intended use.
4. Verify that all safety devices of the suppository filling machine are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform capability and consistency studies to check the weight variation of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be as per manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Machine must be in statistical control as per capability and consistency studies.

18.19 LABELING MACHINE

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications of speed, temperature, and vacuum, or the range of intended use.

4. Verify that all safety devices of labeling machine are operating as specified in the manual.
5. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
6. Perform inspection to check the labeling on each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices must operate as specified in the manual.
5. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
6. The labeling is performed in accordance with the acceptance criteria.

18.20 CAPPING MACHINE

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications of speed, or the range of intended use.
4. Verify that all safety devices of capping machine are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform the torque test on different bottle sizes and check the capping on each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be according to manufacturer recommendations.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. Torque of the caps should meet specifications.

18.21 CARTONATOR

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications of feeding speed, or the range of intended use.
4. Verify that all safety devices of cartonator are operating as specified in the manual.
5. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
6. Check that change parts of each size are available.
7. Perform inspection to check the cartoning on each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.

4. Safety devices must operate as specified in the manual.
5. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
6. The cartoning operation meets the acceptance criteria.

18.22 SHRINK-WRAPPING MACHINE

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications of shrink-wrapping speed, temperature, and vacuum, or the range of intended use.
4. Verify that all safety devices of the shrink-wrapping machine are operating as specified in the manual.
5. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
6. Perform inspection to check the shrink-wrapping on each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
6. The shrink-wrapping operation meets the acceptance criteria.

18.23 OVER-PRINTING MACHINE

Test Functions

1. Perform Installation Qualification
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications of printing speed, or the range of intended use.

4. Verify that all safety devices of the over-printing machine are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Perform inspection to check the over-printing on each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The over-printing operation meets the acceptance criteria.

18.24 TRAYS AND RACK WASHER

Test Functions

1. Perform Installation Qualification. Verify equipment identification, required documents, utilities, components material, drawings, and manuals.
2. Perform general operational controls verification testing. Check header drive circulation pump, rinse pump, detergent pump, exhaust fan, and drying fan.
3. Operate system throughout the range of operating design specifications or range of intended use at fixed speed. Verify switches and push-buttons and calibration requirements.
4. Verify that all safety devices of tray/rack washer are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
7. Perform the study to check the time of washing and detergent contamination on each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General alarms and controls operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The safety devices operate as specified in the manual.
5. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
6. The tray and rack washer operation shall meet the acceptance criteria.

18.25 AUTOCLAVE (STEAM STERILIZER)

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Perform vacuum pump evacuation rate test to verify that the vacuum pump evacuates the chamber at the rate specified.
5. Perform chamber vacuum and positive pressure integrity verification studies to verify that the chamber does not leak.
6. Perform controller security challenges to verify that sterilization cycle parameters cannot be altered without appropriate supervisory control.
7. Take pressure and temperature measurements to verify that the steam is 100% saturated during the dwell period.
8. Perform simulated steam supply failures to verify that the controller either resets the dwell timer or stops incrementing upon a drop in temperature below the set point.
9. Perform three (3) empty chamber heat distribution studies to determine the thermal characteristics of the sterilization cycles. A Kaye Validator equipped with thermocouples shall be used to map the internal chamber temperatures.
10. Perform three (3) loaded chamber heat penetration studies to determine the coolest point within a specified load and configuration. A Kaye Validator equipped with thermocouple-probed containers will be used to provide an equal representation among layers in the chamber.

11. Perform microbiological challenge studies to determine the degree of process lethality provided by the sterilization cycle. The microorganisms most frequently utilized to challenge steam sterilization cycles are *Bacillus Stearothermophilus* and *Clostridium Sporogenes* of 10^6 population.

    A Kaye Validator equipped with thermocouple-probed containers and the containers previously inoculated with the biological indicator will be positioned in the detected cool points of the load configuration. After the sterilization cycle is complete, the inoculated containers are recovered and subjected to microbiological test procedures.
12. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during operational and performance qualifications testing.
13. Air filters must be tested for integrity.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The vacuum pump evacuates the chamber to the target pressure at a rate equal to or greater than specified.
5. The average chamber leak rate is in accordance with the manufacturer recommendations.
6. Unauthorized changes to cycle parameters are not allowed without supervisory control or password.
7. The temperature and pressure during the dwell period must indicate 100% saturated steam.
8. The controller must either reset the dwell timer or stop incrementing upon a drop in temperature below the set point.
9. The chamber temperature recorded by the sterilizer temperature control system must be within ±0.5°C of the set point during the stabilized portion of the dwell period.
10. The maximum temperature deviation from the mean chamber temperature at any one print interval during the stabilized dwell period is within ±0.5°C.

