Validation Standard Operating Procedures

A Step-by-Step Guide for Achieving Compliance in the Pharmaceutical, Medical Device, and Biotech Industries

Syed Imtiaz Haider, Ph.D.

ST. LUCIE PRESS

A CRC Press Company
Boca Raton London New York Washington, D.C.

Some content within Val. 600.90, 200.10, 600.70, 600.30, 1100.10, 1100.20 was excerpted or adapted from USP-24 – Chapter 1225 (pp. 2149-2152), Chapter 1227 (pp. 2152-2154), and Chapter 1116 (pp. 2099-2104), as well as *Water for Injection Specification* (p. 1752) and *Purified Water Specification* (p. 1753). United States Pharmacopoeial Convention, Inc., Rockville, MD. Copyright 1999–2000. With permission.

Some content within Val. 600.30, 600.60 to 600.130 was excerpted or adapted from Carleton, F. J. and Agalloco, J. P., Eds.,*Validation of Aseptic Pharmaceutical Process*, Marcel Dekker, New York, 1998. With permission.

Library of Congress Cataloging-in-Publication Data

Haider, Syed Imtiaz.
Validation standard operating procedures: a step-by-step guide for achieving compliance in the pharmaceutical, medical device, and biotech industries / by Syed Imtiaz Haider.
p. cm.
ISBN 1-57444-331-3
1. Pharmaceutical technology—Quality control. 2. Pharmaceutical industry—Standards—United States. 3. Biotechnology industries—Standards United States. 4. Medical instruments and apparatus industry—Standards—United States. I. Title.

RS192 .H353 2001
681′.761′021873—dc21 2001048505
CIP

International Standard Book Number 1-57444-331-3
Library of Congress Card Number 2001048505
Printed in the United States of America 1 2 3 4 5 6 7 8 9 0
Printed on acid-free paper

CONTENTS

Section VAL 100.00

100.10 Introduction to Validation

Section VAL 200.00

200.10 Fundamentals of Validation SOPs
200.20 Validation Master Plan and Guideline for DQ, IQ, OQ, and PQ
200.30 Design Qualification Guideline for Minimizing the Risk of Product Cross-Contamination by Air Handling System
200.40 Design Qualification Guideline for Minimizing the Risk of Cross-Contamination of Facility, Equipment, and Process
200.50 Design Qualification Guideline for HVAC System of a Pharmaceutical Plant
200.60 Design Qualification for the Prevention of Contamination of Non-Sterile Pharmaceutical Products
200.70 Design Qualification Guideline for Cross-Contamination and Decontamination
200.80 Design Specifications for Process Water
200.90 Design Specifications for Water for Injection Production and Distribution
200.100 Design Specifications for Purified Water (DIW) Production and Distribution
200.110 Design Specifications for Pure Steam Production and Distribution

Section VAL 300.00

300.10 Validation Glossary
300.20 Organization for Validation
300.30 Revalidation
300.40 Retrospective Validation
300.50 Validation Change Control

Section VAL 400.00

400.10 Calibration of Instruments
400.20 Periodic Review of the Calibration Program
400.30 Calibration and Validation Equipment

Section VAL 500.00

500.10 Training on the Job
500.20 Good Manufacturing Practices

Section VAL 600.00

600.10 Guidelines for Area Classification and Air Handling
600.20 Guideline for Area Validation: Clean Area
600.30 Aseptic Area Validation Procedures
600.40 Microbiological Monitoring of Areas Used for Production of Solids, Semi-Solids, and Liquids
600.50 Efficiency Testing for Disinfectants
600.60 Drinking Water
600.70 Purified Water
600.80 Water for Injection
600.90 Validation of a Water System
600.100 Oil-Free Compressed Air System
600.110 Nitrogen Distribution System
600.120 Clean Steam
600.130 Vacuum System
600.140 Validation of an HVAC System

Section VAL 700.00

700.10 Validation of a Steam Sterilizer
700.20 Hot Air Sterilization Tunnel Certification and Validation Guideline
700.30 Freeze Drier
700.40 Ampule and Vial Washing Machine
700.50 Washing, Sterilizing, and Drying Machine for Stoppers
700.60 Ampule and Vial Filling Machine
700.70 Media Fill Run
700.80 Half-Automatic Inspection Machine
700.90 Ampule Crack Detection Machine
700.100 Laminar Flow Installations
700.110 Sterile Filtration Validation
700.120 Cleaning Efficiency of Production Equipment for Parenterals

Section VAL 800.00

800.10 Kneading Machine
800.20 Oscillating Granulator
800.30 Milling Machine
800.40 Fluid Bed Drier
800.50 Blender
800.60 Tablet Press
800.70 Metal Check Device for Tablets
800.80 Tablet Coater

Section VAL 900.00

900.10 Blistering Machine
900.20 Blister Filling Machine
900.30 Code Reader
900.40 Sachetting Machine
900.50 Cartoning Machine
900.60 Labeling Machine
900.70 Check Weigher
900.80 Shrink Wrapping and Bundling Machine
900.90 Tube Filling and Closing Machine
900.100 Liquid Filling and Closing Machine
900.110 Tablet Filling and Closing Machine

Section VAL 1000.00

1000.10 Installation Qualification of Computerized Equipment
1000.20 Operational Qualification of Computerized Equipment
1000.30 Performance Qualification of Computerized Equipment

Section VAL 1100.00

1100.10 Validation of Microbiological Methods
1100.20 Validation of Analytical Methods

Section VAL 1200.00

1200.10 Vendor Certification

Section VAL 1300.00

1300.10 Facility Qualification

Recommended Reading

PREFACE

As the validation master plan execution program proceeds and the facility is integrated into regulatory guidelines of the FDA, current good manufacturing practice (cGMP), good laboratory practice (GLP), and the need for comprehensive and well-defined validation supporting standard operating procedures are required. As the validation program progresses and the systems are integrated into routine operation, there are fewer deviations and the standard operating procedures become more precise and complete.

This book and CD-ROM provide an administrative solution for management. The execution of test functions defined in the validation master plan procedures is provided in the text and the electronic files. The validation standard operating procedure can help your company comply with GMP, GLP, and validation requirements imposed by the FDA.

The formats and style provided are generic and can be further amended. The contents of the standard operating procedures (SOPs) are intended to build quality into the regulatory requirements. However, having a set of validation standard operating procedures does not preclude adverse inspection findings, as contents that satisfy one inspector may not satisfy another.

The author strongly believes that the facility's technical management and staff should read the procedures to ensure that particular needs are addressed with reference to operational control within the organization and individual countries' regulatory requirements. It is, however, guaranteed to provide management with a tool to develop a set of validation SOPs in order to support the road map established for the on-time successful start-up of the facility operation in compliance with the GMP requirement.

Pharmaceutical, medical, and biotech industries are regulated worldwide to be in compliance with cGMP and GLP principles. Each company is required to create validation SOPs to qualify its equipment, utilities, buildings, and personnel. The template validation SOPs available enable end users to understand principles and

elements of good manufacturing practice and provide documentation language ranging from generic to specific, depending on the detail level of the requirements.

Compliance to FDA regulations by the health care industry over the last decade has been a major goal, including those companies intending to export their product to the US market. As a result, almost 300 companies are inspected around the world by the FDA every year for their GMP and GLP compliance. Only five to six companies are able to seek approval for exportation; one of the reasons behind this is the absence or inadequacy of validation SOPs. Key benefits involve but are not limited to:

- Successful facility operational start-up
- Minimized noncompliance
- Reduced reworks
- Reduced rejected lots
- Avoidance of recalled lots
- Help in new drug approval
- Satisfactory inspections
- Corporate image
- Financial gain
- Secure third-party contracts
- Corporate legal protection
- Utility cost reduction
- Minimized capital expenditures
- Fewer complaints
- Reduced testing
- Improved employee awareness

The validation standard operating procedures on the CD-ROM are valuable tools for companies in the process of developing or revising VSOPs to achieve FDA, GMP, and GLP compliance. The documentation package is especially relevant to quality assurance personnel, engineers, utilities engineers, computer engineers, validation designers, internal and external auditors, or to anyone interested in developing a qualification documentation matrix.

The author believes that by following the broadly based example of these VSOPs, both new and experienced companies can benefit by enhancing their existing documentation to meet FDA and other regulatory requirements. Currently, no GMP document specifically describes the format of these validation standard operating procedures.

Syed Imtiaz Haider, Ph.D.
July 2001

DEDICATION

This book is dedicated to my loving father Syed Mohsin Raza for his continuous motivation. I am also indebted to my wife Shazia for her patience while I compiled this book.

ACKNOWLEDGMENT

The author would like to thank his friends and colleagues, especially Mr. Javed Zamir and Mr. Zahid Haleem for their help and encouragement and for creating a professional environment. Special thanks to the staff of CRC Press, particularly Drew Gierman and Judith Simon Kamin for their patience and diligence in the production of this book.

ABOUT THE AUTHOR

Syed Imtiaz Haider earned his Ph.D. in chemistry and is a quality assurance specialist with over ten years experience in aseptic and nonaseptic pharmaceutical processes, equipment validation, and in-process control and auditing. Dr. Haider is the author and co-author of more than 20 research publications in international refereed journals dealing with products of pharmaceutical interest, their isolation, and structure development. A professional technical writer, Haider has authored more than 500 standard operating procedures based on FDA regulations, ISO 9001, and ISO 14001 standards. He is a certified auditor of IRCA and a registered associate environmental auditor of EARA. He has written more than ten quality system 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 and holds the copyright certificate of registration on an electronic documentation package on ISO 14001 from the Canadian intellectual property office.

ABOUT THE BOOK

This book and CD-ROM take into account all major international regulations, such as FDA, cGMP, GLP, PDA technical monographs, PDA technical reports, PMA's concepts, Journal of PDA, 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 validation procedure for pharmaceutical plants and provides hands-on templates to be tailored to achieve FDA compliance.

Validation standard operating procedures are written to provide explicit instruction on how to achieve the standards for those responsible for writing and executing master validation plans for drug, drug-device combination, diagnostic, pharmaceutical biotechnology, and bulk pharmaceutical chemicals products. Included is the ready-to-use template so that one can immediately save time and expense without missing any critical elements.

The book provides instant answers to validation engineers, validation specialists, quality professionals, quality assurance auditors, and protocol writers about what to include in validation standard operating procedures and how to enhance productivity.

Introduction

- SOP Format
- SOP Number
- SOP Title
- Date
- Author
- Checked by
- Approved by
- Revision
- Subject
- Responsibility

- Purpose
- Procedure
- Reasons For Revision

The book and CD-ROM are designed for individuals specifically involved in writing and execution of master validation plans, development of protocols, and applicable procedures. This book provides a complete, single-source reference detailing conceptual design elements and more than 70 explicit procedures for validation.

INTRODUCTION

This book was designed and written for validation professionals responsible for writing and maintaining quality management systems for the successful operation of their companies. It provides a set of standard operating procedures (SOPs) that can be used to manage and document critical validation and revalidation tasks in a pharmaceutical manufacturing facility.

The numbering of the sections and related SOPs begins with 200 and goes through 1300. In addition the reader may add SOPs that are unique to his facility. The term *responsible person* is used extensively throughout the SOPs. The term refers to the person who has been delegated authority by management and deemed responsible for performing duties associated with validation tasks within the facility.

SOP Format

All SOPs have been uniformally designed and formatted. Information common to all SOPs is described below.

First Page

Company Name — At the top of each SOP, a box is provided to enter your company name.

SOP Number — Each SOP is assigned a unique number that appears at the upper-left corner of each page.

Title — The title of each SOP appears at the top of the first two pages below the SOP number. The title describes the subject of the SOP.

Date — Each SOP is assigned an effective date at the top of the page, to the right of the SOP number. The date describes the month, day, and year of implementation.

Author — Each SOP is assigned a space to provide the author name, title, and the department, along with signatures and dates.
Checked by — Each SOP is assigned a space to provide the name, title, and the department of the person responsible for checking the contents of the SOP requiring the signature and date.
Approved By — Each page of the SOP provides a space for the signature of the quality assurance or manager approving the SOP to prevent unauthorized changes.
Revisions — At the end of each page is the revisions box. This box documents the revision number, section, pages, initials, and date.

Other Pages

Subject — Each SOP begins with the subject to provide key description of the SOP.
Purpose — Each SOP is supported with reasons, describing the purpose.
Responsibility — The space for responsibility clearly identifies who has to follow the procedures and who is responsible for the overall compliance with the SOP.
Procedure — Following the purpose statement are the individual steps of the SOP, arranged in logical order to make the SOP easy to perform.
Reason for Revision — At the end of each SOP, a space is provided to list the reasons why the SOP is changed, along with the date.
CD-ROM — An electronic copy of the generic validation standard operating procedures is provided.

DISCLAIMER

Every effort has been made to ensure that the contents of the generic validation standard operating procedures 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.

The similarity in the contents of the procedure with a particular reference to the test functions, acceptance criteria, qualification protocols, and checks may be incidental because of the similarity in principle and operations of pharmaceutical equipment.

SECTION

VAL 100.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 100.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Introduction to Validation**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 100.10 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Introduction to Validation

PURPOSE

To describe the definition, types, and benefits of validation

RESPONSIBILITY

It is the responsibility of validation team members to follow the procedures. The quality assurance (QA) manager is responsible for SOP compliance.

PROCEDURE

1. Definition of Validation

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

2. Type of Validation

- Retrospective Validation
- Prospective Validation
- Concurrent Validation
- Revalidation

2.1 Retrospective Validation

Validation of a process for a product already in distribution, based on accumulated production, testing, and control dates. Summary of existing historical data.

2.2 Prospective Validation

Validation conducted prior to distribution either of a new product, or a product made under a revised manufacturing process. Validation is completed and the results are approved prior to any product release.

2.3 Concurrent Validation

A combination of retrospective and prospective validation. Performed against an approved protocol but product is released on a lot-by-lot basis. Usually used on an existing product not previously validated or insufficiently validated.

2.4 Revalidation

To validate change in equipment, packaging, formulation operating procedure, or process that could impact product safety, efficacy, or potency. It is important to establish a revalidation program for critical equipment to maintain validity.

3. Importance of Validation

- Increased throughput
- Reduction in rejections and reworking
- Reduction in utility costs
- Avoidance of capital expenditures
- Fewer complaints about process-related failures
- Reduced testing in-process and in finished goods
- More rapid and reliable start-up of new equipment
- Easier scale-up from development work
- Easier maintenance of equipment
- Improved employee awareness of processes
- More rapid automation

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates and contract manufacturers

SECTION

VAL 200.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Fundamentals of Validation SOPs**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.10 **Effective date: mm/dd/yyyy**
Approved by:

SUBJECT: Fundamentals of Validation SOPs

PURPOSE

The purpose of writing fundamentals of validation SOPs is to assist the parent company, affiliates, and contract manufacturers to understand and maintain the validation program to meet the GMP requirements.

RESPONSIBILITY

It is the responsibility of the quality assurance manager to develop and maintain the validation program. The departmental managers and contractors are responsible for the SOP compliance.

PROCEDURE

Introduction

1. Purpose and Scope of the SOP

The quality assurance department is responsible for providing support to the parent company, affiliates, and contract manufacturers in the development, upgrading, and maintenance of GMP requirements. Validation SOPs is required to give step-by-step direction in performing validation.

2. Definitions of Validation

- Action of proving, in accordance with the principles of good manufacturing practice, that any procedure, process, equipment, material, activity, or system actually leads to the expected result
- Documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes and characteristics
- Obtaining and documenting evidence to demonstrate that a method can be relied upon to produce the intended result within defined limits
- Action to verify that any process, procedure, activity, material, system, or equipment used in manufacture or control can, will, and does achieve the desired and intended results

3. Justification of Validation

Validation is basically good business practice. The objective is to achieve success in the first production of a new product.

- Government regulations
  Current good manufacturing practices (GMPs) have been established all over the world. The GMPs basically serve as guidelines but do not provide step-by-step directions on how to achieve them. However, the validation master plan and associated SOPs exactly define responsibilities: who, when, where, and how much is sufficient to demonstrate.
- Assurance of quality
  Validation provides confidence in the quality of products manufactured as the over quality of a particular process cannot be established due to the limited sample size. Validation leads to less troubleshooting within routine production. As a result, it reduces the number of customer complaints and drug recalls.
- Cost reduction
  Processes running at marginal levels often cause costs because of necessary reinspection, retesting, rework, and rejection. Validation leads to the optimization of processes and results in minimization of those expenses.

4. Background of Validation

4.1 History

Since the mid-1970s validation has become an increasingly dominant influence in the manufacture and quality assurance of pharmaceutical products. In 1976 the FDA proposed a whole set of current GMP regulations which were revised several times.

4.2 Legal requirements

In several major countries GMP regulations are considered official law and non-compliance is prosecutable. Additional compliance policies, guides, and guidelines are not legally binding. However, the pharmaceutical industry follows them as a part of good management and business practice.

4.3 Market requirements

The demands in the health care industry are greater than ever because customers (government, physicians, pharmacists, patients, and health insurance companies) are more interested in product safety, efficacy, and potency and asking value for money.

Pharmaceutical products' quality must be consistent and meet the health and regulatory requirements. The pharmaceutical industry has the obligation to validate GMP to their process to be in compliance with GMP requirements.

4.4 Validation philosophy

All reputable companies have recognized the commitment for validation and laid down the respective policies in the quality assurance manual.

5. The Basic Concept of Process Validation

1. Requalification or revalidation
2. Calibration, verification, and maintenance of process equipment
3. Establishing specifications and performance characteristics
4. Selection of methods, process, and equipment to ensure the product meets specifications
5. Qualification or validation of process and equipment
6. Testing the final product, using validated analytical methods, in order to meet specifications
7. Challenging, auditing, monitoring, or sampling the recognized critical and key steps of the process

SOP No. Val. 200.10 **Effective date: mm/dd/yyyy**

Approved by:

6. The Basic Concept of Equipment Validation

Equipment validation comprises installation qualification, operational qualification, and performance qualification. The intention is to demonstrate that equipment is qualified for processing.

7. The Basic Concept of Area and Facility Validation

The purpose of area and facility qualification is to demonstrate that the area and facility meet the design qualification requirements for temperature, humidity, viable, and nonviable count.

8. The Basic Concept of Utilities Validation

This validation demonstrates that the utilities required to support the process meet the desired standard for quality.

9. The Basic Concept of Cleaning Validation

The cleaning validation is required to demonstrate that, after cleaning, the equipment and surfaces are essentially free from product residues and traces of cleaning agents to prevent cross-contamination.

10. The Basic Concept of Computerized System Validation

Computer systems are used worldwide in the pharmaceutical industry and have direct bearing on product quality. The purpose of validation is to demonstrate that the intended product manufactured, packed, or distributed using a computerized controlled system will meet the safety, efficacy, and potency requirements per the individual monograph.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company affiliates and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.20 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Validation Master Plan and Guideline for DQ, IQ, OQ, and PQ**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.20 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Validation Master Plan and Guideline for DQ, IQ, OQ, and PQ

PURPOSE

To provide the guideline for the preparation of validation master plan to meet the design qualification requirement

RESPONSIBILITY

It is the responsibility of all supervisors, validation officers, engineers, and managers to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Policy

A validation master plan, or other equivalent document, must be prepared and approved. This must be initiated at the earliest practical point and must be reviewed and updated throughout the project. The validation master plan must address all the relevant stages of DQ, IQ, OQ, and PQ.