11. Heat distribution thermocouples at each 1-minute print interval must be within ±1.0°C of the mean chamber temperature of all distribution thermocouples during the dwell period after stabilization.
12. The slowest-to-heat location (coolest point) in each test run must receive an F_0 (121°C) of at least 20 minutes, as calculated during the dwell period only.
13. A minimum Solution Microbiological Challenge Spore Log Reduction (SLR) of equal to or greater than 6 must be shown for each run.
14. Air filters must pass integrity test.

18.26 HOT AIR TUNNEL (DRY HEAT STERILIZER)

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Document the system operation, including performance checks of safety interlocks and values of operating parameters, during a minimum of three (3) consecutive acceptable runs.
5. Verify that particulate levels within the chamber are within acceptable limits.
6. Perform three (3) empty chamber heat distribution studies to determine the thermal characteristics of the sterilization cycles. A Kaye Validator equipped with thermocouples should be used to map the internal chamber temperatures.
7. Perform three (3) loaded chamber heat penetration studies to verify that the temperature distribution is uniform for the load configuration, and that all measured points within each load configuration receive thermal treatment sufficient for depyrogenation and sterilization. A Kaye Validator equipped with thermocouple-probed containers shall be used to provide an equal representation among layers in the chamber.
8. Perform microbiological challenge test. Confirm through laboratory testing that all endotoxin samples in each load are reduced by a minimum of 3 logs. Endotoxin reduction of 3 logs or greater will also ensure a greater than 12 log reduction of biological organisms.
9. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during Operational and Performance Qualifications testing.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. All monitoring and functional testing of the system will be completed and approved. The Performance Qualification will document that the system is capable of operating within specified parameters and is ready for validation.
5. The endotoxin content of all endotoxin indicators must be reduced to levels of <0.025 EU (or undetectable), or at least demonstrate a minimum 3 log reduction for three (3) consecutive runs.
6. Positive control for endotoxin indicator must yield a minimum of 1000 EU.
7. Negative control for endotoxin indicator must be <0.03 EU/ml.
8. Temperature distribution thermocouples in the heat penetration and distribution test studies for three (3) consecutive runs must be within ±5°C of the set point temperature during the dwell period.
9. All thermocouples within the load must be at or above 250°C.
10. Testing is to be repeated until a minimum of three (3) consecutive tests meet requirements.
11. All test instruments used during the Performance Qualification shall be calibrated and certified using NIST traceable standards.
12. F_H(250°C) shall be calculated.

18.27 VIALS/AMPOULES WASHING MACHINE

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Three (3) sets of vials will be spiked with an NaCl solution, dried, and then washed. Baseline data will be established using unwashed, NaCl-spiked bottles. The washed vials will be tested for conductivity (NaCl), particulate count (WFI), and concentrations of the three solutions. Also, one load will be run with all vials in

the load spiked with fluorescent dye. These vials will be inspected for dye residue.
5. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during Operational and Performance Qualifications testing.
6. The pressure/temperature of cleaning media (DIW, WFI, compressed air) must be documented.
7. Machine speed (amp/min or vials/min) and exposure time of cleaning media must be documented.
8. All in-line filters are to be tested for integrity.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. No dye residue is detected at >1 ppb in any of the washed vials.
5. The rinse solution from each washed, NaCl-spiked vial must have a conductivity <1 μmho.
6. The rinse solution from each washed, NaCl-spiked vial must have no precipitate when tested per USP 24 Monograph for Sodium Chloride.
7. Both the rinse solutions from the NaCl-spiked and unspiked vials must have particulate counts that meet the specifications listed in USP 24, Physical Test, Particulate Matter in Injections.
8. The rinse solutions from the NaCl-spiked and unspiked vials must meet the specifications for Water for Injection listed in USP 24 Monograph for Water for Injection.
9. The rinse solutions from the unspiked vials must contain no more than 0.25 EU/ml.

18.28 AMPOULES/VIALS/SYRINGES FILLING MACHINE

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.

3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that all safety devices of ampoules, vials, and syringes filling machine are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Verify that all lubricants such as oil and grease are kept in clean, sealed containers so that no dust or moisture penetrates, and that the oxidizing effect of the air is minimal.
7. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
8. Perform capability studies to check the volume variation of each product as per SOP.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Safety devices must operate as specified in the manual.
5. The recommended lubricants must be used as specified in the manual.
6. The storage location of the lubricants must be dry and cool.
7. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
8. The machine must be in statistical control as per capability studies.

18.29 FREEZE DRYER (LYOPHILIZER)

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Perform vacuum pump evacuation rate test to verify that the vacuum pump evacuates the chamber at the rate specified.

5. Perform chamber vacuum and positive pressure integrity verification studies to verify that the chamber does not leak.
6. Perform controller security challenges to verify that lyophilization cycle parameters cannot be altered without appropriate supervisory control.
7. Upon completion of the filling operation, the product is placed on the shelves in the lyophilizer. A number of temperature probes should be placed in product vials located throughout the batch. The temperature probes can be placed at multiple positions in a select number of vials. Having probes at these positions will yield results indicating that the entire batch of product is at the same temperature.
8. Verify that the temperature throughout the chamber is maintained at set point(s). Gather baseline data on time vs. temperature profile in the event of a power failure.
9. Record the range of all process or equipment parameters (set points, flow rates, speeds, timing sequences, concentrations, etc.) verified during operational and performance qualifications testing.
10. Heat distribution study should be performed (3 consecutive runs) with documentation for pressure, temperature set points, and exposure time.
11. WFI conductivity, flow rate, temperature, and pressure should be checked.
12. N_2 filter should be tested for integrity.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. The vacuum pump must evacuate the chamber to the target pressure at a rate equal to or greater than specified.
5. The average chamber leak rate must be in accordance with the manufacturer recommendations.
6. Unauthorized changes to cycle parameters must not be allowed without supervisory control or password.
7. All temperature monitoring points (thermocouples) are maintained within a specified range during the specified testing period.
8. F_0 (121°C) of at least 20 minutes.

9. Water for Injection (WFI) must meet specifications.
10. N_2 filter must pass the integrity test.

18.30 LAMINAR FLOW UNIT

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Integrity test all HEPA filters with dioctylphthalate (DOP) smoke.
5. Measure the average face velocity of each terminal HEPA filter. Measure the average velocity 1 ft above the workspace, exposed product areas, or exposed component areas in all Class 100 laminar flow rooms or areas.
6. Verify that system air flows have been balanced to within ±10% of design criteria.
7. Verify that air flow patterns within Class 100 laminar flow areas are nonturbulent and unidirectional by performing smoke-stick air flow studies and recording the test on videotape.
8. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during Operational and Performance Qualifications testing.
9. Verification of particle count (Class 100).
10. Verification of decontamination time.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. HEPA filters are 99.99% efficient when tested with DOP smoke.
5. All terminal HEPA filter face velocity measurements are within ±30% of the average filter velocity.
6. The average face velocity of terminal HEPA filters servicing Class 100 laminar flow rooms is 90 ft/min ±20% with no points below 75 ft/min or above 105 ft/min.

7. Directional air flows (as determined by room differential pressure) must be consistent with design drawings.
8. Each room must maintain the design temperature range.
9. Air flow in Class 100 laminar flow areas must be nonturbulent and unidirectional, as demonstrated by smoke-stick studies.
10. AHU, fans, and heat exchanger operations meet or exceed their respective design ratings.
11. Particle count must meet specifications.

18.31 PASS-THROUGH

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that both doors of the pass-through cannot be open simultaneously.
5. Verify that directional air flows are consistent with design drawings by verifying relative differential air pressures.
6. Verify air flow patterns by performing smoke-stick air flow studies and recording the test on videotape.
7. Integrity test HEPA filter with dioctylpthalate (DOP) smoke.
8. Particle count test (Class 100).
9. Air velocity.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specifications throughout the operating range or range of intended use.
4. Both doors of the pass-through should not be open simultaneously.
5. Pass-through shall be under positive pressure in relation to adjacent areas of other than an equal or higher Class 100 classification. In sterile powder handling areas, an airlock must be under negative pressure to prevent the movement of dust from one sterile area to another.

6. Air flow in Class 100 pass-through must be outward directional, as demonstrated by smoke-stick studies.
7. HEPA filter is 99.99% efficient when tested with DOP smoke.
8. Particle count must meet specifications.
9. Face velocity = 0.45 ±20%.

19

VALIDATION OF SUPPORT PROCESSES

19.1 WASHING OF COMPONENTS

The washing of components will be validated for each load configuration in the vial washer. Cycle Development Testing and Performance Qualification testing will qualify each washing process. A separate performance qualification and cycle development testing report will be written for each load configuration. The processes will be considered validated when the acceptance criteria is met for three (3) successful consecutive runs.

Cycle Development Testing

Perform one or more cycle development test runs with vials to determine appropriate time for each cycle (wash and rinse), temperature for each cycle, load size, WFI supply pressure, and air supply pressure.