1.1 Introduction

The validation master plan is a summary document stating the intention and the methods to be used to establish the adequacy of the performance of the equipment, systems, controls, or process to be validated. It is approved by the quality assurance, validation, production, and engineering groups.

1.2 Validation master plan requirement

A validation master plan, or other equivalent document, will be prepared for all projects.

1.3 Validation master plan format

The physical format of the validation master plan is flexible.

1.4 Validation master plan content

Content may include the following descriptions (but not be limited to):

1. Introduction
   - 1.1 Project Description
   - 1.2 What a Validation Master Plan Is
   - 1.3 Scope of Validation Master Plan
   - 1.4 Definition for the Term *Validation*
   - 1.5 Validation Team Member
   - 1.6 Validation Team Responsibility
2. Concept of Qualification or Validation
   - 2.1 Fundamentals
   - 2.2 Concept of a Validation Life Cycle
   - 2.3 Elements of Validation
   - 2.4 Documentation Format of Qualification Programs
   - 2.5 Numbering System
3. Revalidation
4. Facility Description
5. Description of Building
   - 5.1 Dry Production Facility
   - 5.2 Liquid and Semi-Solid Production Facility
   - 5.3 Parenterals Production Facility
6. Equipment Description
   - 6.1 Dry Production
   - 6.2 Liquid and Semi-Solid Production
   - 6.3 Parenterals Production
   - 6.4 Overprinting Area
   - 6.5 Quality Control
   - 6.6 Quality Assurance (In-Process)
   - 6.7 Product Development Laboratories
7. HVAC Description
   - 7.1 Dry Production Facility
   - 7.2 Liquid and Semi-Solid Production Facility
   - 7.3 Parenterals Production Facility
   - 7.4 Overprinting Area
   - 7.5 Quality Control
   - 7.6 Quality Assurance (In-Process)
   - 7.7 Product Development Laboratories

8. Utilities Description
9. Validation Program Overview
   - 9.1 Validation Project Management
   - 9.2 Validation Responsibilities
   - 9.3 Design and Validability Review
   - 9.4 Validation Documents
   - 9.5 Installation Qualification Protocols
   - 9.6 Operational Qualification Protocols
   - 9.7 Change Control Initiation
   - 9.8 Cycle Development
   - 9.9 Performance Qualification Protocols
   - 9.10 Process Validation Protocols
   - 9.11 Validation Final Reports
   - 9.12 Validation Package
   - 9.13 Certificate for Use in Manufacturing
   - 9.14 Required Protocols and Procedures for Dry Production
   - 9.15 Required Protocols and Procedures for Liquid and Semisolid Protocols
   - 9.16 Required Protocols and Procedures for Parenterals Production
10. Calibration Program Summary
11. Preventive Maintenance Program Summary
12. Key SOPs
13. Validation of Building Test Functions and Acceptance Criteria
    - 13.1 Civil Work
    - 13.2 Drainage System
14. Validation of Utility Systems, Test Functions, and Acceptance Criteria
    - 14.1 Plant Steam
    - 14.2 Pure Steam
    - 14.3 Water for Injection
    - 14.4 Compressed Air
    - 14.5 Nitrogen (N_2)
    - 14.6 Carbon Dioxide (CO_2)
    - 14.7 Heating Ventilation and Air Conditioning (HVAC)
    - 14.8 Emergency Power
15. Process Description Dry Products
    - 15.1 Process Flow, Variables, and Responses: Tablets

15.2 Process Flow, Variables, and Responses: Powder for Suspension
15.3 Process Flow, Variables, and Responses: Capsules
16. Process Description
Liquids and Semi Solid Products
16.1 Process Flow, Variables, and Responses
Syrups, Suspension, and Drops Products
16.2 Process Flow, Variables, and Responses
Cream, Ointment, and Suppository Products
17. Process Description
Parenterals Product
17.1 Process Flow, Variables, and Responses
Aseptic Fill Products
17.2 Process Flow, Variables, and Responses
Aseptic Fill 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
Test Functions and Acceptance Criteria
18.1 Commuting Mull
18.2 Oven
18.3 V-Shell Blender
18.4 Tablet Compression
18.5 Capsulation
18.6 Powder Filling
18.7 Capsule Polisher
18.8 Tablet Coating
18.9 Syrup Manufacturing Vessel
18.10 Suspension Manufacturing Vessel
18.11 Drops Manufacturing Vessel
18.12 Mixer
18.13 Emulsifying Mixer
18.14 Filter Press
18.15 Cream, Ointment, and Suppository Manufacturing Vessel
18.16 Syrup, Suspension, and Drop Filling Machine
18.17 Cream and Ointment Filling Machine

- 18.18 Suppository Filling Machine
- 18.19 Labeling Machine
- 18.20 Capping Machine
- 18.21 Cartonator
- 18.22 Shrink Wrapping Machine
- 18.23 Overprinting Machine
- 18.24 Trays and Rack Washer
- 18.25 Autoclave (Steam Sterilizer)
- 18.26 Hot Air Tunnel (Dry Heat Sterilizer)
- 18.27 Vial and Ampule Washing Machine
- 18.28 Vial, Ampoule, and Syringe Filling Machine
- 18.29 Freeze Dryer (Lyophilizer)
- 18.30 Laminar Flow Unit
- 18.31 Pass Through

19. Validation of Support Processes Test Functions and Acceptance Criteria
    - 19.1 Washing of Components
    - 19.2 Sterilization of Components
    - 19.3 Depyrogenation of Components
    - 19.4 Aseptic Filling Validation (Media Fill Studies)
    - 19.5 Cross-Contamination Control
    - 19.6 Computerized Pharmaceutical System
20. Quality Assurance/Control Laboratory Validation
    - 20.1 Laboratory Equipment Qualification
    - 20.2 Computer-Related Systems in QA and QC
21. cGMP Procedures and Programs
    - 21.1 Engineering Change Control
    - 21.2 Calibration
    - 21.3 Preventive Maintenance Program
    - 21.4 Standard Operating Procedure (SOP)
    - 21.5 Facility Cleaning and Sanitization
    - 21.6 Environmental Monitoring Program
    - 21.7 HEPA Filter Integrity Testing
    - 21.8 Filter Integrity Testing
    - 21.9 Label Control Program
    - 21.10 cGMP Training
    - 21.11 Equipment Log Book, Status Tags, and Room Clearance
    - 21.12 Validation Files

22. Validation Schedule
23. Drawings and Layouts
    - 23.1 Dry Production Facility
    - 23.2 Liquid and Semisolid Production Facility
    - 23.3 Parenterals Production Facility
    - 23.4 Deionized Water System
    - 23.5 HVAC
    - 23.6 Water for Injection
    - 23.7 Steam Distribution
    - 23.8 Compressed Air Distribution
    - 23.9 Nitrogen Distribution
    - 23.10 Drainage System
    - 23.11 Personnel Flow
    - 23.12 Materials Flow
    - 23.13 Electrical Drawings
    - 23.14 Equipment Installation Drawings

1.5 Validation master plan review and update

The validation master plan is a dynamic document which will be reviewed, updated, and approved as required during the lifecycle of the project.

2. Guideline — Design Qualification

Design qualification is documented evidence that quality is built into the design of facilities and operations.

Policy: the company must prepare or adopt appropriate guidelines for design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

2.1 Background

The standard of any facility of operation is highly dependent upon the quality of the design and, therefore, the staff employed to undertake the work. A design qualification protocol, or report document, should detail and record the disciplined, structured approach followed. This will provide a useful lead into the installation qualification (IQ) stage.

2.2. Typical document

The principlal information included should be as follows:

- HAZOPs (hazard and operability studies)
- Modular design, with drawings and specifications produced
- Zone classification studies, etc.

Confirmation of the structured and rigorous approach to design, including comments on confirmation of design standards adopted referring to:

- Key issues underwritten by QA
- Company standards
- Confirmation of the use of appropriately qualified staff
- Confirmation of the attention paid to GMP issues (e.g., by GMP audits)
- Key reference texts on cGMP issues
- National and international codes
- Confirmation that available technology transfer information has been used
- Confirmation that change control systems have operated effectively

2.3 Design qualification report

Policy: upon completion of each stage (DQ, IQ, OQ, PQ), a document review or report detailing results compared against the requirement and recommendations for future work must be prepared and accepted by appropriate management before proceeding to the next stage of validation or implementing the process.

3. Guideline — Installation Qualification

This qualification is a documented demonstration that facilities and operations are installed as designed and specified and are correctly interfaced with systems.

3.1 Installation qualification protocol

The IQ protocol should include a statement of the data required and acceptance criteria to be met for installation of the system or equipment to verify that the specification has been satisfied.

The protocol should include as applicable, but not be limited to:

- Engineering drawing and documents
- Building finishes
- Process and utilities (services) flow diagrams
- Piping and instrumentation diagrams
- Equipment and instrument specifications
- Manufacturers' drawing, equipment maintenance, and operating manuals
- Spare lists
- Maintenance schedules

The IQ protocol should also ensure that equipment and instrumentation is clearly described and suitably labeled as to vendor, model, capacity, materials, and other critical criteria.

The IQ protocol should ensure that instrumentation has been calibrated according to approved procedures and that the measurements are traceable to defined national or international standards. All such calibrations and detailed control parameters must be recorded and records securely kept.

It should also ensure that change control systems are in operation, and that all systems have been verified to operate under no load conditions.

3.2 Installation qualification report

- Results as compared against the protocols
- Recommendations for future work
- Must be prepared and accepted by appropriate management, as defined under 3.6 (responsibility), before proceeding to the next stage of validation or implementing the process

4. Guideline — Operational Qualification

The operational qualification provides a documented demonstration that facilities an operation's function as specified.

4.1 Operational qualification (OQ) protocol

The OQ protocol should:

- Include a complete description of the purpose, methodology, and acceptance criteria for the operational tests to be performed
- Ensure that instrumentation is in current calibration
- Ensure that detailed control parameters have been established and recorded for each instrument loop
- Ensure change control systems are in operation
- Ensure that standard operating and maintenance procedures have been developed (drafted) for each system, to ensure continued operation under defined conditions
- Ensure that training modules and training sessions for production, engineering, and support personnel have been developed, conducted, and documented during this stage

Where appropriate and documented in the validation master plan, the IQ and OQ protocols may form a single document which clearly defines the acceptance for each test(s).

4.2 Operational qualification report

- Results as compared against the protocols
- Recommendations for future work

5. Guideline — Performance Qualification

The performance qualification is a documented program to demonstrate that an operation, when carried out within defined parameters, will consistently perform its intended function to meet predetermined acceptance criteria.

Operation, maintenance and calibration procedures: Before commencing performance qualification, authorized procedures must be in place for routine use of the facility or operation, training of operators, routine calibration and maintenance, notification and recording of problems, and for the definition of actions to be taken in the event of breakdown.

5.1 Performance qualification (PQ) protocol

The PQ protocol should:

- Include a complete description of the purpose, methodology, and acceptance criteria for the performance tests to be performed
- Ensure that change control systems are in operation
- Ensure that any outstanding actions (exceptions) from IQ or OQ are recorded and recommendations for remedial actions are justified and approved
- Ensure that maintenance and calibration routines are in operation
- Ensure that all SOPs have been finalized and approved at this stage
- Ensure that operating staff have been trained according to the approved SOPs
- Ensure that performance qualification testing has been carried out using the same personnel who will routinely operate the system or equipment
- Ensure that all deviations from the validation protocol are investigated and documented
- Ensure that sufficient lots or samples will be evaluated to demonstrate adequate process control
- Ensure that, before approval is given to allow PQ testing to proceed, all IQ and OQ results are reviewed and accepted

5.2 Performance qualification (PQ) report

- Results as compared against the protocols
- Recommendations for future work
- Must be prepared and accepted by appropriate management before proceeding to the next stage of validation or implementing the process

6. Guideline — Validation Review

A validation review procedure must be formally defined. Any validation review must be documented in detail and the results of any test should be compared to the original validation results. If the results are satisfactory, the facility or operation may continue to be used. If the results are not satisfactory, operations must be suspended. The facility or operation must be validated before further use.

6.1 Validation review procedure

The frequency of the validation review should be addressed in the final validation report and may be determined against elapsed time or the number of batches processed, anomalies in results of in-process and end-product testing, and questions arising from internal or external audits.

7. Guideline — Actions to Be Taken Following Test Failures

Any test failure during a validation exercise must be reviewed or analyzed to identify the origin of the failure. Action to be taken following test failure must be documented and authorized through a formal system.

7.1 Introduction

Test failures should be considered as *useful* events during validation exercises. The more failures detected during the validation, the more problems avoided during the future routine work.

7.2 Procedure

Appropriate qualified staff must study the results to identify the reason for failure, which may not be due to the facilities or operations under test, but instead due to:

- Inadequate test protocols

- Incomplete or substandard installation (at IQ and early stages of OQ)

- Badly calibrated off-line control apparatus
- Sampling errors
- Materials of the wrong specification
- Human factors

The failure may be justified as arising from the facilities or operations if:

- Required parameters cannot be achieved
- Equipment specification is incorrect
- Results are inconsistent or divergent
- Precision is poor

7.2.1 Actions to be taken once the source of the defect has been identified:

- For failures due to incomplete or substandard installation during IQ or early stages of OQ, authorized remedial action may be taken and the test repeated.
- For all other failures, an approved group will decide the correct course of action, for example:
  - To retest in the case of unreliable initial analytical tests, or resample according to a defined or authorized procedure
  - To introduce a change in order to correct or solve the problem (raw material, operation parameter, part of equipment, new step, the process, control system)
  - To apply more or less severe limits in the use of the process or equipment and update the SOP

7.3 Documentation

All remedial corrective action and preventive measures must be documented and records retained.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.30 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Design Qualification Guideline for Minimizing the Risk of Product Cross-Contamination by Air Handling System**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.30 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Design Qualification Guideline for Minimizing the Risk of Product Cross-Contamination by Air Handling System

PURPOSE

To provide the guideline to be followed for minimizing the risk of product cross-contamination with respect to the air handling system

RESPONSIBILITY

It is the responsibility of all key supervisors, validation officers, engineers, and managers to build guidelines into the plant architectural structure at the design phase, while placing orders, making purchase requisitions, and in the standard operating procedures to ensure prevention of cross-contamination. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

This guide is intended to outline some of the considerations to be taken into account in the design of air handling systems in order to minimize the risk of product cross-contamination.

1. Potential Sources of Cross-Contamination

- Dispersal of product around manufacturing facilities through inadequately designed (non GMP) air handling system zoning, air locks, and room pressure differentials
- Spread of product around manufacturing facilities via environmental and process air handling systems
- Dispersal of product during the cleaning and maintenance of environmental and process air handling plant and equipment

2. Containment of Product and Collection at Source

The practice of containment of product within the manufacturing process system should be maximized in order to minimize the potential sources of product cross-contamination outlined above.

Wherever product or material is exposed, adequately designed localized containment should be carefully considered, for example, local exhaust ventilation and containment booths, etc.

3. Zoning of Air Handling Systems

Specific air handling system consideration should be given to minimizing the dispersal of product by careful design of air handling zones including the following factors:

- Dedicated air handling system for specific manufacturing departments, for example, dry, liquid, and sterile product manufacture
- Separate air handling systems for manufacturing and non-manufacturing operations, for example, manufacturing and primary packing, secondary packing, QC laboratories such as in-process and administration facilities, etc.
- Dedicated air handling units for products containing specific active ingredients where possible
- Once-through air handling plants (i.e., no recirculation) or recirculation type systems (see Section 6)
- Air locks between air handling zones

4. Air Locks

Adequate consideration should be given to the design of air locks to minimize the spread of product between air handling zones.

- **Negative pressure air locks:** Account shall be taken of the risk of bringing product-contaminated air streams from two air handling zones closer together when using negative air locks.
- **Positive pressure air locks:** Careful consideration should be given to ensuring that air is not supplied to positive pressure air locks from a product-contaminated source.

5. Room Pressure Differentials

Room pressure differentials should be adequate to minimize the dispersal of product by ensuring air movement in a controlled and predetermined direction.

6. Recirculation vs. Once-Through Air Handling Systems

The following factors should be considered:

- Return air to air handling plant shall not be product contaminated.
- HEPA filters in air handling system give adequate protection against product cross-contamination. Select correct HEPA filter.
- Is air handling system serving other critical product manufacturing areas?

7. Room Air Distribution

The key function of an air handling system is to facilitate environmental conditions of temperature and humidity.

Provisions for reducing room particle count during manufacture operations should be provided through careful dilution of particle-contaminated room air with particle free supply.

8. The Use of HEPA Filters

The following are some of the factors which should be considered:

- Are terminal HEPA filters on room air supplies necessary to prevent risk of product migration from one manufacturing area to another through ductwork distribution systems when air handling plant is inoperative?
- Are terminal HEPA filters on room air returns necessary to prevent product contamination of air handling plant components *and* ductwork distribution system *or* risk of product migration from one manufacturing area to another through ductwork distribution systems?
- Are HEPA filters on main returns to air handling plants necessary to prevent product contamination of air handling plant components?
- Will production area, and hence return ductwork and air handling plant, be product contaminated? Is this acceptable?

9. Air Handling Plants

Careful consideration should be given to the risk of product cross-contamination from one air handling plant to another during cleaning and maintenance procedures.

Precautions could include:

- The location of dust collection system air handling plants external to manufacturing building
- The use of safe-change filters where located in product contaminated air streams
- Segregation of air handling system plants

10. Fresh Air Intakes and Exhausts

The location and sign of fresh air intakes and discharge air exhausts to the atmosphere from air handling plants should be designed to eliminate the risk of product cross-contamination by short circuiting of air streams.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.40 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Design Qualification Guideline for Minimizing the Risk of Cross-Contamination of Facility, Equipment, and Process**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.40 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Design Qualification Guideline for Minimizing the Risk of Cross-Contamination of Facility, Equipment, and Process

PURPOSE

To provide the guideline to be followed for minimizing the risk of cross-contamination with respect to facility, equipment, and process design

RESPONSIBILITY

It is the responsibility of all key supervisors, validation officers, engineers, and managers to build the guidelines into the plant architectural structure at the design phase, while placing orders, making purchase requisitions, and in the standard operating procedures to ensure prevention of cross-contamination. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Good Design Practices

The design of facilities, equipment, and processes can minimize but not eliminate the risk of cross-contamination. The application of good design practices, if applied and monitored throughout the development of construction documents, will help prevent a high degree of cross-contamination. However, good design cannot overcome poor operating or quality control practices during operation of any facility.

The following points shall be given due consideration during facility design. Equipment which contains product contact surfaces or noncontacting potentially contaminating surfaces shall be reviewed for adequacy.

2. Process Design

- The product handling and transfer should be carried out in a closed system for minimizing cross-contamination from the environment and from personnel.
- Processes should also prevent contamination of the working environment and subsequent dispersal problems.

- Manual handling shall be minimal and only where desirable. No direct discharge from one vessel or system to another shall be allowed to maintain the process in a close environment. Where containment is not possible, contaminants should be collected at the source.
- Process lines and instrumentation are initially designed with the use of process flow diagrams (PFDs) and piping and instrument diagrams (P&IDs); these drawing are important in cross-contamination prevention. Piping should be designed to prevent mixing of gases, water, and other foreign substances. Check valves, backflow preventers, and other devices may be designed into processes to avoid mixing or backflow of fluids and gases.

3. Facility Design

Architectural finishes and room layout are important considerations. Personnel and product movements through the facility are key aspects in the minimization of cross-contamination. The directions of air flows, and air flow rates, are critical and should be considered during facility design.