Performance Qualification Test Functions

1. Identify and document the quantity and placement of vials in the load configuration. Determine load configuration from Cycle Development Test studies.
2. Prepare a full load of vials spiked with dye. Wash the vials as per the proposed operating procedure. Inspect each vial for dye residue.
3. Spike three (3) sets of vials with NaCl solution. Allow vials to dry and then wash them per the proposed procedure. Baseline data will be established using unwashed, NaCl-spiked vials. Test the washed vials for conductivity (NaCl) and particulate count (WFI).

Acceptance Criteria

1. No dye residue is detected at >1 ppb in any of the washed vials.
2. The rinse solution from each washed, NaCl-spiked vial must have a conductivity <2 μmho.
3. The rinse solution from each washed, NaCl-spiked vial must have no precipitate when tested per USP 24 Monograph for Sodium Chloride.
4. Both the rinse solutions from the NaCl-spiked and unspiked vials must have particulate counts that meet the specifications listed in USP 24 Monograph for Physical Test, and Particulate Matter in Injections.
5. The rinse solutions from the NaCl spiked and unspiked vials must meet the specifications for Water for Injection listed in USP 24 Monograph for Water for Injection.
6. The rinse solutions from the unspiked vials must have no more than 0.25 EU/ml.

19.2 STERILIZATION OF COMPONENTS

The sterilization of components and equipment will be validated for each load configuration using the cGMP autoclave. Cycle Development Testing and Performance Qualification Testing will qualify each sterilization process. A separate Performance Qualification and Cycle Development Testing Report will be written for each load configuration. The process will be considered validated when the acceptance criteria is met for three (3) successful consecutive runs.

Cycle Development Testing

Perform one or more cycle development test runs used in the load configuration to determine appropriate cycle type, temperature and dwell period, hard-to-heat items or areas, load item preparation, and minimum and maximum load configurations.

Performance Qualification Test Functions

1. Identify and document the quantity, placement, and physical description of each component to be included in the load configuration. Determine the load configuration from Cycle Development Test studies.

2. Perform load and chamber temperature mapping and verify that the temperature distribution in the chamber is uniform for the load configuration, and that all measured points within the load configuration receive thermal treatment sufficient for sterilization. Perform three (3) runs on the maximum load and a minimum of three (3) runs on the minimum load.
3. Perform microbiological challenge studies using the Overkill Approach Sterilization Validation. Place *Bacillus stearothermophilus* spores throughout the load configuration, at points where steam penetration may be incomplete, and at hard-to-heat locations. Perform a minimum of three (3) runs on the maximum load configuration and a minimum of three (3) runs on the minimum load configuration. Perform spore quantification verification on each manufacturer's lot of spore strips or suspensions. Perform microbiological challenge studies simultaneously with loaded chamber heat penetration and distribution studies.
4. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during cycle Development and Performance Qualifications testing.

Acceptance Criteria

1. During load and chamber temperature mapping, the maximum load configuration, the mean of the F_0 values from the single slowest-to-heat point from each of the three (3) test runs minus 3 standard deviations of the these three F_0 values must be greater than 20 min.
2. During load and chamber temperature mapping, the minimum load configuration, the mean of the F_0 values from the single slowest-to-heat point from each of the three (3) test runs minus 3 standard deviations of the these three F_0 values must be greater than 20 min.
3. During microbiological challenge studies, all *Bacillus stearothermophilus* spore strips/suspensions must show negative test for the growth of *B. stearothermophilus*.
4. During microbiological challenge studies, positive controls for the *B. stearothermophilus* spore strips/suspensions must test positive for the growth of *B. stearothermophilus*.
5. During Microbiological Challenge studies, spore strips/suspension quantification test must indicate that the population of each manufacturer's lot of spore strips/suspensions is within ±50% of their labeled population.

19.3 DEPYROGENATION OF COMPONENTS

The depyrogenation of components will be validated for each load configuration using the depyrogenation hot air sterilization tunnel. Cycle Development Testing and Performance Qualification Testing will qualify each depyrogenation process. A separate Performance Qualification and Cycle Development Testing Report will be written for each load configuration. The processes will be considered validated when the acceptance criteria is met for three (3) successful consecutive runs.

Cycle Development Testing

Perform one or more cycle development test runs with item used in the load configuration to determine appropriate cycle type, temperature and dwell period, hard-to-heat items or areas, load item preparation, and minimum and maximum load configurations.

Performance Qualification Test Functions

1. Identify and document the quantity, placement, and physical description of each component to be included in the load configuration. Determine load configurations from Cycle Development Test studies.
2. Perform load and chamber temperature mapping and verify that the temperature distribution in the chamber is uniform for the load configuration, and that all measured points within the load configuration receive thermal treatment sufficient for depyrogenation. Perform three (3) runs on the maximum load and a minimum of three (3) runs on the minimum load.
3. Perform pyrogen challenge studies and verify through laboratory testing that the endotoxin contents of all indicators in each load are reduced by a minimum of 3 logs. Endotoxin reduction of 3 logs or greater will also ensure a greater than 12 log reduction of biological organisms.
4. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during Cycle Development and Performance Qualifications Testing.

Acceptance Criteria

1. Temperature distribution thermocouples in the heat penetration and distribution test studies for three (3) consecutive runs must be within ±5°C of the mean chamber temperature during the dwell period at any one print interval.

2. During heat penetration studies, all thermocouples must receive a minimum temperature of 250°C. F_H (250°C) must be calculated.
3. The endotoxin content of all endotoxin indicators must be reduced to levels of <0.025 EU (or undetectable), or at least demonstrate a minimum of 3 log reduction for three (3) consecutive runs at half-cycle.
4. Positive controls for endotoxin indicators must yield a minimum of 1000 EU.
5. Negative controls for endotoxin indicators must be <0.03 EU/ml.

19.4 ASEPTIC FILLING VALIDATION (MEDIA FILL STUDIES)

Protocols will be developed to demonstrate that the product is aseptically filled into a final dosage container. These studies will consist of exposing media capable of supporting a broad spectrum of microbiological growth to all operations and procedures normally performed during the manufacturing process. Vials will be filled at the normal working volume. Each study will include filling approximately 3000 vials/ampoules. The vials/ampoules will be incubated at 20 to 25°C for 14 days.

"Worst-case," challenges such as personnel breaks, equipment adjustments, and additional personnel in the fill room will be incorporated into all media fill studies. Stoppers and vials or ampoules will be sterilized. The time between sterilization and the start of the first media fill will be the maximum validated storage time for sterile stoppers, vials, and ampoules, provided the media fills meet all other acceptance criteria.

All environmental monitoring supplies will be growth promoted on the release date and fill date. Agar strips will be growth promoted after being exposed to the same environmental conditions as those experienced during the fill. Growth promotion will be performed for organisms required by USP 24 Monograph for Indigenous Organisms and Anaerobes using vials/ampoules collected during the fill and upon completion of the 14-day incubation period.

The protocol will include acceptance criteria for sterility assurance level and growth promotion.

Also included will be details of data collection, growth promotion sampling, environmental and personnel monitoring schedule, personnel movement documentation, incubation time and temperature, etc.

Acceptance Criteria

Upon successful completion (end-point contamination level of not more than 0.1%) of three (3) consecutive media fills for the vial/stopper combination and ampoules, the aseptic process will be considered validated.

19.5 CROSS-CONTAMINATION CONTROL

Test Functions

1. Verification of HVAC design, zoning of air handling units, airlocks, room pressure differentials, recirculation vs. once-through air handling systems, room air distribution, use of HEPA filters on main return ducts to air handling plants, supply and return duct work, fresh air intakes and exhaust for buildings A, B, and C.
2. Verification of materials and product dispersal around manufacturing facility in buildings A, B, and C.
3. Verification of spread of materials and products during maintenance and cleaning of environmental and process air handling plant and equipment.
4. Verification of containment of materials and products during processing.
5. Verification of dust collection system as per design.
6. Verification of movement of personnel, gowning, and laundry as per design.
7. Verification of utilities design, mix-up, identification, check valves, and back-flow prevention.
8. Verification of facility design, architectural finishes, and room layout.
9. Verification of equipment design, construction materials, clean in-place (CIP) units where possible, and cleaning out-of-place practice.
10. Verification of cross-contamination prevention by performing air sampling and machine swabs.
11. Verification of prevention of cross-contamination by cleaning system validation.
12. Verification of prevention of cross-contamination through residual analysis of finished products.
13. Verification of pallets transfer and interlocks as per design.

Acceptance Criteria

1. The system is installed in accordance with design specifications based on manufacturer recommendations and cGMP guidelines and documented.
2. Materials and product dispersal around manufacturing facility in buildings A, B, and C with design specification.
3. Spread of materials and products during maintenance and cleaning of environmental and process air handling plant and equipment is maintained and demonstrated through environmental monitoring.