4. Equipment Design

4.1 General considerations

Process equipment selection, design, and surface that contain product contact surfaces or potentially contaminating surfaces should be specified such that cross-contamination is minimized and clean ability is maximized. Design review should be conducted before the actual fabrication begins.

- Where possible, equipment should be dedicated to specific products.
- Equipment should be designed such that areas which would collect or retain drug residues are minimized. All surfaces should be smooth and free of pitting.
- The surface should not be reactive, additive, or absorptive as noted in 21CFR211.65, current good manufacturing practices: equipment construction
- Where possible, incorporate cleaning apparatus into the equipment. This can be accomplished either with spray nozzles, spray wands, or spray ball diffusers. Drains should be carefully placed in the equipment so that rinse waters and solvents are allowed to fully drain.

- Sanitary fittings and valves should be used for product contact applications.

4.2 Clean in place (CIP)

Clean in place (CIP) is a system which involves circulating or once-through water rinses and chemical or sanitizing solutions which are discharged through plant and equipment while kept in an assembled state. The rinses and solutions are used such that all contaminated or soiled product contact surfaces are cleaned to an acceptably high and consistently reproducible state.

CIP systems are commonly used to eliminate environmental and personnel exposure to the contaminant. They are effective when the shut-down and disassembly of equipment in production would impact manufacturing efficiency. They are also used to improve the consistency and reproducibility of the cleaning process.

Computer control of CIP systems is common and programmed recipes can help control the consistency and quality of the cleaning procedure. Validated computer systems used for CIP should be considered.

4.3 Clean out of place (COP)

COP is used to describe the removal, disassembly, and opening of process equipment and systems for cleaning in other than its normal operating conditions. Care should be taken to minimize environmental exposure leading to cross-contamination and personnel interference.

4.4 Equipment Seals

Equipment seals on rotating shafts such as agitators, pumps, and compressors should avoid contact with products. Otherwise, seal lubricants should be food grade where permitted by the manufacturer.

4.5 Computer controls

The microprocessor-based systems should be programmed, challenged, and validated to eliminate the exposure of one product to another through control failure. Valves and actuation devices used to divert product flows should be programmed properly and validated for their adequate functionality.

5. Dust Collection Equipment

Adequate dust collection systems' "point of use" are recommended in areas where materials are handled. Where recovery of product is required from the dust collector systems, it is desirable that the system be dedicated to a single process or product line.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.50 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Design Qualification Guideline for HVAC System of a Pharmaceutical Plant**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.50 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Design Qualification Guideline for HVAC System of a Pharmaceutical Plant

PURPOSE

To provide the qualification design guide line for the HVAC design of pharmaceutical manufacturing plant

RESPONSIBILITY

It is the responsibility of all key supervisors, validation officers, engineers, and managers to build guidelines into the plant architectural structure at the design phase, while ordering materials and making purchase requisitions, and in the standard operating procedures to ensure prevention of cross-contamination. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Heating Ventilation and Air Conditioning

The HVAC assigned to the project should use the following guidelines to control the quality of the design from a cGMP perspective. The checklist that follows should be completed and used to control the quality of working drawings, revisions, and related documents.

2. Guideline For HVAC Design

As a predecessor to detailed design, the HVAC should meet with your company's basic project management. Parameters should be designed for the facility on an area-by-area basis. Meeting results should be documented and form the basis for design criteria. The approval of these criteria must be obtained prior to proceeding with design.

The purpose of the design criteria is to establish a basis for facility HVAC design and to provide your company with a document for FDA facility review.

The design criteria should address both outside and inside design criteria. Outside design criteria should be obtained from ASHRAE (American Society for Heating, Refrigeration, and Air Conditioning Engineers) data. Inside design criteria

should include, but not be limited to, temperature, relative humidity, filtration level, minimum air change rate pressurization requirements, exhaust requirements, and cleanliness level.

Both temperature and humidity should be listed as design set points/minus tolerances. A listing of temperature and humidity ranges is subject to interpretation and should be avoided. Filtration should address final filter efficiency and location. Air change rates may be required for cooling load, or as required for a given area classification. Pressurization should be noted on the drawing in the form of actual room pressure levels from a common reference point, which should be noted on the design documents, along with any special exhaust requirements. The location of laminar flow hoods, biosafety hoods, and fume exhaust hoods should also be noted on these documents if the room is to be validated as a clean room or containment area.

2.1 Calculations

2.1.1 Airflow leakage rate calculations

In general, the calculation of the airflow leakage rate for a room should be based on the pressure differential established on the design criteria sheet. Assumed leakage rates based on a percentage of supply air are unacceptable. For leakage calculations, each wall should be considered separately regardless of whether the room is interior or exterior. In addition, it should be noted whether leakage is into or out of the room. Leakage calculation should contain a safety factor to compensate for less than ideal construction, deterioration of gasket sealing, and so on.

2.1.2 Cooling load calculations

Cooling load calculations should be done on a room-by-room basis. Careful attention should be given to process equipment loads because these can be significant heat generators. In calculating this load, consideration should be given to motor load, convection, and radiation from heated vessels and thinly insulated process and utility piping. Attention should also be given to potential heat gain from the air handling unit supply fan due to the high air change rates and multistage filtration. The actual operation of process equipment should be understood so that realistic assumptions on heat gain factors and diversity can be made. Process equipment heat loads with basis should be included in design criteria and reviewed and approved by responsible management and quality assurance manager.

2.1.3 Heating calculations

Heating is generally accomplished by a "reheat." Therefore, the heating calculation should include the energy required to raise the supply air temperature from its summertime design point to room temperature plus sufficient energy to offset winter heat loss.

2.1.4 Fan static pressure calculation

Fan static pressure should always be calculated, rather than relying on rules of thumb.

2.2 Airflow diagrams

Airflow diagrams should show the air handling unit components arranged in their proper sequence, flow measuring stations, reheat coils, location of each level of filtration, humidifiers, exhaust, and any other system components. Airflow diagrams should show supply, return, exhaust, infiltrations, and exfiltration airflows from each room. Obtaining engineering and quality assurance approval of airflow diagrams is required prior to starting ductwork layout.

2.3 HVAC P&IDs

P&IDs should be developed for each individual air handling system. The HVAC discipline should generate P&IDs for chilled water and hot water. Each of these systems should be independent from similar process-related systems and should be the responsibility of HVAC engineers, not process engineers. The HVAC department may also be required to produce P&IDs for other general utilities.

2.4 HVAC ductwork and equipment arrangement drawings

Detailed HVAC drawings are an absolute necessity for a facility with the complexity common to pharmaceutical facilities. Single line drawings are unacceptable. All ductwork should be drawn as double-lined, fully dimensioned duct (including centerline elevation for round ducts and bottom of duct elevation for rectangular ducts). The location should be shown from the column lines. All ductwork should be coordinated with piping and electrical disciplines. Density may require multiple levels of duct drawings. Sections are required at any points where the plans do not completely and clearly define the design. A meeting must be convened to preplan special requirements for duct, pipe, and electrical prior to commending any design. Ductwork plans must clearly indicate duct material, insulation type, and pressure classification using duct construction tags.

When sizing return air ducts, keep in mind that calculated room leakage rates are empirical and will vary depending on construction tolerances; the acutal return air (R.A.) quantities may vary from theoretical design. Return ducts should be sized to handle at least 25% more than design airflow. Return air plenum designs should be avoided unless there is no potential for contamination problems.

2.5 General specifications of ducts

- Construction material *or* re ducts capital.
- The air duct must be constructed with galvanized steel.
- Other materials are authorized if specific uses (i.e., chemical resistance) are required.
- The perimeter of the duct must be constructed with the same material.
- The inside surface of the ducts must be smooth, except if specific equipments are required (noise attenuator, damper, etc.).
- The minimum thicknesses required are:

Circular section:

8/10mm	for diameter ð 200 mm
10/10mm	for diameter ð 600 mm
12/10mm	for diameter Š 600 mm

Rectangular section:

8/10mm	for the greatest side ð 400 mm
10/10mm	for the greatest side ð 600 mm
12/10mm	for the greatest side ð 850 mm
15/10mm	for the greatest side Š 850 mm

2.6 Design of ducts

- The use of ducts with circular section is preferred.
- The duct system must be airtight.
- The rectangular sections must be reinforced with folds or reinforcement to resist deformations and vibrations.
- The duct system, including elbows, change of section and other equipment, must be selected and designed to minimize the static pressure losses and the level of noise.
- The assembly of the rectangular ducts must be executed with riveted sleeves and retractable adhesive strips.
- The duct system must be designed to allow the cleaning of the ducts (access door, etc.).
- line before the opening). Obturable openings (∅ 25 mm) must be located in the ducts to allow the measurement of the air velocity (minimum 2 m of duct in straight
- All the external openings must be protected against small animals with a wire mesh (maximum opening: 10 mm).
- The connecting of the movable parts (filters) can be executed with semi-flexible metallic ducts. Their lengths must be as short as possible.
- The sections of the ducts must be designed to obtain the following air velocities:

ð 5 m/s	in the blow ducts
Š 4 m/s and ð 7 m/s	in the return or exhaust ducts
Š 13 m/s	in the return or exhaust ducts of powder production rooms

2.7 Supports

The anchors and the hangings must be selected and positioned to allow the possible dismantling of the ducts (type "clamping").

The number of the anchors must be selected to keep the bending of the ducts under L 300.

All the hangings must be cut to avoid the cutting parts.

The anchors, hangings, and other metallic parts must be protected against rust (galvanized or rust-preventing paint).

2.8 Piping for air conditioning

The piping installation for air conditioning must be executed with usual steel welded or wiredrawed.

They must be designed with a water velocity between 1.5 and 2 m/s.

This piping must be insulated following the characteristics of the air inside:

T° > 18°C should be insulated with armaflex thickness = 25 mm.

The insulation must be glued on the pipes and the joints between two strips of insulation must be airtight (gluing of an insulation strip on the joints) to prevent condensation on the pipes.

Pipes with T° > 18°C should be insulated with rockwool or glasswool (thickness = 25 mm) recovered by a metallized vapor barrier.

2.9 Supports for piping

The supports of the piping must be galvanized steel. The contact between the pipes and the anchor must be insulated to prevent heat transfer (condensation on cold piping). Do not rigidly anchor tubing.

The distance between two supports must be at maximum 1 m for horizontal tubing (∅ 1/2"); 1.5 m for horizontal tubing (∅ 3/4 to 4/4"); 2 m for vertical tubing (→ 4/4"). Place a support at every change of direction.

2.10 Control diagrams

Control diagrams should be drawn in P&ID format and should show all coil piping, including all valves, line numbers, and so on. A separate P&ID should be developed for each air-handling unit and should show all devices individually. Control diagrams should supplemented with sequences of operation either on the drawing or as part of the specifications. Control diagrams should include a control valve schedule that supplies the size and specifications for each valve.

3. Air Handling Units (AHUs)

3.1 General specifications

The air handling unit shall be made up of modular sections to suit each particular application. The sections shall be made with double skin isolated panels assembled on a galvanized steel base frame. The panels shall be constructed designed with two galvanized steel sheets (minimum thickness: 0.8 mm) and insulation (minimum thickness: 50 mm). The insulation must be non-flammable and conform to fire class A1 (according to DIN 4102). The panels must be reinforced (fold in the sheet or integrated reinforcement) to resist deformations and vibrations.

The assembly of the panels and the modular sections must be executed to obtain a perfectly smooth inside surface and a perfectly airtight volume. The panels must be fastened by stainless steel screws and must be removable. The sections shall be fitted with an access door for easy cleaning and maintenance of the equipment (fan, filters, heat exchanger, etc.) The access door must be locked with a mechanism able to press the door on an airtight seal; this must be continuous to guarantee the air-tightness. The air handling unit must be designed without thermal bridges. The connecting of the ducts to the air handling unit must be done by flexible sleeves made with flame resistant materials (DIN 4102-A2).

3.2 Heat exchanger sections

- The heater must be designed with copper tubes, aluminium fins, and steel connections with male thread.
- The cooler must be designed with stainless tubes fines and frame. They must be installed in modular sections (description above) and must be laterally removable on guide rails (drawer). The equipment and the connections of the heat exchanger must be designed to allow the heat exchanger to be removed easily.
- The cleaning of the heat exchanger must be done easily (provide, if necessary, an empty section with access door).
- The cooling exchanger must be provided with a polipropylene droplets separator and a stainless steel tray to connect across a trap to the drain.

- The height of this trap and the diameter of the drain shall be calculated following the characteristics of the unit pressure and amount of water to eliminate.
- The heat exchanger must be calculated with an over capacity of 15%.
- The air velocity in the heat exchangers must be less than 3 m/sec.

3.3 Insulation

Air handling units should not contain internal insulation exposed to the air-stream. Double wall construction sandwiching insulation between two metal panels of single wall construction with external insulation is a requirement.

3.4 Filters

Air handling units should be provided with prefilters, 2 in. thick at minimum, Farr 30/30s or equal, and 80 to 85% efficient filter. If HEPA filters are located within the air handling unit, they should be the last component in the direction of the airflow into the room.

The air filters must be made and used in accordance with ASHRAE 52-76 and EUROVENT 4/5 standards.

To assure filtration in the pharmaceutical industry, several types of filters must be used:

Sand trap:	to be placed on the fresh air inlet
Prefilter:	to be placed on the inlet of mixed air (fresh air and recycled air)
Filters:	to be placed directly after the fan section before the outlet of the air handling unit
Terminal filters:	to be placed directly after the fan section before the outlet of the air handling unit
Terminal filters:	to be placed in the room

The filters must be designed and fastened to allow an easy removal to change the filter and to keep a perfect peripheral airtightness. They must be provided with differential manometer to check them. (option: equipped with maximum contact

point). An obturable opening (+/– 100 mm) must be placed before the fan section to inject the DOP. The number of terminal filters must be calculated to guarantee the same air velocity out of the different filter of the same air handling unit. For each filter, a manometer should be connected upstream and downstream of the filter housing and pressure drop measured. When the pressure drop across the filter exceeds the recommended change point, the filter must be replaced.

Filter efficiency is defined by ASHRAE 52/76 or EUROVENT 4/5.

3.5 Fans

Air handling unit fans should contain a provision for modulating airflow to compensate for increased static pressure losses as the loading of filters increases. This is usually accomplished through the use of inlet vanes; other methods would be discharge dampers and variable speed drives.

Fan motors should be sized at 25% above the brake horsepower. Fans should be belt driven with variable pitch drives up to and including 25 HP and fixed pitch drives at about 25 HP. Fans must be radial and they must be balanced (static and dynamic) and mounted on anti-vibration supports. The connection of the fan outlet to the inside panels must be done by means of an internal flexible connector.

The transmission motor or fan is operated by drive belts and pulleys. The support frame of the motor must be designed to obtain the tension of the belts without modification of the alignment of the pulley and to adjust this alignment. The motor class must be calculated with an over capacity of 30% of the used power and must be connected through a safety switch placed on the air handling unit.

3.6 Dampers

Dampers must be designed with profiled damper blades operating in opposite directions, with an additional seal mounted on external, reinforced, polyamide, cogged wheels with slide bearings.

3.6.1 Coils

Air handling unit coils should have no more than eight fins per inch and be no more than six rows in depth to facilitate coil cleaning. Where more than four rows are required to obtain the cooling capacity, two coils should be placed in series. Spacing between the coils should be piped so that counterflow of air and water is achieved. Fins should be of the continuous, flat (noncorrugated) type.

Note: On large air handling unit systems, consideration should be given to bypassing the cooling coil with part of the return air to minimize the amount of reheat required. With coil bypass, pretreating the outside air for dehumidification may be required.

3.6.2 Notes

The HVAC specifications should state that before the activation of any air handling unit, all construction debris should be cleared away and the unit thoroughly vacuumed. Units should be vacuumed again before the installation of cartridge or bag filters. Prefilters should be installed before initial unit start-up. Cartridge or bag filters should be stored in a clean, dry place and should be installed after room finishes are complete. If HEPA filters are contained within the air handler, these should also be installed at this time. Comprehensive cleaning guidelines for duct and equipment must be provided as part of the construction specifications.

3.6.3 Sealing

All ductwork should be sealed in accordance with SMACNA Class A rating, which requires all seams, joints, fasteners, penetrations, and connections to be sealed. Sealant should be FDA acceptable for the application, and non-hydrocarbon based. Leakage rates as low as 1% total airflow are not uncommon. All ducts passing through a clean room wall or floor should be provided with stainless steel sheet metal collars and sealed at the opening. Details of sealing methods should be provided on the design documents.

3.6.4 Leak testing

Before ductwork is insulated, the installing contractor should leak test each duct system at 125% of the operating pressure. Leak testing should be witnessed and signed off to signify approval. Acceptable leakage rates and leak testing procedures and reports should be based upon the SMACNA HVAC Duct Leakage Test Manual.

3.6.5 Insulation for HVAC ductwork

All insulation should be in accordance with the "flame-spread" and "smoke-develop" ratings of NFPA Standard 255. Ductwork should be externally insulated.

The use of internal duct liner is not acceptable. Some criteria will not allow the use of fiber glass insulation even on the exterior of the ductwork. Whenever ductwork is exposed in clean spaces, it should be insulated with a rigid board-type insulation and jacketed with either a washable metallic or PVC coated jacket. Jacketed ductwork should be of sufficient density to minimize the dimpling effect when the jacket is applied. Flexible blanket insulation is acceptable in concealed spaces. No insulation should be applied on the ductwork until the leak test has been performed, witnessed, and approved. Rigid duct insulation should also be used in mechanical rooms.

3.6.6 Insulation of the ducts

The ducts must be insulated following the characteristics of the air inside: T° ð 18°C should be insulated with armaflex thickness = 25 mm. The insulation must be glued on the ducts. The joints between two strips of insulation must be airtight (gluing of an insulation strip on the joints) to prevent condensation on the pipe. Return ducts, blow ducts (T > 18°C) should be insulated with rockwool or glasswool (thickness = 25 mm recovered by a metallized vapor barrier).

3.6.7 Marking of the ducts

The ducts and other equipment must be marked after insulation by:

- Arrows to give the direction of the air flows
- A red strip on the blow ducts
- A blue strip on the return or exhaust ducts
- A green strip on the fresh air
- The number of the equipment (AHU, damper, sensors, etc.) corresponding to the P&I

3.6.8 Damper

The regulation dampers — air flow (blow, return, or exhaust) by room or by intake or return opening — must be manual with mechanical locking (minimal looseness allowed) located in the ducts. The general dampers, or those for most important

sections, must be similar to the dampers for air handling unit; a suitable model should be selected.

3.6.9 Sound attenuators

Sound attenuators should not be used in systems requiring sanitizing because the perforated face (interior) of the sound traps can collect dust and microorganisms.

3.6.10 Humidifier

Humidifiers serving clean areas and process areas should use only clean steam for humidification. Carbon steel piping and headers are not acceptable; 316L grade stainless steel should be used. All humidifier components (main body, valves, piping, manifold, etc.) should be made of 316L stainless steel.

3.6.11 Air distribution

Standard type (turbulent flow) diffusers should be used in class 100,000 areas. Terminal HEPA filters should be used in the ceilings of the areas that are class 10,000 or cleaner.

3.6.12 Return or exhaust air

Ceiling return or exhaust is acceptable in class 100,000 areas. Low wall returns should be used in class 10,000 or cleaner areas. All returns or exhausts must be louvered, removable types.

3.6.13 Intake and return openings

The number and the location of the openings must be selected to have a good distribution of the changing of air (cleanless class, t° uniformity).