4. Containment of materials and products during processing is demonstrated through environmental monitoring.
5. Dust collection system operates in accordance with design specifications throughout the operating range or range of intended use.
6. General control of movement of personnel, gowning, and laundry is demonstrated through SOP compliance and training.
7. General controls, alarms, identification, and interlocks operate in accordance with design specifications.
8. Facility construction and architectural finishes demonstrate adherence to specifications and cGMPs.
9. Equipment design, construction materials, CIP, and cleaning out-of-place practice are in compliance with cGMPs.
10. Air sampling and machine swabs results meet the acceptance criteria established.
11. Area/equipment cleaned in accordance with the written SOPs and meet the acceptance criteria.
12. The pallet transfer units and interlocks operate as per design and in accordance with the written SOPs.

19.6 COMPUTERIZED PHARMACEUTICAL SYSTEM

Test Functions

1. Perform Installation Qualification.
2. Confirm that hardware and software descriptions are available.
3. Confirm that the documentation is appropriate, up-to-date, relevant, and complete.
4. Verify the digital transmission inputs and outputs as appropriate.
5. Verify analog transmission inputs and outputs as appropriate.
6. Verify data entry and boundary testing as appropriate.
7. Verify access control testing as appropriate.
8. Verify SOPs for operation, maintenance, and change control.
9. Verify training records.
10. Verify system recovery procedure.

Acceptance Criteria

1. The system is installed in accordance with design specifications based on manufacturer recommendations and cGMP guidelines. Instruments are calibrated, identified, and entered into the calibration program.
2. Hardware and software systems are verified as per manual.

3. The documentation is appropriate, up-to-date, relevant, and complete as per protocol.
4. The digital transmission inputs and outputs are verified.
5. The analog transmission inputs and outputs are verified.
6. The data entry and boundary testing meets the specification design.
7. The access control testing meets the specification design.
8. SOPs are available for operation, maintenance, and change control.
9. Training records are available.
10. System recovery procedure is available.

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QUALITY ASSURANCE/CONTROL LABORATORY VALIDATION

The Quality Assurance/Control Laboratory serves one of the most critical functions in the ABC Pharmaceutical facility. Consequently, a comprehensive validation program will be initially performed for procedures and equipment used for all products, as well as any analytical procedures required for the first scheduled product. Thereafter, the analytical methods requirements and resulting validation will be evaluated and performed as necessary for each new product.

The Quality Assurance/Control staff will evaluate in detail the analytical requirements and the procedures. Where applicable, the validated laboratory equipment and analytical methods will be utilized.

Equipment and methods will be operated/performed in accordance with cGMPs. Instruments will be calibrated, automatic analyzers and equipment will be qualified; computer-related systems will be validated; analytical methods from USP/NF will be verified; and glassware preparation, media preparation, and noncompendial methods will be validated.

20.1 LABORATORY EQUIPMENT QUALIFICATION

Laboratory equipment such as incubators, refrigerators, laminar flow hoods, depyrogenation ovens, sterilizers, etc., will be qualified using the same approach as that used for process equipment and utility systems.

The processes of sterilization and depyrogenation of laboratory equipment and microbiological media will be validated using the same approach as that used for production processes. Test functions and acceptance

criteria for these validation protocols are summarized in Chapter 19.2 and 19.3, respectively.

Automatic analyzers will be qualified by performance of Installation and Operation Qualifications. The purpose of the qualification for automatic analyzers is the same as that for any other piece of cGMP equipment: to verify that it has been installed and operates in accordance with design specifications, manufacturer recommendations, and cGMPs.

Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.

Acceptance Criteria

1. The system is installed in accordance with design specifications, manufacturer recommendations, and cGMPs. Instruments are calibrated, identified, and entered into the calibration program.
2. General controls and alarms operate in accordance with design specifications.
3. The system operates in accordance with design specification throughout the operating range of intended use.

20.2 COMPUTER-RELATED SYSTEMS USED IN THE QA/QC LABORATORY

Computer-related systems used in the laboratory for control of automatic analyzers and/or laboratory information management systems will be validated; however, additional emphasis will be placed on the following specific concerns:

- Authorization for data entry
- Features to prevent deletion of data (changes must be made as amendments; deletion of data is not permitted)
- Security of the database (database must be as tamper-proof as possible)
- Procedures for ensuring the validity of the data

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cGMP PROCEDURES AND PROGRAMS

21.1 ENGINEERING CHANGE CONTROL

Change Control will be written to ensure that systems and processes remain in a state of validation. The procedure outlines steps to follow when a change is proposed. 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.

21.2 CALIBRATION

The calibration program will ensure that all critical instruments used are maintained in a calibrated state. Specific acceptance criteria limits will be established based on system and processing requirements.

Periodic calibration orders generated by the calibration program will contain information such as department, location, accuracy, data sheet number, SOP number, etc. needed by the calibration technician. Instrumentation in this program will include, but is not limited to, timers, monitoring probes (temperature, relative humidity, etc.), pressure gauges, balances, etc.

Each instrument will be placed in one of three categories: Critical, Non-critical, and Convenience. A critical instrument is one whose failure or precision directly affects the quality, purity, and/or integrity of the product. A non-critical instrument does not fall into the Critical category, but can be used in troubleshooting, mainting, controlling, or monitoring

a process or test that is potentially hazardous. A Convenience instrument is any instrument that does not fall into the Critical or Non-critical category.

Instrument calibrations are required at intervals based on the criticality of the instruments, instrument capability, and instrument calibration history. An instrument will also be calibrated following the repair of the instrument, following the repair of the system that the instrument is monitoring/controlling, if the repair could have affected the instrument accuracy, and/or after installing the instrument into a system. All equipment used to perform calibrations will be calibrated to standards traceable to the National Institute of Standards and Technology (NIST) or other approved standards and maintain the following:

- Standards
- Instrument numbering system
- Instrument calibration files

21.3 PREVENTIVE MAINTENANCE PROGRAM

A preventive maintenance program is developed and implemented to maintain production systems in proper working condition and reduce equipment malfunctions.

The manufacturer's specifications, past experience, and history of the equipment will be used to establish the preventive maintenance schedule. Procedures will be developed for issuing work orders, performing the maintenance work, documenting the work in the proper logbooks and files, frequency of performing preventive maintenance, reviewing the impact of maintenance on validation state, etc.

21.4 STANDARD OPERATING PROCEDURES (SOPs)

The standard operating procedure (SOP) system is established, procedure number WXY-001 "for Preparation, Approval and Issue of Standard Operating Procedure." The procedure includes instructions for preparation, review, approval, issuance, control, modification, and document retention. The modification to procedure WXY-001 will include establishment of the review and approval.

All new procedures will be written to address all activities performed in the facility, including documentation systems, raw materials handling and control, personnel movement, equipment operation, product formulation, handling and testing, etc.

21.5 FACILITY CLEANING AND SANITIZATION

A comprehensive Facility Cleaning and Sanitization Program with an initial schedule for each room will be developed, with procedures based on the initial sanitization validation results, the criticality of operation performed in each area, and the frequency of use. The initial schedule will be modified as necessary based on routine environmental monitoring. The environmental monitoring results will be compared against alert and action levels.

The program will include a schedule for rotation of sanitizing agents to prevent the proliferation of resistant organisms in the facility. Cleaning and sanitizing will be documented in logbooks, the status of each room will be marked, and all cleaning will be performed per written procedures (SOPs). Sanitizing agents will be routinely monitored for bacterial contamination. Logbooks will be periodically reviewed by Quality Assurance.

21.6 ENVIRONMENTAL MONITORING PROGRAM

A comprehensive Environmental Monitoring Program will be developed to ensure that the environmental conditions are maintained within validated limits. The program will include critical utility systems, microbiological testing areas, and manufacturing areas. Parameters that may affect the integrity of the product or manufacturing process, personnel safety, or the cleaning and sanitization program will be monitored. These parameters include nonviable particulate, bioburden, purity, identity, temperature and relative humidity.

Most of the testing procedures required for this program will be adapted from Quality Assurance and Quality Control procedures. The existing analytical and microbiological procedures have been validated or verified. Any additional analytical or microbiological test procedures will be validated or verified.

Alert and action levels for each parameter in each area or critical utility will be established based on the results from validation testing, compendia requirements, and cGMPs. Area or room limits will be based on the environmental data collected during the validation of the aseptic filling process validation. Specific action plans will be developed for addressing excursions beyond alert and action limits for each area or utility.

21.7 HEPA FILTER INTEGRITY TESTING

A procedure will be developed that identifies the certification requirements for all High Efficiency Particulate Air (HEPA) filters in the Injectable facility. This will include HEPA filters mounted in ceilings, flow hoods, biosafety

cabinets, cleanroom vacuum cleaners, microbiology testing rooms, and air handling units. HEPA filters will be certified by the DOP test method for proper face velocity profile, velocity at the workspace, and integrity. HEPA filters will be initially tested as part of the installation, and all test documentation will be verified and included in the Validation Package for the HVAC system, biosafety cabinets, and laminar flow hoods. Terminal HEPA filters servicing Class 100 areas will be certified more frequently than those in Class 1000 or greater areas.