They must be designed following the requested air flows, velocities (at the opening and in contact with people), and level of noise.

The openings must be constructed with stove enamelled steel or stainless steel.

They must be mounted flush with the ceiling or the walls (or partitions) and sealed with paintable silicone.

Models should be selected as appropriate.

3.6.14 Intake or return openings with filters

In the classified rooms 10,000, 100, 100 with LAF (following F.S. 209E), the intake openings must be fitted with absolute filters. The number and size must be selected to obtain the same air velocity (± 10%) for all the terminal filters of the same air handling unit. The absolute filters' housing shall be airtight, mounted flush with the partitions, walls, or ceilings (maximum 2 mm of difference). The sealing gasket between the housing and the filter should be provided to prevent bypass of unfiltered filter. A manometer should be connected upstream and downstream of the filter housing and pressure drop measured. When the pressure drop across the filter exceeds the recommended change point, the filter must be replaced.

The recommended air velocity of a HEPA filter is 0.45 m/s. The HEPA filter and its housing must be tested mounted on site with the DOP. For return openings for powder production, the housing with HEPA filter must be fitted with a prefilter removable from the front. The recommendation is to use HEPA filter presealed in the housing located in a stainless steel frame.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.60 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Design Qualification for the Prevention of Contamination of Non-Sterile Pharmaceutical Products**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.60 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Design Qualification for the Prevention of Contamination of Non-Sterile Pharmaceutical Products

PURPOSE

To ensure that air supplied to manufacturing areas where product is exposed is not a source of significant contamination

RESPONSIBILITY

It is the responsibility of production manager, packaging manager, and technical service manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

This procedure applies to air supplied to all non-sterile secondary manufacturing and final stage primary manufacturing areas.

1. Policy

1.1 Air quality standards

The quality of air at or near the points of supply to manufacturing areas where product is exposed must comply with the following:

- Particles equal to or greater than 5 μm: 24,700 per m^3
- Number of viable microorganisms permitted: 500 per m^3

The quality of air at or near the points of supply of large volume forced air supplied coming into direct contact with products (e.g., fluid bed dryers, tablet coating machines, etc.) must comply with the following standards:

- Particles equal to or greater than 0.5 μm: 3,530 per m^3
- Number of particles equal to or greater than 5 μm: 5 per m^3
- Number of viable microorganisms: 5 per m^3

1.2 Design of air systems

Air supply systems must be designed to avoid the introduction of contaminants into air flows or into manufacturing areas' local environmental conditions and associated risk factors. Air supply systems must be validated, operated, monitored, and controlled to deliver the required air quality.

1.3 Documentation and records

Documents must be compiled and kept up-to-date for each air supply system and must contain:

- Schematic as-built drawings
- Validation data
- Routine operating specifications
- Cleaning schedules
- Standard operating procedures
- A history of installation, changes, and modifications

The following records must be maintained:

- Monitoring, performance, and test data
- Engineering maintenance and calibration data
- Operating control data

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.70 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Design Qualification Guideline for Cross-Contamination and Decontamination**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.70 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Design Qualification Guideline for Cross-Contamination and Decontamination

PURPOSE

To provide the guideline to be followed for the prevention of cross-contamination and decontamination

RESPONSIBILITY

It is the responsibility of all key supervisors, validation officers, engineers, and managers to build the guidelines into the plant architectural structure at the design phase while placing orders, making purchase requisitions, and in the standard operating procedures to ensure prevention of cross-contamination. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Sources of Cross-Contamination

The following potential sources should be considered to assess the risk of cross-contamination.

1.1 Purchased product (semifinished) and raw material

Precontaminated due to poor control by the manufacturer

1.2 Retention of product

- In poorly designed equipment
- Poor cleaning practices

1.3 Product dispersion

- Around processing areas via working garments, due to inadequate changing or laundering procedures
- Via HVAC systems, fluid bed driers, film-coaters, vacuum systems, and product containers

- Poorly designed facilities or processes, or poor handling practices (e.g., during sampling or dispensing)

1.4 Product spillage

- Poorly designed processes, or due to poor handling during processing
- Poor handling during the cleaning of air conditioning plant air filter, dust extraction plant, or vacuum plant

2. Control of Cross-Contamination

The following are among the measures which may be necessary to control cross-contamination:

2.1 Containment

Closed manufacturing systems
Closed transfer systems
Clean-in-place systems
Containment boxes or isolators

2.2 Collection

Localized dust extraction
Containment booths

2.3 Other

Correct operating procedures
Good engineering practices in the design of equipment and facilities
Segregated plant
Safe-change filters
Product dedicated equipment
Disposable containers
Validated changing procedures
Validated laundering procedures

3. Monitoring Methods

3.1 Analytical methodology

All analytical methods should be validated and should have a detection limit at or below that necessary to show compliance with the product limit. Before each test, the recovery of the sampling method should be determined. Appropriate corrections should be made in the final calculation.

3.2 Start-Up validation

Equipment — On introduction of each new piece of equipment or process, the cleaning method should be validated, using one or an appropriate combination of the following methods:

- Taking samples of rinse solvents from manufacturing equipment and measuring active residues
- Manufacturing a placebo batch after the manufacture of the active batch and measuring residues of the active in the placebo
- Taking several representative or "worst-case" swab samples from equipment and measuring active recovered from the swab

Facilities — Immediately after the start-up of a new or modified facility, potential for cross-contamination should be determined. Samples may be taken from the environment by air sampling, or from surfaces by swabbing.

3.3 Routine production

Visual checks for cleanliness before each use of a piece of manufacturing equipment should be made in addition to chemical testing. Air monitoring should be implemented to ensure that any contamination released during manufacturing operations is not being spread. Both product-contact and non-product-contact surfaces should be monitored to determine the level of contamination settling out from the environment. A product or placebo batch may also be tested to show the absence of residues from previous batches.

3.4 Validation review

A formal validation review should be carried out periodically to determine the necessity for revalidation.

3.5 Cross-Contamination limit

Limits for the monitoring program should be derived from product limits, which should be defined based on reasoned assessment of the risks and historical data.

4. Air handling systems

See SOP No. Val. 200.30, Guideline for Minimizing the Risk of Product Cross-Contamination Air Handling Systems.

5. Gowning

The gowning and laundry for each building shall be separate.

6. Cleaning

6.1 Introduction

The challenge to the cleaning procedure should be minimized by the use of dedicated equipment and facilities where possible (e.g., fluid bed drier filter bags). Segregation and transportation of used equipment should be considered. Areas of high risk should be recognized in cleaning procedures (e.g., dispensaries, sampling utensils, containers, pallets).

6.2 Procedures

Standard operating procedure should define cleaning of process equipment and facilities. Operators should be trained in cleaning SOPs.

6.3 Cleaning agents

Cleaning agents should be approved before use. Water used for cleaning and rinsing should comply with the requirements specified in the relevant SOP.

6.4 Validation

Removal of cleaning agents at the end of the cleaning procedure should be validated. Validated cleaning procedures should be used.

6.5 Records

All cleaning should be recorded.

7. Facility, Equipment, and Process Design

See SOP No. Val. 200.40, Design Qualification Guideline for Minimizing the Risk of Cross-Contamination of Facility, Equipment and Process.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.80 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Design Specifications for Process Water**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.80 **Effective date: mm/dd/yyyy**
Approved by:

SUBJECT: Design Specifications for Process Water

PURPOSE

To provide guidelines for the selection of material to be used for the construction of equipment and supporting accessories to manufacture the process water

RESPONSIBILITY

It is the responsibility of the technical services manager and contractors to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

The following design specifications are establishing based on guidelines provided in USP 24. They can be further fine-tuned according to the individual company's requirement. For general guidelines refer to section D.

1. Construction Material

1.1 Stainless steel

All parts in contact with the process water, except gaskets and membrane of valves, must be AISI 316L stainless steel (distillator, tubing, heat exchangers, sensors, valves, fittings, tank, pump, and all instrumentation).

Finishing inside (contact with the process water): Ra < 0.8μm and electropolished; outside: 150 Grit Finish.

1.2 Tubing

Tubing should not be welded longitudinally.

Tubing should be supplied with a material certification sheet for material construction and rugosity and be precleaned and capped. Handle material in such a way as to prevent introduction of contaminants into the piping system.

- Tolerances: minimum tolerances to assure proper alignment for automatic welding — ASTM A270
  Outside Diameter:0.5, 0.75, 1 in. + 0.002 over to 0.008 under in.

1.5 in. + 0,002 over t0 0.008 under in.
2.3 in. + 0.002 over to 0.011 under in.

- Wall thickness:+ 0.0065 in.
- Ovality:+ 0.010 in.
- Plane angularity:+ 0.005 degrees
- Angle angularity:+ 0.005 degrees (fittings)
- Squareness: face to tangent: + 0.005 in.

1.3 Valves

All the valves in contact with the product must be diaphragm valves:

- Weir type 316L stainless steel body
- Interior finish as specified for tubing
- Self draining
- Weld connection with tubing or clamps
- Diaphragm: Teflon (214S) + EPDM (325) (resistant to sterilization temperature)
- Tolerances: inside dimensions as specified for tubing

1.4 Fittings

Material, wall thickness, and finishing should be as specified for tubing

1.5 Connections

The largest possible number of connections should be automatic TIG orbital welding without external filler wire (butt-welded). Manual welding or tri-clamp connections are authorized case–by–case, but have to be minimized and reserved; manual welding is needed for inaccessible orbital welding, tri-clamp for sensors connections, and moving equipment (pump, hose pipe, etc.).

1.6 Tri-Clamps

- **Ferrules** — Material, tolerances, wall thickness, and finishing as specified for tubings in welding type with one end for clamp connection

- **Gasket** — Teflon envelope with EPDM insert, steam resistant, inside diameters as specified for tubing
- **Clamps** — Type 304 stainless steel, three segments heavy-duty type with metal wing nut

1.7 Sampling valve

Type: Millipore, TC sampling valve

1.8 Distribution pumps

- Centrifugal type, sample stage nonoverloading, long coupled end-suction
  - Pump casing, back plate impeller pin, one type, back shrouded impeller and shaft shall be 316 stainless steel, 240 grit finish, electro-polished
  - Suction and discharge connections — sanitary clamp type
- Provide seal flush kit including valves, tubing and gauges as required for WFI Service
  - Working pressure: minimum 12 bar
  - Fully drainable
  - Steam sterilizable

1.9 Heat exchanger

- Welded double concentric tube or double tube sheet with tri-clamp sanitary fittings (tube side)
- Surface in contact with WFI: 316 L electro-polished (Ra ð 8 μ)
- Fully drainable
- All necessary fittings to remove the cooling water from the exchanger to enable efficient steam sterilization

1.10 Storage tank

The inside surface should be 316-L electro-polished (Ra ð 0.8 μ); the tank must be totally drainable. Storage tanks must be equipped with a spray ball on the circulation return line to sanitize all internal parts of the tank and to assure that the tank interior surfaces above the water level are continuously flushed. Tanks must be equipped with a vent filter (0.2 μm hydrophobic) installed in such a way as to prevent condensate from being trapped. The technical services manager and QA manager must approve the model.

Tanks with vent filters must be designed for pressures of –20 kPa and +100 kPa and must be equipped with a rupture disk. Tanks for hot loop and steam sterilizable line must be designed to withstand steam sterilization (121°C). A steam jacketed sterile vent filter must be used to avoid condensation in the filter and the vent filter housing temperature controlled. The tank for hot storage is steam jacketed and insulated for temperature maintenance. Minimum instrumentation shall include level indication, temperature recording controller, pressure gauge, and pressure relief valve.

1.11 Sensors

All required sensors (temperature, pressure, conductivity, flow meter, etc.) in contact with the process waters must be the sanitary type, connected by tri-clamp, and well mounted (temperature). The length of the electrical connections must be long enough to allow the calibration of the sensors.

1.12 Insulation

The insulation must be chloride free, minimum of 25 mm thickness, and protected by a jacket. The jacket must be stainless steel for the technical rooms and fully closed in the classified rooms (PVC pre-molted type, PVC sealed).

2. Calculation Criteria

The installation (pump, loop, tubing) should be designed to meet the following parameters:

- No dead leg Š 6 of the internal diameter of the unused pipe (measured from the axis of the pipe in use)
- For tubing larger than 3 cm, no dead leg Š 3 internal diameter of the unused pipe
- Water flow velocity Š 1.5 m/sec without any sampling or during sampling (long times)
- Water flow velocity Š 0.9 m/sec during sampling (short time)

3. Execution

Tubing must be provided precleaned and capped. The prefabricated parts must be stocked cleaned and capped to prevent introduction of contaminants into the piping system. The bending of tubes is not allowed.

3.1 Drainage

The supports in contact with the tubing must be stainless steel 302:

- 1 m for horizontal tubing (∅ 0.5 in.)
- 1.5 m for horizontal tubing (∅ 0.75 to 1 in.)
- 2 m for vertical tubing (→ 1 in.)
- 3 m for tubing (> 1 in.)

Do not rigidly anchor tubing. Place a support at every change of direction.

3.2 Welded stainless steel connections

3.2.1 Certification

Welders shall be certified to a qualified welding procedure for the applicable material in accordance with ASME Section IX. Welders shall be certified in the use of the specific equipment and material used in the welding process.

3.2.2 Procedure

To perform automatic TIG orbital welding, the use of a machine with a printout of the welding parameters is preferable. Develop a set of acceptable parameters for the tubing that will be welded, subject to approval. The welding machine supplier shall provide a written procedure for the calibration of the welding controller. Equipment shall be set up by a designated welding supervisor or inspector who shall check the settings, comply with the master program, and sign and date the welding log to that effect. Check inert gas bottles at each setting change and at suitable intervals throughout the day.

Use bench welding whenever possible (automatic). Field welding (manual) shall be kept to a minimum. Hand welding will be permitted only with approval on a case–by–case level. Do not use ferrous material, tools, or equipment (carbon steel cutting tools) in the fabrication or installation of systems.

3.2.3 Purging

Purge oxygen from the weld area before commencing welding, using an inert gas back-up. Back-up gas shall utilize full line purge. Use 99.996% minimum purity argon gas for the back-up purge and for the torch gas. Provide certificates.

3.2.4 Alignment and tacking

Accomplish tack welding in a manner that will not cause any deleterious effect on completed welds. Make tacks as light as possible to reduce excessive heat that may cause structural changes to the granular composition of the system components. Do not allow tacks to penetrate the inner surface of components. Use back-up purge gas for tack welding. Provide four tacks per weld maximum. Cracks or improper tack welds will be rejected. When welding, center the electrodes over the butt weld joint by the use of setting gauge.

3.2.5 Inspection

Examine each external weld visually to ensure there are no surface defects, and record. Examine each interior weld and adjacent areas, both visually and by the use of a boroscope. Welds not accessible with the boroscope must be examined by γ-ray with photo. 3 shot by weld two perpendicular to the tube axis (moved at 90°) and one oblique compared to the tube axis.

SOP No. Val. 200.80 **Effective date: mm/dd/yyyy**
Approved by:

Document and log each weld as follows:

- Provide the "as built" isometric view with the number, location, and type of welds (manual, automatic)
- Engrave each weld with a number
- Location and number of weld
- Name of welder
- Name of inspector
- Name of boroscope user
- Videotape of 10% of automatic welds and 100% of manual welds; One "test" weld per day in automatic mode
- Date

3.2.6 Weld defects

Welds will be rejected and removed (including the heat affected zone) under the following conditions:

- Internal concavity of the weld: none allowed
- Internal convexity of the weld: ð 25% of the wall thickness
- Full penetration of the entire interior weld joint periphery: required
- Lack-of-fusion:none allowed
- Crevices:none allowed
- Slag-or-inclusions:none allowed
- Cracks:none allowed
- Burn through:none allowed
- Sugaring:none allowed
- M.S. alignment (high/low): maximum allowable is 0.02 in.

Rewelding of defective welds is not permitted.

3.3 Pressure tests

The pressure tests must be done before each cleaning and passivation. A first test must be executed during 1 hour with an inert gas. The second test must be hydraulic with DI water, during 6 hours, without loss of the initial pressure. The test pressure must be 1.5 times the used pressure.

3.4 Cleaning and passivation

- **Cleaning 1** — Cleaning medium shall be compatible with electro-polished tubing and finish. Cleaning is mandatory. Operate according to a written preapproved procedure. Record and log cleaning dates and steps.
- **Passivation** — Passivation is mandatory. Use a 15 to 20% weight/weight nitric acid solution in water. Circulate at least 1 hour. Operate according to a written preapproved procedure. Do not use fluorhydric acid for passivation. Record and log passivation dates and steps. Drain the system completely.
- **Rinsing** — Fill the system with DI water. Circulate for 15 min, then flush each use point outlet and equipment connection until the pH of discharge water is balanced with the inlet pH. Record and log cleaning dates and steps.

3.5 Identification

The whole equipment (pump, tank, sensor, valves, heat exchangers, etc.) must be tagged with an engraved stainless steel tag. The tag number must follow the number of the P&I.

4. Installation and Material of Construction and Component Selection

4.1 General

Adequate consideration should be given to installation techniques; they can adversely affect the mechanical, corrosive, and sanitary integrity of the system. Following are the considerations which shall be built in the system:

- Valve installation attitude should promote gravity drainage.
- Pipe supports should provide appropriate slopes for drainage and should be designed to support the piping adequately under worst-case thermal conditions.
- Methods of connecting system components, including units of operation, tanks, and distribution piping, should preclude problems.
- Stainless steel welds should provide reliable joints that are internally smooth and corrosion free. Low carbon stainless steel, compatible wire filler where necessary, inert gas, automatic welding machines, and regular inspection and documentation help to ensure acceptable weld quality.

- Final cleaning and passivation shall be performed for removing contamination and corrosion products and to reestablish the passive corrosion resistant surface.
- Plastic materials can be fused (welded) in some cases and also require smooth, uniform internal surfaces. Adhesives should be avoided due to the potential for voids and chemical reaction.
- Mechanical methods of joining, such as flange fittings, shall be performed carefully to avoid the creation of offsets, gaps, penetrations, and voids.
- Control measures shall include good alignment, properly sized gaskets, appropriate spacing, uniform sealing force, and avoidance of threaded fittings.

4.2 Materials of construction

- Materials of construction selected should be compatible with control measures such as sanitizing, cleaning, and passivation.
- Materials selected should be able to handle elevated operating, sanitization temperature, and chemicals or additives to be used to clean, control, or sanitize the system.
- Materials should be capable of handling turbulent flow and elevated velocities without wear on the corrosive barrier impact such as the passivation-related chromium oxide surface of stainless steel.
- The finish on metallic materials such as stainless steel, whether it is a refined mill finish, polished to specific grit, or an electro-polished treatment, should complement system design and provide satisfactory corrosion and microbial activity resistance.
- Auxiliary equipment and fittings that require seals, gaskets, diaphragms, filter media, and membranes should exclude materials that permit the possibility of extractable, shedding, and microbial activity.
- Insulating materials exposed to stainless steel surfaces should be free of chlorides to avoid the phenomenon of stress corrosion cracking that can lead to system contamination and the destruction of tanks and critical system components.
- Specifications are important to ensure proper selection of materials and serve as a reference for system qualification and maintenance.
- Information such as mill reports for stainless steel and reports of composition, ratings, and material handling capabilities for nonmetallic substances should be reviewed for suitability and retained for reference.

- Component (auxiliary equipment) selection should be made with the assurance that it does not create a source for contamination intrusion.
- Heat exchangers should be double tube sheet or concentric tube design.
- Heat exchangers should include differential pressure monitoring or utilize a heat transfer medium of equal or better quality to avoid problems if leaks develop.
- Pumps should be of sanitary design with seals that prevent contamination of the water.
- Valves should have smooth internal surfaces with the seat and closing device exposed to the flushing action of water, such as occurs in diaphragm valves.
- Valves with pocket areas or closing devices (e.g., ball, plug, gate, and globe) that move into and out of flow area should be avoided.

4.3 Sanitization

- Microbial control in water systems should be achieved primarily through sanitization practices. Systems should be sanitized using either thermal or chemical means. In-line ultraviolet light at a wavelength of 254 mm can also be used to sanitize water in the system continuously.
- Thermal approaches to system sanitization shall include periodically or continuously circulating hot water and the use of steam.
- These techniques are limited to systems that are compatible with the higher temperatures needed to achieve sanitization, such as stainless steel and some polymer formulations. Although thermal methods control biofilm development, they are not effective in removing established biofilms.

SOP No. Val. 200.80 **Effective date: mm/dd/yyyy**
Approved by:

- Chemical methods, where compatible, shall be used on a wider variety of construction materials. These methods typically employ oxidizing agents such as halogenated compounds, hydrogen peroxide, ozone, or peracetic acid. Halo-

genated compounds are effective sanitizers but are difficult to flush from the system and tend to leave biofilms intact. Compounds such as hydrogen peroxide, ozone, and peracetic acid oxidize bacteria and biofilms by forming reactive peroxides and free radicals (notably hydroxyl radicals). The short half-life of these compounds, particularly ozone, may require that they be added continuously during the sanitization process. Hydrogen peroxide and ozone rapidly degrade to water and oxygen; peracetic acid degrades to acetic acid in the presence of ultraviolet light.

- Ultraviolet light impacts the development of biofilms by reducing the rate of new microbial colonization in the system; however, it is only partially effective against planktonic microorganisms. Alone, ultraviolet light is not an effective tool because it does not eliminate existing biofilm. However, when coupled with conventional thermal or chemical sanitization technologies, it is most effective and can prolong the interval between system sanitizations. The use of ultraviolet light also facilitates the degradation of hydrogen peroxide ozone.
- Sanitization steps should be validated to demonstrate the capability of reducing and holding microbial contamination at acceptable levels.
- Validation of thermal methods should include a heat distribution study to demonstrate that sanitization temperatures are achieved throughout the system.
- Validation of chemical methods should demonstrate adequate chemical concentrations throughout the system. In addition, when the sanitization process is completed, effective removal of chemical residues must be demonstrated.
- The frequency of sanitization derived from the trend analysis of the microbiological data should be used as the alert mechanism for maintenance. The frequency of sanitization should be established such that the system operates in a state of microbiological control and does not exceed alert levels.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.90 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Design Specifications for Water for Injection Production and Distribution**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SUBJECT: Design Specifications for Water for Injection Production and Distribution

PURPOSE

To provide guidelines for the selection of material to be used for the construction of equipment and supporting accessories to manufacture the process water

RESPONSIBILITY

It is the responsibility of the technical services manager and contractors to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

The following guidelines and technical specifications must be followed:

1. Principle

The water for injection is produced by distillation of purified water. The distillator filling the storage tank shall be located at a suitable location per approved layout. Connection shall be provided per plan, e.g., 1 for the CIP of the mfg. tank and 1 for the distribution in building and to allow filling of the tanks.

Some points of use are cold points and work with a cold exchanger followed after the point of use by a heat exchanger. From the two secondary tanks, start two small loops with cooling and heating. The main storage tank is automatically filled by the distillator (level switch) and must be full at the beginning of a production day. The secondary storage tanks are filled during the night and can only be filled during the day in case of low level.

2. Main Characteristics

- Obtained from:purified water
- Quality:following the USP 24
  microbiology: < 10 CFU/100 ml
- Production:distillator 4 effect
  capacity: 500 kg/h
- Temperature:Š 80°C at each point of the loop
- Pressure:Š 2 bars
- Temperature keeping:obtained by heating the jacket of the tank; if necessary, installation of a heat exchanger in the loop.

3. Sterilization

The tanks and the loops must be steam sterilized; each pump must be separately sterilized. During the sterilization, the cooling or heating waters of the exchangers must be drained; the Fo. value must be Š 15 at each point of the loops.

4. Consumption Points

The consumption shall be evaluated for full time during the production day (e.g., washing machine and freeze drier).

5. Monitoring and Control

The following characteristics must be monitored: conductivity, C°T at the return of the loop, and flow at the return of the loop. A sampling valve must be located near each main point of use.

6. Secondary Loops — Cold Point

For the cold points of use, a secondary loop is used. The velocity of the water must follow the recommended values in each loop (primary and secondary). A regulation valve shall be provided to balance the loss of pressure between primary and secondary.

SOP No. Val. 200.90 **Effective date: mm/dd/yyyy**

Approved by:

When requested by the user located at the point of use, the first exchanger on the secondary loop starts to cool the water. This one is automatically heated at minimum 85°C before the return in the primary loop. When the temperature asked for the cold point of use is reached, the sampling value is automatically opened. The users ask to stop the sampling. A safety timer must be installed to prevent the draining of the installation. Safety timing is adjustable (maximum 1 h); temperature of cold point: 30°C ± 5°C.

7. Federal Regulation

USP XXIV specifies the limits and method of testing for chemical and pyrogenic contaminants for various compendial classifications of water, such as purified water and water for injection.

The U.S. Food and Drug Administration has established various good manufacturing practices for pharmaceutical products. Selected excerpts of these that have impact on water quality are reproduced on the following pages.

Note: The underlined words have been added by the author for emphasis.

§210.3 Definitions

a) The following definitions of terms apply to Parts 210 through 229 of this chapter.
b) The terms are as follows:
   (3) "Component" means any ingredient intended for use in the manufacture of drug product, <u>including those that may not appear in such drug product.</u>

* * *

   (5) "Fiber" means any particle with a length of at least three times greater than its width.
   (6) "Non-fiber releasing filter" means any filter, which after any appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered. All filters composed of asbestos or glass fibers are deemed to be fiber-releasing filters.

* * *

(2) "Batch" means a specific quantity of a drug that has uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

* * *

(10) "Lot" means a batch, or a specific identified portions of a batch, having uniform character and quality specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

§211.48 Plumbing

(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could cause continuous contamination to any drug product. Potable water shall meet the standards prescribed in the Public Health Service Drinking Water Standards set forth in Subpart J of 42 CFR Part 72. Water not meeting such standards shall not be permitted in the plumbing system.

§211.72 Filters

(a) Filters used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these drug products unless it is not possible to manufacture such drug products without the use of such a filter.

(b) If use of a fiber-releasing filter is necessary, an additional non-fiber-releasing filter of 0.22 micron maximum mean porosity (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the drug product. Use of an asbestos containing filter, with or without subsequent use of a specific non-fiber-releasing filter, is permissible only upon submission of proof to the appropriate bureau of the Food and Drug Administration that use of a non-fiber-releasing filter will or is likely to, compromise the safety or effectiveness of the drug product.

§212.3 Definitions

* * *

(11) "Static line" means any pipe containing liquid that is not emptied or circulated at least once every 24 hours.

Subpart B — Organization and Personnel
§212.22 Responsibilities of quality control unit

(a) The quality control unit shall have the responsibility and authority to test and accept or reject the design, engineering, and physical facilities of the plant, the equipment, and the manufacturing process and control procedures to be used in the manufacture, processing, packing, and holding of each large volume parenteral drug product. The quality control unit shall reject any such plant, equipment, process, or procedure if it does not comply with the provisions of this part or if, in the opinion of the quality control unit, it is not suitable or adequate to assure that the drug product has the characteristics it purports or is represented to possess.

* * *

(c) The quality control unit shall have the responsibility and authority to test and approve or reject any changes in previously approved plant, equipment, processes, procedures, and container-closures and delivery systems before utilization in the manufacture, processing, packing and holding of a large volume parenteral drug product.

Subpart C — Buildings and Facilities
§212.42 Design and construction features

* * *

(c) There shall not be horizontal fixed pipes or conduits over exposed components, in-process materials, drug products, and drug product contact surfaces, including drug product containers and closures after the final rinse.

(d) In each physically separated area, pipes or conduits for air or liquids shall be identified as to their contents. Such identification shall be by name, color code, or other suitable means.

§212.49 Water and other liquid-handling systems

(a) Filters may not be used at any point in the water for manufacturing or final rinse piping system.

(b) Backflow of liquids shall be prevented at points of interconnection of different systems.
(c) Pipelines for the transmission of water for manufacturing or final rinse and other liquid components shall:
(1) Be constructed of welded stainless steel (nonrusting grade) equipped for sterilization with steam, except that sanitary stainless steel lines with fittings capable of disassembly may be immediately adjacent to the equipment of valves that must be removed from the lines for servicing and replacement.
(2) Be sloped to provide for complete drainage.
(3) Not have an unused portion greater in length than six diameters of the unused pipe measured from the axis of the pipe in use.

§212.67 Equipment cleaning and maintenance

The following requirements shall be included in written procedures and cleaning schedules:

(a) All equipment and surfaces that contact components, in-process materials, drug products or drug product contact surfaces such as containers and closures shall be cleaned and rinsed with water meeting the quality requirements stated in §212.224.
(b) Immediately prior to such contact, equipment and surfaces specified in paragraph (a) of this section shall be given a final rinse with water meeting the quality requirements stated in §212.225.
(c) Steam used to sterilize liquid-handling systems or equipment shall be free of additives used for boiler control.

§212.68 Equipment calibration

(a) Procedures shall be written and followed designating schedules and assigning responsibility for testing or monitoring the performances or accuracy of automatic or continuously operating equipment, devices, apparatus, or mechanisms, such as, but not limited to, the following:

(1) Alarms and controls on sterilizing equipment
(2) Temperature-recording devices on sterilizers.
(3) Pressure gauges
(4) Mechanisms for maintaining sterilizing medium uniformity
(5) Chain speed recorder
(6) Heat exchanger pressure differential monitor
(7) Mercury-in-glass thermometer
(8) Written records of such calibrations, checks, examinations, or inspections shall be maintained, as specified in §212.183.

§212.72 Filters

(a) The integrity of all air filters shall be verified upon installation and maintained through use. A written testing program adequate to monitor integrity of filters shall be established and followed. Results shall be recorded and maintained as specified in §212.183.

§212.76 Heat exchangers

Heat exchangers, other than the welded double-concentric-tube type or double-tube sheet type, must employ a pressure differential and a means for monitoring the differential. The pressure differential shall be such that the fluid requiring a higher microbial quality shall be that with the greater pressure. Written records of the pressure differential monitoring shall be maintained as required in §212.183

§212.78 Air vents

All stills and tanks holding liquid requiring microbial control shall have air vents with non-fiber-releasing sterilizable filters capable of preventing microbial contamination of the contents. Such filters shall be designed and installed so that they do not become wet. Filters shall be sterilized and installed aseptically. Tanks requiring air vents with filters include those holding water for manufacturing or final rinsing, water for cooling the drug product after sterilization, liquid components, and in-process solutions.

§212.100 Written procedures, deviations

* * *

SOP No. Val. 200.90 **Effective date: mm/dd/yyyy**
Approved by:

(b) Written procedures shall be established, and shall be followed. Such procedures shall:
    (1) Ensure that all static lines are flushed prior to use. Such procedures shall require that flushing produce a turbulent flow for 5 minutes and that all valves on the line are opened and closed repeatedly to flush the valve interior.

§212.182 Equipment cleaning and use log

(a) Written records of the corrective action taken pursuant to §212.24 (a) and (c), and §212.225 (a) and (b), including validation of the effectiveness of the action, shall be maintained.
(b) Written records of equipment usage shall include documentation of the length of time the equipment was in use as indicated in §212.111.
(c) Written records demonstrating a positive pressure differential, as described in and required by §212.76, shall be maintained.

* * *

(e) For filtration equipment, or devices, written records documenting the installation, replacement, and sterilization (where appropriate) of filters such as those indicated in §§212.72, 212.77(b) and (c), 212.78, and 212.222(a) shall be maintained.

§212.183 Equipment calibration and monitoring records

Written records of calibration and monitoring tests and readings performed shall be maintained for at least 2 years after the expiration date of each batch of drug product produced by the equipment.

(a) Calibration records shall include:
    (1) A description of the equipment
    (2) The date the equipment was purchased
    (3) The operating limits of the equipment
    (4) The date, time, and type of each test
    (5) The results of each test
    (6) The signature of each person performing a test
    (7) The date the equipment was installed
(b) Monitoring records shall include:
    (1) A description of the equipment
    (2) The date the equipment was installed
    (3) The date the equipment was last calibrated, if appropriate
    (4) The operating limits of the equipment
    (5) The date and time of the recording

(6) The reading
(7) The signature of each person performing the monitoring

(c) Corrective measures employed to bring the equipment into compliance with its operating specification shall be:
(1) Recorded in the appropriate equipment log
(2) Noted in the calibration and/or monitoring record
(3) Immediately followed by testing to assure that the corrective measures were adequate to restore the required operating characteristics

§212.183 Batch production and control records

These records shall include the following information where appropriate:

(1) Verification that static lines were flushed prior to use according to established written procedures in §212.100(b).

§212.188 Batch production and control records

The review and approval of production and control records by the quality control unit shall extend to those records not directly related to the manufacture, processing, packing, or holding of a specific batch of large volume parenteral drug product but which have a bearing on the quality of batches being produced. Such indirectly related records shall include:

(a) Those dealing with equipment calibration or standardization
(c) Those demonstrating the quality of water produced by various processing systems.
(d) Those demonstrating the quality of air produced by various systems

§212.190 Air and water monitoring records

Written records of the air and water monitoring test results, readings, and corrective measures taken shall be maintained for at least 2 years after the expiration date of each batch of drug product produced in the area being monitored or containing the water as a component.

The record shall include at a minimum, the following information:

(a) Identity of the material being monitored
(b) Each characteristic being monitored
(c) Each specification limit
(d) Each testing method used
(e) Site sampled or monitored
(f) The date and time of each monitoring or testing
(g) The result of each test or monitoring reading
(h) Batch number and expiration date of the drug product being processed in the area or equipment, or to which the component is being added at the time of monitoring or sampling
(i) Corrective measures employed to bring the area, component or product into compliance with specifications
(j) Retesting results to verify the adequacy of the corrective measures

Subpart L — Air and Water Quality

§212.220 General requirements

(a) Air or water as described in this part may not be used until the plant, processes, and procedures used in producing and distributing it have been tested and approved by the quality control unit as capable of consistently producing air or water meeting the requirements set forth in this subpart.
(b) In addition to the requirements of this subpart, air and water quality shall be monitored as specified in Subpart J.
(c) The results of all testing and data generated shall be recorded and maintained as required by §212.180.
(d) Procedures designating schedules, assigning responsibility, and describing in detail the action to be taken to assure that the systems produce and deliver air and water that conform to the requirements set forth in this subpart shall be written. Such procedures shall also specify the corrective action to be taken when testing reveals that the established standards are not being met. Records of corrective actions shall be maintained, as specified in §212.190.

§212.224 Water for cleaning or initial rinsing

Water used to cleanse or initially rinse drug product contact surfaces such as containers, closures, and equipment shall:

Drinking Water Standards set forth in Subpart J of 42 CFR Part 72;

(b) Be subjected to a process such as chlorination for control of microbial population;

(c) Contain not more than 50 microorganisms per 100 millimeters in three consecutive samples from the sampling site when tested by the method specified in §212.225(b) after neutralizing bacteriocidal agents, if present.

§212.225 Water for manufacturing or final rinsing

Water used as a component or as a final rinse for equipment or product contact surfaces shall:

(a) Conform to the specifications in the U.S.P. for "Water for Injection":

(b) Contain not more than 10 microorganisms per 100 millimeters in three consecutive samples from the same site when samples of 250 millimeters or more are tested for total aerobic count by the plate method set forth in Microbial Limit Tests in the current revision of the U.S.P. Alternate methodology may be used provided that data are available to demonstrate that the alternate method is equivalent to the official method. When the microbial quality falls below that specified in this section, use of such water shall cease, and corrective action shall be taken to clean and sterilize the system so that the water conforms to the limit.

(c) Be stored in a suitable vessel or system including a piping network for distribution to points of use:

(1) At a temperature of at least 80°C under continuous circulation, or

(2) At ambient or lower temperature for not longer than 24 hours, after which time such water shall be discarded to drain.

§212.226 Water for drug product cooling

Water used in the sterilizer as a drug product cooling medium shall:

(a) Be treated to eliminate microorganisms:
(b) Contain not more than one microorganism per 100 millimeters in three consecutive samples from the same sampling site when one liter or more are tested for total aerobic count by a membrane filtration method and placing each membrane filter on appropriate nutrient media after neutralizing any bacteriocidal agents present in the water samples.

§212.227 Boiler feed water

Feed water for boilers supplying steam that contacts components, in-process materials, drug products, and drug product contact surfaces shall not contain volatile additives such as amines or hydrazines.

§212.233 Water quality program design

(a) Water quality monitoring shall include:
    (1) Sampling and testing of water for manufacturing or final rinsing at least once a day. All sampling ports or points of use in the distribution system shall be sampled at least weekly.
    (2) Sampling water for drug product cooling at a point just before entry into the sterilizer at least once each sterilizer cycle and testing by the method described in §212.226.
    (3) Sampling and testing water for cleaning or initial rinsing at least once a week. All sampling points or points of use in the distribution system shall be sampled at least monthly.
(b) Boiler feed water shall be sampled and tested periodically for the presence of volatile additives.
(c) If three consecutive samples of drug product cooling water exceed microbial limits, the sterilizer loads shall be rejected and shall not be reprocessed.

§212.231 Monitoring of air and water quality

(a) After the plant, equipment, manufacturing processes, and control procedures have been tested and approved by the quality control unit, there shall be performed in accordance with written procedures and schedules a sampling and testing program that is designed to monitor the microbial flora of the plant and its environment. The design of the sampling and

testing program shall include monitoring of air and water quality in accordance with requirements set forth in this subpart and taking corrective action when such requirements are not met.

(b) If the results of any one sample of air or water exceed the quality limits specified in this subpart, more frequent sampling and testing shall be required to determine the need for corrective action.

(c) Representative colonies of microorganisms found by the monitoring required in this section shall be identified by genus. The colonies shall be quantified.

(d) Written records of all test findings and any resultant corrective measures taken shall be maintained, as specified in §212.190.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.100 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Design Specifications for Purified Water (DIW) Production and Distribution**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.100 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Design Specifications for Purified Water (DIW) Production and Distribution

PURPOSE

To provide guidelines for the selection of material to be used for the production and distribution of DI water

RESPONSIBILITY

It is the responsibility of the technical services manager, validation manager, and contractors to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

The following guidelines and technical specifications must be followed:

1. Principle

Purified water is produced by the water treatment of available drinking water. The water treatment unit filling the storage tank shall be located at a suitable place per approved layout. From this tank, start hot loops, e.g., one for the recirculation in the water treatment unit (if required) and one for distribution in the building, to allow filling of the tanks and to feed the distillator and the steam generator. From the two secondary tanks start two loops to provide several points of use in the buildings (as required).