21.8 FILTER INTEGRITY TESTING

A filter testing procedure will be developed to ensure that bacterial retentive air and liquid filters are integrity tested and replaced as necessary. This program will include those filters not directly in the process stream, such as vent filters on tanks and autoclaves, and compressed gas filters. This procedure will include filter integrity testing instructions, schedules, and acceptable test results.

Filters that are directly in the process stream, such as product sterilizing filters and media sterilizing filters, will be tested before and after the processing of each batch and documented in the actual batch production records.

The automatic filter integrity tester will be operationally qualified, and all test parameters and acceptable test results will be verified in the Operational and Performance Qualifications of the equipment, for example, the Sterilizing Filter and the Media Preparation System.

21.9 LABEL CONTROL PROGRAM

The label control program and procedure includes labeling requirements. The program is structured to ensure the following:

- Issuance is strictly controlled and performed by authorized personnel only.
- Labeling materials issued are carefully examined for identity and conformity to the labeling specified in the batch production record for the product being labeled.
- Reconciliation of quantities issued, used, and returned, as well as investigation of any discrepancies.
- Excess labeling bearing lot numbers is destroyed.
- Returned labeling is stored in a manner to prevent mix-ups and provide proper identification.

21.10 cGMP TRAINING

A GMP training system which ensures that all personnel are trained in current Good Manufacturing Practices as required by Title 21 CFR Part 211.25 (a) will be developed in all operations that they are required to perform. The program will be designed so that training is performed and/or coordinated by the Quality Assurance Manager. All training will be documented and retained in a training file.

21.11 EQUIPMENT LOGBOOKS, STATUS TAGS, AND ROOM CLEARANCE CHECKLISTS

A system for determining the day-to-day status of critical systems, areas, and activities will be developed. Activities such as batch production, cleaning, preventive maintenance, calibration, load sterilization, etc. will be controlled and documented by procedure in logbooks and reviewed and filed as critical processing documentation.

Status tags will be utilized to indicate the status, such as under cleaning, clean, in-process, quarantine, released, etc. Procedures will be developed for the placement and removal of status tags.

A checklist will be developed to establish proper room clearance prior to initiating a production batch. Checklist development, handling, control, and review will be incorporated into procedures for ongoing control.

21.12 VALIDATION FILES

A program to ensure control of critical system documentation will be established. The files will be controlled by QA. Validation and centralized for easy retrieval. Equipment validation data such as operating and service manuals, purchase orders, manufacturer specifications, as-built drawings and schematics, spare parts lists, and any other information pertaining to the system will be included in the file. Separate validation files for Facility, Systems, and Process validation of each product, including all related data, will be maintained. Procedures will be developed to create files for new equipment, update information for existing equipment, control, removal, and return of information, etc.

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VALIDATION SCHEDULE

Validation schedule is the last but not the least important component of overall validation activity. The validation schedule prepared for ABC Pharmaceutical Industries defines a time line chart for the execution of IQ, OQ, PQ, PV, CLV, etc., to attain sufficient documented evidence to give reasonable assurance that the process under consideration does and/or will do what it purports to do.

Room No.	*Description of Equipment/Facility/Utilities/ Process/Cleaning*	*Validation Requirement IQ/OQ/PQ/PV/CLV etc.*	*Year*			
			Quarter			
			1Q	*2Q*	*3Q*	*4Q*

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DRAWINGS FOR ABC PHARMACEUTICAL PLANT

S. No.	Description	Drawing No.
1	**Machine Layout**	
	Building A	Machine - 01
	Building B	Machine - 02
	Building C	Machine - 03
2	**Civil Layout**	
	Building A	Civil - 01
	Building B	Civil - 02
	Building C	Civil - 03
3	**Nitrogen Piping Layout**	
	Building A	Piping - 01
	Building B	Piping - 02
	Building C	Piping - 03
4	**Chilled Water Piping Layout**	
	Building A	Piping - 01
	Building B	Piping - 02
	Building C	Piping - 03
5	**Steam Piping Layout**	
	Building A	Piping - 01
	Building B	Piping - 02
	Building C	Piping - 03
6	**Hot Water Piping Layout**	
	Building A	Piping - 01
	Building B	Piping - 02
	Building C	Piping - 03
7	**Compressed Air Piping Layout**	
	Building A	Piping - 01
	Building B	Piping - 02
	Building C	Piping - 03
8	**Deionized Water Piping Layout**	
	Building A	Water - 01
	Building B	Water - 02
	Building C	Water - 03

S. No.	Description	Drawing No.
9	**Water for Injection Piping Layout**	
	Building C	Water - 01
10	**HVAC**	
	GA & Ducting Layout	
	Building A	HVAC - 01
	Building B	HVAC - 02
	Building C	HVAC - 03

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