2. Main Characteristics

- Obtained from: available drinking water analysis report
- Quality: following USP 24
  microbiology: < 20 CFU/ml
- Production: to propose by the supplier
- Temperature: ð 20°C ± 5°C at each point of the loop
- Pressure: Š 2 bars
- Temperature keeping: obtained by a cold exchanger located at the return of the loop

3. Sanitization

The tanks and the loops must be sanitized NLT 80°C. The DIW is heated at 80°C and maintained at this temperature for 1 h once a day, during the night. After 1 h at 80°C, the loop must be cooled at 20°C by the cold exchanger located at the return of the loops.

4. Consumption Points

Provide the points as necessary (distillator, steam generator, tanks DIW, etc.).

5. Monitoring and Control

The following characteristics must be monitored: conductivity, °T at the return of the loop and between the two heat exchangers, and flow at the return of the loop. A sampling valve must be located near each main point of use.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 200.110 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Design Specifications for Pure Steam Production and Distribution**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 200.110 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Design Specifications for Pure Steam Production and Distribution

PURPOSE

To provide guidelines for the selection of material and techniques to be used for the construction of equipment and supporting accessories used to manufacture the process water

RESPONSIBILITY

It is the responsibility of the technical services manager and contractors to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

The following guidelines and technical specifications must be followed:

1. Principle

The pure steam is produced by the steam generator of the purified water. The steam generator shall be located at a suitable place per approved layout. From this, start the tubing to the different points of use. A system to collect the condensate must be provided for the most important point of use. The collected condensate could be used to feed the industrial steam generator.

2. Main Characteristics

- Obtained from: purified water
- Quality: the condensate must have the qualities required for water for injection
- Production: to propose by the supplier
  power: industrial steam (6 bars)
- Pressure available: 4 bars (relative)

3. Consumption Points

These points shall be established considering the requirements, they can be used simultaneously during a production day.

- Autoclave
- The SIP of the freeze drier

The sterilization of the WFI installation must be done beyond the workings hours.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

SECTION

VAL 300.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 300.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Validation Glossary**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 300.10 **Effective date: mm/dd/yyyy**
Approved by:

SUBJECT: Validation Glossary

PURPOSE

To provide the glossary of terms used in the SOPs with a particular reference to the validation and cGMP

RESPONSIBILITY

It is the responsibility of the validation team to understand and implement the terms defined in the validation lexicon. The QA manager is responsible for the SOP compliance.

PROCEDURE

Batchwise Control

The use of validated in-process sampling and testing methods in such a way that results prove that the process has done what it purports to do for the specific batch concerned, thus assuring that control parameters have been appropriately respected.

Calibration

Demonstrating that a measuring device produces results within specified limits of those produced by a reference standard device over an appropriate range of measurements. This process results in corrections that may be applied if maximum accuracy is required.

Calibration Program

An element of quality assurance ensuring that all tests and measurements used to control and monitor the process or to test the product are capable of producing results that are accurate and precise to the extent dictated by importance of the measurement.

Certification

Documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed appropriately and that the results are acceptable.

Control Parameters

Those operating variables that can be assigned values that are used as control levels.

Control Parameter Range

Range of values for a given control parameter that lies between its two outer limits or control levels.

Edge of Failure

A control parameter value that, if exceeded, means adverse effects on state of control or fitness of use for the product.

Installation Qualification

Documented verification that all key aspects of the installation adhere to appropriate codes and approved design intentions and that manufacturers' recommendations are suitably considered.

Operating Variables

All factors, including control parameters, that may potentially affect process state of control or fitness for use of the end product.

Operational Qualification

Documented verification that the system or subsystem performs as intended throughout all anticipated operating ranges.

Process Development

Establishing evidence that all process control parameters and all control parameter ranges are validated and optimized.

Process Validation

Establishing documented evidence that a process does what it purports to do.

Prospective Validation

Establishing documented evidence that a system does what it purports to do based on a preplanned protocol.

Proven Acceptable Range

All values of a given control parameter that fall between proven high and low worst case conditions.

Quality Assurance

The activity of providing, to all concerned, the evidence needed to establish confidence that the quality function is being performed adequately.

Quality Control

The regulatory process through which industry measures actual quality performance, compresses it with standards, and acts on the difference.

Retrospective Validation

Establishing documented evidence that a system does what it purports to do based on review and analysis of historic information.

Revalidation

Repetition of the validation process or a specific portion of it.

State of Control

A condition in which all operating variables that can affect performance remain within ranges that the system or process performs consistently and as intended.

Sterilization Process

A treatment process from which probability of any microorganism survival is less than 10^{-6}, or one in a million.

The Quality Function

The entire collection of activities from which industry achieves fitness for use, no matter where these activities are performed.

Validation

Establishing documented evidence that a system does what it purports to do.

Validation Change Control

A formal monitoring system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect validated status and cause corrective action to be taken so that the system retains its validated state of control.

Validation Protocol

A document that spells out what tests are to be performed, how the tests are to be performed, what data are to be collected, and what the acceptance criteria are.

Validation Report

A scientific report of the results derived from executing a validation protocol.

Worst Case

The highest or lowest value of a given control parameter actually evaluated in a validation exercise.

SOP No. Val. 300.10 **Effective date: mm/dd/yyyy**
Approved by:

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 300.20 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Organization for Validation**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 300.20 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Organization for Validation

PURPOSE

To describe the functions and responsibilities of the validation team to meet the cGMP compliance

RESPONSIBILITY

It is the responsibility of all concerned departments to follow the procedure. The QA manager is responsible for SOP compliance.

PROCEDURE

1. Validation Coordinator

All validation activities through the different progress steps should be coordinated by one person, preferably the quality assurance manager.

2. Validation Task Force/Certification Team

The team should consist of managers of the departments involved in the validation and outside vendors (if applicable); for example:

- Quality assurance manager
- Production manager
- Technical services manager
- Product development manager
- Calibration manager
- Quality control manager
- Approved vendors (outside)

2.1 Responsibilities

- Scope of validation
- Validation priorities
- Acceptance criteria

- Approving of validation protocols and reports
- Validation change control

3. Validation Working Groups

The executive part of the validation work should be delegated to dedicated personnel:

- A member of the validation task force
- Representatives from relevant departments
- A representative from quality assurance
- A representative from technical services
- A representative from product development laboratory
- A representative from quality control
- A representative from the vendor (outside)

4. Validation Planning and Scheduling

- Manpower resources
- Document preparation
- Filed execution
- Calibration
- Lab support
- Test and balance/filter certification
- Start-up and commissioning

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 300.30 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Revalidation**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 300.30 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Revalidation

PURPOSE

To describe the necessity and reasons for revalidation

RESPONSIBILITY

It is the responsibility of the validation team members to follow the procedures. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Evaluation of Revalidation Necessity

Revalidation provides a guarantee of consistent system, process, or equipment usage. It assures that monitoring controls are sensitive enough to identify major problems or drifts in quality and that process or equipment variations have no adverse effect on quality.

2. Reasons for Revalidation

A revalidation has to be performed in cases of:

- Change of (or in):Formula of the product
  Process
  Equipment
  Facility (influencing process)
  Control methods
  Batch size
  Hardware and software
  Cleaning agents
  Material changes
  Supplier change
- Deviations in results of in-process and final controls
- Extensive maintenance or repairs of equipment

Note: Prior to starting the revalidation, it should be evaluated whether the whole or only a part of the system, process, or equipment has to be revalidated.

3. Revalidation Cycle

In the event that no major changes are brought into the systems, process, and facilities, retrospective validation shall be conducted every 3 years.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and third-party manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 300.40 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Retrospective Validation**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 300.40 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Retrospective Validation

PURPOSE

To describe the requirements and criteria for retrospective validation

RESPONSIBILITY

The validation team is responsible for following the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Definition

Retrospective validation is the most pertinent for use by most pharmaceutical companies, establishing documented evidence that a system does what it purports to do based on review and analysis of historical information.

2. Objective

To demonstrate that the process has performed satisfactorily and consistently over time and, therefore, can be relied upon to deliver the same product quality in the future on a continuous basis.

3. Product Selection Criteria for Retrospective Validation

Following are criteria to establish the fact that the process can be categorized for retrospective validation:

- Used analytical test methods and results adequately specific
- Unchanged process
- Personnel procedures consistent in performance
- Available data from process history and testing clearly identified
- Unchanged suppliers of materials

A minimum of 20 batches should be evaluated over a specified time interval.

4. Retrospective Validation

- Setting up of process equipment
- Identification of measuring equipment
- Discussion of the influence possibilities on critical process parameters
- Identification of process equipment
- Selection of process and product parameters to be considered
- Fixing of requirements for process and product parameters
- Fixing of setting up the statistical evaluation
- Average value
- Minimum value
- Maximum value
- Standard deviation
- Correlation coefficient

5. Assessment of the Investigation

After review of all statistical data per approved standard operating procedure, assessment should be made to suggest important steps for future production or further investigations, if necessary.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued to your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 300.50 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Validation Change Control**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 300.50 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Validation Change Control

PURPOSE

To describe the procedure to prevent uncontrolled changes in validated equipment and processes

RESPONSIBILITY

All concerned departmental managers are responsible for following the procedures. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Definitions

Change:	Any subsequent departure from the approved flow chart and activities, or a modification to documentation, equipment, packaging, utilities, facilities, formulations, processes, or computer systems.
Change control:	A formal monitoring system by which qualified representatives of the appropriate discipline review actual changes that might affect a validated status to determine the need for corrective action ensure that the system retains its validated state.

2. Process Change Request (PCR)

- Changes will be needed or at least desired for a variety of reasons, such as new or improved functions, errors not detected earlier, alterations to accept new equipment in the system, etc.
- The changes may involve, but are not restricted to:
  a) Equipment: (e.g., fluid bed instead of lytzen drier, etc.)
  b) Procedure and process (e.g., addition, deletion, or revision of an existing procedure, changing any parameters, etc.)
  c) Material (e.g., excess quantity to be added, etc.)

- The departmental manager will initiate a **process change request** form prior to any change in the approved and authorized procedure.
- The form will be forwarded to the quality assurance manager to review and approve.
- The approved document will be sent back to the initiating department.
- A copy of the approved form will be sent to the initiator, with a copy to the QA manager.
- The change may be approved on a case–by–case basis, or may be suggested to be incorporated in the current document as a permanent change.
- In case of dispute, a management review committee or material review board meeting will be called to resolve the problem.

3. Engineering Change Control

- To make any changes in existing equipment configuration, parts, or software or in utilities (HVAC), facility systems, etc., the engineering change control form will be raised.
- The purpose is to monitor and ensure that a validated system remains validated by recognizing and addressing the potential impact of the change of the existing system.
- Prior to the change, the concerned engineer will raise the engineering change control form signed by the departmental engineer, clearly mentioning the proposed change (and, if applicable, attaching the drawing of current and proposed systems).
- The form will be forwarded to the QA manager and for approval and a decision regarding the requirement for validation.
- The approved form will be sent back to the initiating department.
- Copies will be marked to validation and department file.

4. Change Request Control in Technical Documents

- The departmental manager (initiator) will initiate the change request form prior to implementing any change in the approved and authorized technical document.

- The change may involve:
  a) Standard test methods (STMs)
  b) Standard control procedure (SCPs)
  c) Raw material purchase specifications (RMPSs)
  d) In-process packaging specifications (IPSs)
  e) In-process manufacturing specifications (IMSs)
  f) Finished product specifications (FPSs)
  g) Packaging material specifications (PMSs)
  h) Master packaging instructions (MPIs)
  i) Manufacturing formula and method (MFM)
- The form will be sent to the QA manager to approve the change in specification.
- A copy of the approved form will be sent to the initiator, and a copy to all other concerned departmental managers, if required, by the systems manager.
- The changes may be approved on a case–by–case basis or they may be suggested to be incorporated in the current document as a permanent change.

5. Packaging Materials (New and Existing) Design Change Control

- The packaging materials involved are labels, leaflets, and boxes. The procedure describes how to manage change control in new and existing (in-use) specifications and to place orders for purchase.
  - New packaging materials specifications: products for which the labels, leaflets, and box specifications are designed, developed, and approved for the first time.
  - Existing packaging materials specifications: products for which packaging material specifications (leaflets, labels, and boxes) are already in use.
- The changes in the test and color or design of leaflets, labels, and boxes of (in-use) packaging materials specifications are followed as stated in the change control approval matrix of the company.
- The changes in the existing packaging materials may be initiated by the following departments marketing (promotional requirements), registration (regulatory or registration requirement), or the drug information department (to update any information and implement changes required by health authorities).

SOP No. Val. 300.50 **Effective date: mm/dd/yyyy**
Approved by:

REASONS FOR REVISIONS

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

SECTION

VAL 400.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 400.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Calibration of Instruments**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 400.10 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Calibration of Instruments

PURPOSE

This procedure describes conditions pertaining to an adequate and organized calibration system of measuring devices.

RESPONSIBILITY

The calibration manager is responsible for establishing an adequate and organized calibration program. Supervision of the whole program should be done by the quality assurance manager.

PROCEDURE

- Upon receipt, all equipment should be reviewed by the calibration lab manager and the user department to establish if the equipment has to be kept on calibration program.
- Inclusion and exclusion lists should be maintained with reasons, location, and final approval by the QA manager.
- Classification of equipment as critical or noncritical with regard to calibration necessities should be maintained.
- The equipment variables affecting the product quality shall be identified as critical for calibration.
- Determination of accuracy requirements of the instrument should be in consent with the quality assurance and calibration departments.
- Calibration of the instrument should be on time prior to expire of calibration date by informing the calibration department.
- New, changed, or repaired instrument should be prior to use.

1. Tasks of Calibration Department

- Decide which instruments can be calibrated internally and which have to be calibrated by subcontractors.

- Purchase and control measuring equipment and reference material necessary for internal calibration certification of calibrated instruments. Label them with the date when last calibrated and also date when the next calibration is due. Write a calibration report and, if necessary, an incident report or a calibration variance report.

2. Reference Standards

The reference standards used for calibration of instruments should be checked for accuracy annually by an authorized measuring institution (e.g., Office of Weights and Measures or Bureau of Standards). The reference standard employed should have an uncertainty of measurement which is 1/10 to 1/5 the uncertainty required in the measurement equipment.

3. Cumulative Effect of Errors

The uncertainties of all equipment used in the calibration procedure and the method of combining them should be shown on the calibration certificate.

4. Training of Personnel Performing the Calibration Work

Only trained personnel should be employed for performing the calibration work. The above requirements are applicable for subcontractors performing calibration work on behalf of your company. Outside calibration laboratories should be inspected.

5. Intervals of Calibration

All critical items should be calibrated every 6 months. Noncritical items should be calibrated every 12 months. If necessary, recalibration frequency should be reviewed and revised.

6. Periodic Review of the Calibration Program

Periodic review of the calibration system should happen once a year using an established inspection checklist.

7. FDA Regulations

Some specific GMP calibration regulations that address the pharmaceutical and device industries are:

CFR 21 Part 58 — Good Laboratory Practice for Non-clinical Laboratory Studies

Section 58.63 — Maintenance and Calibration of Equipment

(a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated, and/or standard.

(b) The written standard operating procedures required under Section 58.81(b)(11) shall set forth in sufficient details the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration and/or standardization of equipment, and shall specify remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation, and copies of the standard operating procedures shall be made available to laboratory personnel.

(c) Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of non routine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered and any remedial action taken in response to the defect.

* * *

Current Good Manufacturing Practices for Finished Pharmaceuticals

Section 211.25 — Personnel Qualifications

(a) Each person engaged in the manufacture, processing, packing, or holding of drug product shall have the education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in Current Good Manufacturing Practice (including the Current Good Manufacturing Practice regulations in this chapter and writ-

ten procedures required by these regulations) as they relate to the employee's functions. Training in Current Good Manufacturing Practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them.

Section 211.68 — Automatic, Mechanical, and Electronic Equipment

(a) Automatic, mechanical, or electronic equipment of other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, or holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization, or other automated processes. In such instances, a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

Section 211.160 — General Requirements

(a) The establishment of any specification, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the

written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity. Laboratory controls shall include:

(4) The calibration of instruments, apparatus, gauges and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

Section 820.61 — Measurement Equipment

All production and quality assurance measurement equipment, such as mechanical, automated, or electronic equipment, shall be suitable for its intended purposes and shall be capable of producing valid results. Such equipment shall be routinely calibrated, inspected, and checked according to written procedures. Records documenting these activities shall be maintained. When computers are used as part of an automated production or quality assurance system, the computer software programs shall be validated by adequate and documented testing. All program changes shall be made by a designated individual(s) through a formal approval procedure.

(a) Calibration
Calibration procedures shall include specific directions and limits for accuracy and precision. There shall be provisions for remedial action when accuracy and precision limits are not met. Calibration shall be performed by personnel having the necessary education, training, background, and experience.

(b) Calibration Standards
Where practical, the calibration standards used for production and quality assurance measurement equipment shall be traceable to the national standards of the National Bureau of Standards, Department of Commerce. If national standards are not practical for the parameter being measured, an

independent reproducible standard shall be used. If no applicable standard exists, an in-house standard shall be developed and used.

(c) Calibration Records
The calibration date, the calibrator, and the next calibration date shall be recorded and displayed, or records containing such information shall be readily available for each piece of equipment requiring calibration. A designated individual(s) shall maintain a record of calibration dates and of the individual performing each calibration.

[The last GMP included in this listing is the original document that identified calibration program requirements but was never formally issued.]

CFR 21 Part 212 — Good Manufacturing Practices for Drugs

Section 212.68 — Equipment Calibration

(a) Procedures shall be written and followed designating schedules and assigning responsibility for testing or monitoring the performance or accuracy of automatic or continuously operating equipment, devices, apparatus, or mechanisms such as, but not limited to, the following:
(1) Temperature-recording devices on sterilizing equipment
(2) Temperature-recording devices on sterilizers
(3) Pressure gauges
(4) Mechanisms for maintaining sterilizing medium uniformity
(5) Chain speed recorder
(6) Heat exchanger pressure differential monitor
(7) Mercury–in–glass thermometer

(b) Written records of such calibrations, checks, examinations, or inspections shall be maintained, as specified in Section 212.183.

SOP No. Val. 400.10 **Effective date: mm/dd/yyyy**
Approved by:

Section 212.183 — Equipment Calibration and Monitoring Logs

Written records of calibration and monitoring tests and readings performed shall be maintained for at least 2 years after the expiration date of each batch of drug product produced by the equipment.

(a) Calibration records shall include
    (1) A description of the equipment
    (2) The date the equipment was purchased
    (3) The operating limits of the equipment
    (4) The date, time, and type of each test
    (5) The results of each test
    (6) The signature of each person performing a test
(b) Monitoring records shall include:
    (1) A description of the equipment
    (2) The date the equipment was installed
    (3) The date the equipment was last calibrated, if appropriate
    (4) The operating limits of the equipment
    (5) The date and time of the recording
    (6) The reading
    (7) The signature of each person performing the monitoring
(c) Corrective measures employed to bring the equipment into compliance with its operating specifications shall be:
    (1) Recorded in the appropriate equipment log
    (2) Noted in the calibration and/or monitoring record
    (3) Immediately followed by testing to assure that the corrective measures were adequate to restore the required operating characteristics.

Section 212.192 — Production Record Review

The review and approval of production and control records by the quality control unit shall extend to those records not directly related to the manufacture, processing, packing, or holding of a specific batch of large volume parenteral drug product but which have a bearing on the quality of batches being produced. Such indirectly related records shall include:

(a) Those dealing with equipment calibration or standardization.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 400.20 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Periodic Review of the Calibration Program**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 400.20 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Periodic Review of the Calibration Program

PURPOSE

To ensure that the approved procedures for calibration of all reference standards are effective and meet the cGMP requirements

RESPONSIBILITY

It is the responsibility of the calibration manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Calibration System

- Are there approved procedures for the calibration of all reference standards and measuring equipment?
- Are the management responsibilities defined in SOPs promptly detected?
- Are there deficiencies within the system to prevent subsequent inaccuracies?
- Is there a procedure to ensure corrective action and preventive measures?
- Are limits of calibration uncertainty properly defined?

2. Periodic Review of the Calibration System

- Is there an SOP to review the measuring and calibration system?
- Are the reviews conducted periodically?
- Are the records of the reviews maintained and do they provide objective evidence of the effectiveness of the system?
- Is management informed about the results of the review and is corrective action taken?

3. Planning

- Is there a system to establish and plan needs of calibration and measurement before starting new projects?
- Are the necessary reference standards and measuring equipment determined?
- Have the skills and training required by the calibration and measuring personnel been established?
- Are controlled environments provided where necessary (temperature, humidity, vibration, etc.)?

4. Calibration Limits

- Does the calibration system identify the source and magnitude of uncertainties associated with calibration and product characteristics?

5. Documented Calibration Procedures

- Are the approved procedures for controlling the calibration of reference standards and measuring equipment available and used for product verification?
- Where no in-house procedures are available, are there appropriate and identified published standard practices or manufacturer's written instructions available?
- Is there a system in place to conduct the inspection of the existing system to ensure adherence to existing procedures?
- Are the outside calibration labs audited and certified?

6. Records

- Do the records include details of calibration controls, environmental data, designated error limits, and information necessary to establish traceability?
- Does the system include the retention of calibration certificates or data used in support of all calibration of measuring equipment?
- Does the record system allow for calling forward, at the appropriate interval, equipment requiring calibration?

- Do the records indicate that the equipment is capable of performing measurements within the designated limits?
- Are all the records required maintenance?

7. Calibration Labeling

Is there a procedure of labeling that identifies the calibration status of reference standards and measuring equipment?

8. Sealing for Integrity

Where necessary, is a sealing provided to prevent access to the equipment?

9. Intervals of Calibration

- Have calibration intervals been established for all reference standards and measuring equipment based on the equipment manufacturer's recommendations or knowledge of equipment stability, purpose, and level of usage?
- Are trend data reviewed from previous calibration records to adjust the calibration intervals?

10. Invalidation of Calibration

- Does the SOP ensure the immediate removal from use, or conspicuous identification, of any reference standard or measuring equipment that has not been calibrated in accordance with the established time schedule, has failed in operation in any measurement parameter, or shows evidence of physical damage?
- Does the SOP provide for immediate notification of equipment failures or damage likely to have compromised product quality?

11. Subcontractors

- Do procedures ensure that a subcontractor employs a measurement and calibration system that complies with the company's requirements?

- Is responsibility accepted for ensuring that the procedures employed by a subcontractor for calibration and measurement work are suitable and properly documented?
- Is there a procedure for periodically evaluating subcontractors for adherence to company requirements for traceability, suitability of method, and documentation practices?

12. Traceability

Can all calibrations performed in-house or by subcontractors be traced to a national or international reference standard?

13. Environmental Control

Do the procedures for calibration and measurement of the equipment indicate the environment required to ensure accuracy and precision?

14. Training

Do personnel performing calibration functions have appropriate experience or training applicable to the type of calibration work undertaken?

REASONS FOR REVISIONS

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 400.30 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Calibration and Validation Equipment**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 400.30 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Calibration and Validation Equipment

PURPOSE

To provide the basic instrument list required for validation. This list should be regarded as a collection of examples; several alternatives are possible.

RESPONSIBILITY

It is the responsibility of the calibration manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Instrument Selection

After the selection of instruments required to perform calibration per SOP No. Val. 400.10, the calibration manager will procure the instruments.

2. Equipment Procurement

The basic instruments required for validation are listed in the following table as a guideline; several alternatives are possible.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

Sl. No.	*Equipment Name*	*Model*	*Manufacturer*
1.	Kaye Validator	X1310CE	Kaye Instruments
2.	Aerosol Particle Counter	CI – 500	Climet Instruments
3.	Liquid Particle Sensor	RLLD 1-100H	Climet Instruments
4.	Micro Monometer	AXD – 530	Alnor
5.	Aerosol Photometer	TDA – 2G	Air Techniques (ATI)
6.	Temp. & Humidity Recorder	THDx	Dickson
7.	Hand Held Digital Thermometer	51	Fluke
8.	Bead Probe	80 PK – 1	Fluke
9.	Surface Probe	80 PK – 3A	Fluke
10.	Immersion Probe	80 PK – 2A	Fluke
11.	Exposed Junction Probe	80 PK – 6A	Fluke
12.	Air Probe	80 PK – 4A	Fluke
13.	Tachometer	93-412 E	Connemara Electronics

SOP No. Val. 400.30 **Effective date: mm/dd/yyyy**

Approved by:

Sl. No.	*Equipment Name*	*Model*	*Manufacturer*
14.	Digital Lux Meter	93-1065 L	Connemara Electronics
15.	Temp. & Humidity Meter	HMI/HM 31	Vaisala Helsinki
16.	Air Velocity Meter	TESTO – 440	Testoterm Inc.
17.	Air Contamination	—	
18.	Measurement Device	RCS 94001	Reuter
19.	Conductivity Meter	LF 530	WTW
20.	pH Meter	764	Knick
21.	Analogue Digital Converter	Helios II	Fluke
22.	Digital Multimeter	M 2005	AVO
23.	Oscilliscope	V – 212	Hitachi
24.	Digital Stopwatch	331 – 382	RS
25.	Digital Manometer	P 200 AH	Digitron
26.	Digital Micromanometer	MP –6 KSR	Air Neotronics
27.	Dew Point Meter	SADP-5	Shaw
28.	Thermocouple	KM 2067	Kane May
29.	Temperature Calibrator	TRU	Technosyn
30.	Pressure Calibrator	—	Beamex, Digitron
31.	Current Source	1021	Time Electronics
32.	Millivolt Pot Source	Momocal	Ero Electronics
33.	Resistance Box	1051	Time Electronics
34.	Anemometer	8350	TSI

SECTION

VAL 500.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 500.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Training on the Job**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 500.10 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Training on the Job

PURPOSE

To describe the key elements to be considered part of the training to meet the cGMP requirements

RESPONSIBILITY

The departmental managers are responsible for developing and maintaining the training program. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

Besides the normal cGMP training, personnel should be trained on a regular basis with a particular reference to their daily work. The on-job-training program should ensure the following elements:

- Entry-level training for those who never worked in a pharmaceutical company
- List of all equipment
- Description of relevant equipment
- List of applicable standard operating procedures
- List of applicable drawings of the equipment
- Operational procedures
- Materials flow procedures
- Personnel flow
- Operational sequence of the production process in the equipment
- Identification of critical parameters
- Cleaning procedures
- Operational SOPs read by all operations at least once a year

1. Training Documentation

Training records shall be maintained for all personnel. A list of personnel authorized to work in each department, to operate each piece of equipment, and to carry out each process should be maintained.

2. Training of Personnel

Training should take into consideration, as appropriate, control laboratories (including technical, maintenance, calibration, and cleaning personnel), and other personnel whose activities could affect the quality of the product.

The effectiveness of the training should be assessed periodically. Training records should be maintained and reviewed.

REASONS FOR REVISIONS

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 500.20 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Good Manufacturing Practices**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 500.20 **Effective date: mm/dd/yyyy**
Approved by:

SUBJECT: Good Manufacturing Practices

PURPOSE

To describe and implement the elements of current good manufacturing practice to produce high quality products with optimum potency, efficacy, and safety

RESPONSIBILITY

It is the responsibility of departmental managers to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Introduction

Training new and old employees on cGMP guidelines is an essential requirement of the pharmaceutical industry in order to maintain and produce quality pharmaceutical products on a continuous basis, and to assure patients that the products used meet safety, efficacy, and potency requirements.

Following is the generic audit checklist of which the personnel working in the pharmaceutical industry must be aware:

2. General

Check the following:

1. Workers coming into direct contact with the product who have been medically examined and cleared are allowed in the area.
2. Workers in the area are wearing clean uniforms and caps.
3. All areas are cleaned per respective SOPs.
4. No eating, smoking, or unhygienic practices are allowed in the manufacturing area.
5. Facility is neat and clean, and lockers provided in the facility are clean. SOP of cleaning is followed.
6. All manufacturing operations are carried out in separate areas intended for such purposes.
7. All apparatus and equipment to be used in the operation have been cleaned per their respective SOPs.

8. The contents of all vessels and containers used in manufacturing and storage between manufacturing stages are identified by clearly legible labels having all the required information.
9. All machines and equipment bear legible clearance labels having all the required information.
10. All respective SOPs are followed.
11. Insecticutors on every entrance are available as appropriate.
12. Under-construction or maintenance areas should be well segregated from the manufacturing area.
13. All the specific areas have required temperature, relative humidity (Rh), and air pressures.
14. Clogs are in use instead of street shoes.
15. Gauges and measuring equipment have valid calibration tags.

3. Stores and Weighing Area

1. Weighing and measuring equipment are of appropriate accuracy and are calibrated.
2. All incoming supplies of raw material and packaging commodities are stored per SOP.
3. Stores' receiving labels are fixed on all containers and sample labels are affixed as appropriate.
4. Release labels are fixed on approved items and rejected labels on rejected items.
5. All rejected items are kept segregated from other materials.
6. Cleaning in the area is done according to schedule and is effective.
7. Workers coming into direct contact with product are wearing clean masks.
8. Curtains of the weighing booth are drawn during dispensing to avoid cross-contamination.
9. Dispensed materials are kept in locked, clean cages with proper labels.
10. Log books of the weighing area and calibration records of weighing balances are updated.
11. Raw material card entries are on time, complete, and correct.
12. Temperature and Rh are within requirements and limits, and the records are maintained.
13. Storage of raw materials, packaging materials, bulk products and finished product is appropriate.

4. Packaging Section

1. All packed units after completion of batch are kept in finished goods area in stores.
2. All coded and uncoded labels and boxes are kept in cages with identification labels.
3. Workers coming into direct contact with products are wearing masks.
4. Operators wear disposable gloves while handling the product.
5. There is proper physical separation or segregation between the lines.
6. Temperature and humidity records of the dry and soft packaging area are updated and maintained.

5. Soft and Dry Production

1. All employees are attired appropriately according to the specific garmenting SOP for soft and dry production.
2. Operators are wearing masks and gloves and using beard covers (head cover for covering beard) when necessary.
3. Relevant cleaning procedures for area and equipment should be followed.
4. Cleaning schedules should be followed.
5. Work areas are clearly labeled.
6. All vessels and utensils are labeled as to their cleanliness status.
7. Manufacturing instructions are at hand during processes and are approved and accurately followed.
8. Valid calibration labels are on all equipment.
9. Vessels should be labeled with product lot number and stage of processing.
10. Sampling tools are dedicated for each building and should be used accordingly.
11. Maintenance tools should also be dedicated for each building.

12. Air inlets and outlets are functional.
13. Materials holding containers are intact and can be closed completely.
14. Materials and personnel flow are dedicated and being followed.
15. Temperature and humidity are under the limits.
16. Dispensing and all processing are carried out in the prescribed and dedicated areas.
17. Line clearance procedure should be strictly followed and counter-checked to avoid mix-ups.
18. Devices for the presence of labels and overprinting are challenged prior to initiation of work.
19. Effective segregation of printed materials from not printed and rejected materials is in place.
20. Utilities lines are clearly marked and labeled.
21. Storage of product (bulk and finished) is under their labeled or prescribed storage condition.
22. All records must be completed at the time of action.
23. Employees have undergone training in GMPs, SOPs, and sterile area techniques and respective SOPs are followed
24. Employees have full knowledge about their job functions.
25. The department is well maintained for cleanliness and spacious enough for equipment and operations.
26. Area and equipment are clean at the end of the day's work.
27. Specific procedure for the cleaning of major equipment is followed.
28. Daily calibration records of balances are complete.
29. Correction to writing errors are made by crossing out, initialing, dating, and writing the reason (if necessary).
30. All the products have status labels.
31. All the log books (equipment and area usage records) are updated.

6. Good Documentation Skill

1. The correct ink color and type of proper writing instrument are used (pencils should not be used).
2. Additional documents (e.g., charts, printout) are properly included.
3. Printing and writing can be easily read.

SOP No. Val. 500.20 **Effective date: mm/dd/yyyy**

Approved by:

4. Errors are properly corrected with one line through the original entry, initialed, dated, and explained (if necessary).
5. Calculations are reviewed and verified.
6. Numbers are properly rounded off; the correct significant figures are used.
7. Spelling of the product names and other words is correct.
8. Lot numbers and product ID codes are doublechecked and are correct.
9. Information is recorded as it is obtained.
10. Proper formats for date and time are used.
11. All abbreviations are approved and standardized.
12. Blank spaces are properly handled.
13. The original entry is made into the official record.

In short, good documentation skill should produce proper records with the following characteristics:

- Permanent
- Accurate
- Prompt
- Clear
- Consistent
- Complete
- Direct
- Truthful

7. Parenteral Facility

1. In clean room operations, employees should be correctly attired according to relevant SOP.
2. A fresh set of garments should be used on each entry into the clean room.
3. Sets of garments ready for use should be sealed and labeled.
4. Sterile production area should be in a good state of repair and neat.
5. Relevant cleaning procedures for area and equipment should be followed.
6. Cleaning schedules should be followed.

SOP No. Val. 500.20 **Effective date: mm/dd/yyyy**
Approved by:

7. Cleaning and sanitization agents per the SOP should be labeled with the expiration date.
8. Records should be maintained for the preparation of cleaning and sanitization agents.
9. No simultaneous opening of doors on the clean and lesser clean class.
10. All alarm systems are functional.
11. Work areas are clearly labeled.
12. Product and product components are exposed only where protected by LAF stream providing an air quality of 100 or better.
13. Handling and all working practices should be such to avoid contamination and generation of particles.
14. All vessels and utensils are labeled as to their cleanliness status.
15. Manufacturing instructions are at hand during processes and are approved and accurately followed.
16. Vessels should be labeled with the product lot number and stage of processing.
17. Relevant sterilization and other charts and printouts are fully labeled, verified, and approved.
18. Valid calibration labels are on all equipment.
19. Air inlets and outlets are functional.
20. Material-holding containers are intact and can be closed completely.
21. Materials and personnel flow is dedicated and being followed.
22. Air differentials are maintained between the different areas of processing per their levels of cleanliness.
23. Temperature and humidity are under the limits.
24. Dispensing and all processing are carried out in the prescribed and dedicated areas.
25. Line clearance procedures should be strictly followed and counter-checked to avoid mix-ups.
26. Devices for the presence of labels and overprinting should be challenged prior to initiation of work.
27. Effective segregation of printed materials from not printed and rejected.
28. Utilities lines are clearly marked and labeled.
29. Storage of product (bulk and finished) is under its labeled or prescribed storage condition.
30. All records must be completed at the time of action.
31. Watches, bracelets, jewelry, or rings should not be worn during work.
32. Persons ill or having opened or bandaged wounds should inform the supervisor and should not be allowed in the clean room areas.
33. Monitor that no adhesive tapes are used in the sterile area in future.

8. Dos and Don'ts to Be Followed

- Do wear identification card all the time at work.
- Do follow clothing instructions before entering the plant.
- Do wash hands before entering and leaving the personal facility.
- Do read, understand, and follow standard operating procedures related to work.
- Do follow good manufacturing practices at work.
- Do observe personal hygiene at work.
- Do keep nails clean, and cut them every week.
- Do get a haircut every month.
- Do trim beard every day before coming to work.
- Do not take food and drinks inside the plant, and especially do not chew gum.
- Do not enter the plant in personal clothing, street shoes, or with unwashed hands.
- Do not go to the bathroom or outside the plant in working uniform, head cover, and clogs.
- Do not enter the plant if suffering with some contagious disease or a skin lesion.
- Do not carry anti-dust face mask, disposable hand gloves, or other working tools to lockers.
- Do not keep medicines inside the locker, except as prescribed for personal use by a doctor.
- Do not carry batch record and support documents in pockets or to the lockers.
- Do not remove medicines from the line for personal use.
- Do not taste and touch raw materials for personal experience during dispensing and processing.
- Do not change labels from the container, unless authorized.
- Do not remove items from the pallets, unless authorized.
- Do not cough inside the plant without a handkerchief.
- Do not use cosmetics and jewelry at work.
- Do not keep used sanitary towels inside the lockers.
- Do not sign batch records unless authorized.
- Do not use sampling and other tools dedicated for building A in building B, or vice versa.

SOP No. Val. 500.20 **Effective date: mm/dd/yyyy**
Approved by:

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

SECTION

VAL 600.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Guidelines for Area Classification and Air Handling**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.10 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Guidelines for Area Classification and Air Handling

PURPOSE

To provide the guideline for classification of areas to prevent mix–ups and cross-contaminatio

RESPONSIBILITY

It is the responsibility of all departmental managers to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

The different areas within a pharmaceutical plant must be identified. According to the classification, the following requirements should be fulfilled:

1. Nonclassified Areas

1.1 Black area

Nonmanufacturing areas, such as warehouse, administration, and workshop facilities, comprise the black area. Control of the warehouse storage conditions (temperature and relative humidity) is recommended, where necessary.

1.2 Dark gray area

These are areas where primary packaged products are handled (e.g. visual inspection of ampules, vials, blisters, and final packaging operations). Depending on the product mix manufactured, the control of temperature and relative humidity may be necessary.

2. Classified Areas

2.1 Gray area

These are areas where personnel could come into direct contact with open materials (starting materials, intermediate product, bulk product, and open primary packaging materials), for example, all operations (sampling, compounding, and producing) for manufacturing of solids, semisolids, and liquids for oral and topical use.

2.2 Solids

Classification:	no classification
Air supply:	filter efficiency Š 95%
Air exhaust:	filter efficiency Š 95%
Air pressure:	Generally negative pressure with respect to adjacent areas Material and personnel airlocks should have over-pressure with respect to adjacent areas (e.g., corridors) Continuous monitoring of pressure differences (about 10 to 15 pa)
Air change:	The following number of air changes should be met in working areas Low material potency: at least 10/h High material potency: between 10 and 20/h Recirculation of air is only allowed when working with low potency materials; when working with high potency materials, recirculation is not recommended. In case of built-in HEPAs, recirculation is possible while working with low potency materials
Spot exhaustion:	Local extraction at dust generating points by a separate system leading into a cyclone is recommended
Temperature:	To be monitored
Relative humidity:	To be monitored

2.3 Clean area

These are areas where materials of low viable count are handled. The area should be constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants. The operations can include a sterilizing process.

2.3.1 Semisolids and liquids for oral and topical use

Classification:	Class 100,000 (unmanned)
Air supply:	Filter efficiency Š 95% for particles Š 0.5 μm
Air pressure:	Positive pressure with respect to less clean areas Continuous monitoring of pressure differential with respect to less clean areas
Air changes:	At least 20/h
Temperature:	To be monitored
Relative humidity:	To be monitored

2.3.2 Preparation of parenterals

Classification:	Minimally class 10,000 area (unmanned) Minimally class 100, 000 area (manned)
Air supply:	HEPA filters Š 99.97% efficiency for particles Š 0.5 μm Partly recirculation air is allowed
Air pressure:	Positive pressure with respect to less clean areas Continuous monitoring of pressure differential with respect to less clean areas (about 10 to 15 Ps)
Air changes:	At least 20/h
Temperature:	20 to 25°C recommended, to be monitored
Relative humidity:	40 to 60% recommended, to be monitored

3. Aseptic Area

These are areas within a clean area designed and constructed, serviced, and used with the intention to protect sterile products from microbiological and particulate contamination.

Classification:	Minimally class 100 (unmanned) Minimally class 10,000 (manned) Particle load to be monitored continuously
Air supply:	HEPA filters Š 99.995% efficiency for particles Š 0.5 μm Partial recirculation of air is possible
Air exhaust:	Low level air extraction
Air pressure:	Positive pressure with respect to less clean area

	Continuous monitoring of pressure differential with respect to less clean area (about 10 to 15 Pa)
Air changes:	More than 20/h
Temperature:	20 to 25°C recommended, to be monitored
Relative humidity:	40 to 60% recommended, to be monitored

4. Critical Area

These are areas where the product, prepared under aseptic conditions, as well as open sterile containers and closures, is exposed to the environment.

Classification:	Class 100 (laminar flow installations)
Air velocity:	Flow of 0.30 m/s (vertical) or 0.45 m/s (horizontal)
Air supply:	Filter efficiency 99.997% for particles Š 0.5 μm

5. General Recommendations

At the cross point between nonclassified and classified areas, as well as between the different classified areas, separate airlocks for materials and personnel should be installed. Additionally, airlocks to the clean or to the aseptic areas should be equipped with interlocking doors. Only authorized personnel should be allowed to enter the classified areas.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.20 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Guideline for Area Validation: Clean Area**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.20 **Effective date: mm/dd/yyyy**
Approved by:

SUBJECT: Guideline for Area Validation: Clean Area

PURPOSE

To describe the procedure for the area validation of clean area

RESPONSIBILITY

Concerned departmental managers are responsible for following the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Measurements in Unmanned Condition

1.1 Integrity testing of Hepa filters

Procedure

According to SOP No. Val. 600.30

Requirements

According to SOP No. Val. 600.30

Frequency

Initial validation: once per HEPA filter unit
Revalidation: annually

1.2 Air pressure situation

Procedure

The overpressure situation should be measured with a pressure gauge over 24 h. Also refer to SOP No. Val. 600.30.

Requirements

With regard to less clean adjacent areas, the average overpressure should be at least 10 Pa with a maximum deviation of ±2 Pa with regard to the average value.

Frequency

Initial validation: once for the clean area
Revalidation: annually

1.3 Particulate matter in air

Procedure

The particulate matter in air should be measured with a particle counter

Sampling procedure

The measurements should be performed at a height of 1.5 m above floor level. The minimum volume of air required per sample can be calculated using the following formula:

$$\text{Volume} = 20 \text{ particles/class limit (particles/volume)}$$

Each sample of air tested at each location shall be of sufficient volume such that at least 20 particles would be detected.

The minimum number of sampling points required for measuring the particulate matter in a clean area can be read from Table 1.

Table 1

Square feet	*Square meter*	*Sampling points*
100	9.2	4
200	18.4	8
400	36.8	16
1,000	92.0	40
2,000	184.0	80
4,000	368.0	160
10,000	920.0	400

This means that not less than two locations should be sampled for a clean area. At each location at least 5 measurements of a volume calculated as described in 1.3 should be performed. Afterwards, the average of the obtained values for each sampling location should be calculated. The average value of the measurements from each sampling location should comply with the requirements.

Requirements

ð10,000 particles Š0.5 µm/cft or ð353,000 particles Š0.5 µm/m^3
ð70 particles Š5 µm/cft or ð2,470 particles Š5 µm/m^3

Frequency

Initial validation: once
Revalidation: annually

1.4 Temperature

Procedure

Temperature sensors should be placed on different locations within the clean area. The investigation should be performed over at least 24 hours.

Requirements

The temperature should be between 20 and 25°C.

Frequency

Initial validation: once
Revalidation: annually

1.5 Relative humidity

Procedure

The measurements should be performed with a hygrometer. The investigation should be done over at least 24 h.

Requirements

Within the clean area a relative humidity of 40 to 60% should be maintained.

Frequency

Initial validation: once
Revalidation: annually

1.6 Microbiological quality of air

Procedure

To determine the airborn microbial contamination level, refer to SOP No. Val. 600.30.

Requirements

Class 100	<3 cfu/m^3 of air
Class 10,000	<20 cfu/m^3 of air
Class 100,000	<100 cfu/m^3 of air

Frequency

Initial validation: once
Revalidation: refer to SOP No. Val. 600.40

1.7 Air Changes

Procedure

Determine the number of air changes per hour in the clean area by calculation from the inlet air flow and the area volume.

Requirements

At least 20 air changes/h should be achieved.

Frequency

Initial validation: once
Revalidation: annually

2. Measurements in Manned Condition

2.1 Particulate matter in air

Procedure

The particulate matter in air should be measured with a particle counter.

Sampling procedure

The measurements should be performed at a height of 1.5 m above floor level. The minimum volume of air required sample can be calculated from step 1.3. The minimum number of sampling points required for verifying the particulate matter in a clean area can be read from Table 2 above.

This means that, for a clean area, not less than two locations should be sampled. At each location at least 5 measurements should be performed. Afterward, the average of the obtained values for each sampling location should be calculated.

The average value of the measurements from each sampling location should comply with the requirements:

ð100,000 Š0.5 μm/cft or ð3,530,000 Š0.5 μm/m^3
ð700 Š5 μm/cft or ð24,700 Š5 μm/m^3

2.2 Restoration time

The clean area is classified as class 10,000 in unmanned condition and as class 100,000 in manned condition. The time lapse to comply again with class 10,000 requirements after finishing work and after personnel have left the clean area has to be determined.

Procedure

The particulate matter in air should be measured with a particle counter.

Requirements

The class 10,000 conditions should be reached within 20 min after personnel have left the area.

Frequency

Initial validation: once
Revalidation: annually

2.3 Air pressure situation

For procedure requirements and frequency, see Section 1.3.

2.4 Temperature

For procedure, requirements, and frequency, see Section 1.4.

2.5 Relative humidity

For procedure, requirements, and frequency, see Section 1.5.

2.6 Surface and floor contamination

Procedure

The measurements should be performed in accordance with SOP No. Val. 600.30.

Frequency

Initial validation: once
Revalidation: annually

In addition to these investigations with regard to validation requirements, a monitoring program, as described in SOP No. Val. 600.30. Guidelines for area validation aseptic areas should be implemented.

2.7 Microbiological quality of air

Procedure

Measurements should be performed in accordance with SOP No. Val. 600.30.

Requirements

According to SOP No. Val. 600.30

2.8 Air changes

For procedure, requirements, and frequency see Section 1.7.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.30 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Aseptic Area Validation Procedures**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.30 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Aseptic Area Validation Procedures

PURPOSE

To describe the procedure for the validation of aseptic area to prevent cross-contamination and demonstrate environmental control

RESPONSIBILITY

All concerned departmental managers and validation engineers are responsible for following the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Testing

The controlled areas will be subjected to the following set of performance tests:

1. Air flow, volume, and distribution (also designated as post-balancing verification)
2. HEPA filter/leak (DOP)
3. Temperature control
4. Humidity control
5. Air flow and uniformity
6. Pressure control
7. Airborn particle count
8. Induction leak
9. Air flow patterns
10. Recovery
11. Particle dispersion
12. Airborn microbial
13. Surface bioburden
14. Lighting level

The instruments used for these tests should be calibrated and included with the report. The tests will be performed at rest, dynamic, and stress conditions.

1.1 At-rest testing

Performance tests executed under at-rest (complete and with production equipment installed and operating, but without personnel within the facility) conditions will serve as baseline information, and are needed to determine simulated fully operational conditions. After this analysis certain procedures, equipment, methods, etc., are changed.

1.2 Dynamic testing

Dynamic testing occurs when production equipment is installed and in normal operation with all services functioning, and with personnel present and performing their normal functions in the facility. The tests performed will serve to obtain a clear representation of the prevailing environmental conditions.

1.3 Stress testing

Testing at stress conditions will be performed to determine the ability of the system to remain stable at all times during operation conditions defined as continuity. Stress testing will be used to determine the ability of the system to recover after an unacceptable limit has been reached.

2. Reporting Forms

The protocols define procedures to be used to verify the performance of qualified equipment. As part of validation, the results obtained should be carefully recorded and compared with the design conditions. Deviations or diversions contrary to the specified levels determine the suitability of the controlled environment, so the reporting form represents the document for certification or acceptance of the system. The reporting form should show the following information:

Date, start, and finish time
Name of person performing the test
Location of the test
List of testing equipment with serial numbers
Calibration dates
Temperature (when applicable)
Humidity (when applicable)

Air velocity (when applicable)
Design conditions
Actual conditions
Signatures of those involved in the test
Diagrams showing test locations

The aseptic area validation matrix is summarized in the following table.

Table 1 Aseptic Area Validation Matrix

Tests	*At Rest Initial*	*At Dynamic*	*Stress*
Air Flow, Volume, and Uniformity Test	X	—	NR
HEPA filter/Leak Test (DOP)	X	NR	NR
Temperature Control Test	X	X	X
Humidity Control Test	X	X	X
Air Flow and Uniformity Test	X	X	X
Air Pressure Control Test	X	X	X
Airborn Particle Count Test	X	X	X
Induction Leak Test	X	—	—
Air Flows Patterns Test	X	X	NR
Recovery Test	X	X	—
Particle Dispersion Test	X	—	NR
Airborn Microbial Test	X	X	X
Surface Bio-burden Test	X	X	X

—: Optional

NR: Not Required

3. Air Flow Velocity, Volume, and Uniformity Tests

Purpose

These test procedures are performed to determine average air flow velocity and uniformity of velocity within a cleanroom, clean zone, or unidirectional flow work zone, as well as to determine air supply volume uniformity. Typically, either airflow velocity or air flow volume testing will be performed. Total volume may in turn be

used to determine the air exchange rate (room air volume changes per hour) for the clean room.

Equipment

- Air flow velocity: electronic microanemometer with tube array thermal anemometer, vane-type anemometer, or equivalent
- Air flow volume: electronic micromanometer with appropriate air flow hood, or equivalent
- Suitable support stand where necessary

Method

- Air flow velocity (unidirectional) test: The work zone for which air flow velocities are measured is the unidirectional air flow volume designated for clean work, characterized by an entrance plane normal to the air flow. The entrance plane is typically no more than 30 cm (12 in.) from the supply source. Alternative spacing may be selected, especially for horizontal flow conditions, provided that air flow remains unobstructed in any manner that would significantly affect test results. The unidirectional air flow velocity test should be performed as follows:
  1. Divide the work zone entrance plane into a grid of equal areas. Individual areas should not exceed 0.37 m^2 (4 ft^2).
  2. Support the anemometer sensor probe with a suitable stand. The use of a stand will prevent errors resulting from disruption of the unidirectional air flow that can be caused by the body or arm if the probe is hand-held. Orient the probe perpendicular to the velocity flow vector to be measured. Probe positions for air flow velocity testing are the designated grid test locations, at the work zone entrance plane. All test positions should be within unobstructed, unidirectional air flow.
  3. Measure the air flow velocity at each test position. Allow at least five seconds for each measurement and record the average reading during that period.
- Air flow velocity (nonunidirectional) test: In a nonunidirectional clean room or clean zone, air flow velocity measurements should be made for each terminal HEPA filter (or supply air diffuser, if applicable); there is no entrance plane as such.

Note: The measurement of air flow volume is usually preferable to measurement of air flow velocity and is a more representative test of the final filter air supply for nonunidirectional air flow clean rooms.

The air flow velocity test in a nonunidirectional clean room should be performed as follows:

1. Support the anemometer sensor probe with a suitable stand so that optimum control of test positions can be maintained. Orient the probe perpendicular to the velocity flow vector being measured.
2. Measure and record the velocity at the approximate center of each filter area of 0.37 m^2 (4 ft^2). The probe should be positioned at a distance of no more than 15 cm (6 in) from the filter face. The effect of nonuniform velocity across the filter face can be minimized by taking more readings per unit area or by using a tube array sensor.
   - Air flow volume test: The supply air flow volume is measured by using a flow hood in a manner that includes all of the air issuing from each terminal filter or supply diffuser. The air flow volume test should be performed as follows:
     1. Place the flow hood opening completely over the filter or diffuser, seating the face of the hood against a flat surface to prevent air bypass and inaccurate readings.
     2. Measure and record the volume flow rate in l/sec (ft^3/min) for each filter or diffuser.

Acceptance criteria

- The average air flow velocity, or the average or total air flow volume, for the clean room or clean zone should be within ±5% of the value specified for the clean room or clean zone, or within other standardized tolerance limits.

Note: Air flow volumes must be normalized, if filters or diffusers differ in size, before the average airflow volume can be calculated.

- The relative standard deviation should not exceed 15%.

4. HEPA Filter/Leak Test (DOP)

Purpose

To ensure against HEPA filter failure due to damage during installation or operation

Equipment

DOP polydisperse aerosol generated by blowing air through liquid dioctyl phthalate (DOP) at room temperature. The approximate light-scattering mean droplet size distribution of the aerosol is:

99% + less than 3.0 μm
95% + less than 1.5 μm
92% + less than 1.0 μm
50% + less than 0.72 μm
25% + less than 0.45 μm
11% + less than 0.35 μm

- DOP aerosol generator — compressed-air operated, equipped with Laskin-type nozzles.
- Aerosol photometer — light-scattering type with a threshold sensitivity of at least 10^{-3} mg/l. Capable of measuring concentrations in the range of 80 to 120 mg/l, and with air sample flow rate of 1 ft^3 + 10%/min.

Method

- This test shall be performed only by certified or previously trained personnel.
- Introduce DOP aerosol upstream of the filter through a test port and search for leaks downstream with an aerosol photometer.
- Filter testing shall be performed after operational air velocities have been verified and adjusted where necessary.
- Align the aerosol photometer.
- Position the smoke generator so the DOP aerosol will be introduced into the air stream ahead of the HEPA filters.
- Open the appropriate number of nozzles until a DOP challenge concentration of 100 mg/liter of air is reached. This challenge concentration is

measured upstream of the HEPA filter and is evidenced by a reading between 4 and 5 on the logarithmic scale of the aerosol photometer.

- Scan each filter by holding the photometer probe approximately 1 in. from the filter face and passing the probe in slightly overlapping strokes, at a traverse rate of not more than 10 ft/min, so that the entire face is sampled.
- Make separate passes with the photometer probe around the entire periphery of the filter, along the bond between the filter medium and the frame, and along all other joints in the installation through which leakage might bypass the filter medium

Acceptance criteria

- HEPA filters 99.99% (MIL-STD 282, Eurovent 4/4, UNI 7833) and more: challenge aerosol penetration is lower or equal to 0.01% of the upstream concentration (= filter class EU13 and EU14 [BS 3928, BSI Document 90/73834 and draft DIN 24.184] and class H13, H14, U15, U16 and U17 [draft CEN/TC/195])
- HEPA filters 99.97% (MIL-STD 282, Eurovent 4/4, UNI 7833): challenge aerosol penetration is lower or equal to 0.03% of the upstream concentration (= filter class EU12 [BS 3928, BSI Document 90/73834 and draft DIN 24.184] and class minimum H12 [draft CEN/TC/195])
- HEPA filters 95% (MIL-STD 282, Eurovent 4/4, UNI 7833): challenge aerosol penetration is lower or equal to 5% of the upstream concentration. (= filter class EU10 and EU 11 [BS 3928, BSI Document 90/73834 and draft DIN 24.184] and class minimum H10 and H11 [draft CENT/TC/195])

Repairs

SOP No. Val. 600.30 **Effective date: mm/dd/yyyy**
Approved by:

No repair is authorized without the acceptance of the contractor. If the contractor agrees to repair the filter, the medium to repair the filter should be agreed upon (usually silicones; do not use silicones when interfering with product, e.g., clean rooms for painting purposes). Each repair must be properly documented on the worksheet.

In any case, the maximum surface to be repaired is less than 5% of the visible surface of the filter and any dimension of any repair is maximum 4 cm. Other criteria for repair can be agreed upon with the contractor.

Frequency

Initial validation: once
Revalidation: every six months for class 100 areas; every year for class 10,000 and 100,000 areas respectively

5. Temperature Control Test

Purpose

To demonstrate the ability of the air handling system to control temperature at designed standards all year

Equipment

- Calibrated DICKSON temperature and humidity recorder or equivalent

Method

- Air conditioning systems are to be in continuous operation for at least 24 h prior to performing these tests. All lights in the sterile core are to be on during the testing as well as during the 24-h preconditioning period.
- Measure and record temperatures at 1–h intervals for a period of 8 h (at least 3 days) at each of the indicated locations for each room.
- The test should be repeated for at-rest and dynamic conditions.

Acceptance criteria

The system shall be capable of maintaining temperature and humidity as per designed standards all year round, with the specified occupancy and heat generation

design levels. As a guideline, in practice, the temperature should be to U.S Federal Standards 209E:22.2 ±2.8°C

Frequency

Initial validation: once
Revalidation: annually

6. Humidity Control Test

Purpose

To demonstrate the capability of the air handling system to control humidity at the specified level for each room

Equipment

- Calibrated DICKSON humidity and temperature recorder or equivalent

Method

- Execute this test after all the balancing procedures have been concluded.
- Measure and record humidities for the conditions and locations specified for every room under at-rest and dynamic conditions.
- Operate the system for at least 6 h prior to the start of the test.
- Measure and record the RH at 1–h intervals for the period of 24 h (at least 3 days) at each of the indicated locations for each room.

Acceptance criteria

The relative humidity at each grid point shall be equal to the specified levels and tolerance limits indicated on each recording form. If these levels are attained, the system is accepted.

Requirements

U.S Federal Standard 209E: 30 to 45% relative humidity

SOP No. Val. 600.30 **Effective date: mm/dd/yyyy**
Approved by:

Frequency

Initial validation: once
Revalidation: annually

7. Air Flow and Uniformity Test

Purpose

- To demonstrate that the air system is balanced and capable of delivering sufficient air volumes to maintain a minimum cross-sectional velocity under the absolute terminal/filter modules of at least 90 fpm measured 6 in. downstream of the filters
- To verify air velocities before the air encounters an obstruction; this should be conducted when new filters are installed in the system
- To verify horizontal and vertical air velocity components at the point at which the clean air reaches an obstacle or a surface 40 in. above the floor, whichever occurs first

Equipment

Hot-wire anemometer and stand

Method

- These tests are to be executed in every room where an absolute terminal filter module is installed.
- Draw a grid on the floor as indicated in the room diagram.
- Measure and record the velocity at the center of each grid at the specified heights.
- Allow no objects within 10 ft of the anemometer, except for built-in equipment. Minimize the number of people during the at-rest testing.
- Measurements should be taken for a minimum of 15 sec.
- Record the pressure readings (in inches) from the manometer connected to the module's plenum.

SOP No. Val. 600.30 **Effective date: mm/dd/yyyy**
Approved by:

Acceptance criteria

Average measured clean air velocity shall be according to designed standard at 6 in. downstream from the filter face. Velocity differences within the same plenum should be no more than 25%.

Frequency

Initial validation: once
Revalidation: annually

8. Pressure Control Test

Purpose

To demonstrate the capacity of the system to control pressure levels within the specified limits

Equipment

Inclined pressure gauge with resolution of 0.01 in. of water

Method

- All HVAC and laminar flow systems are to be in continuous operation when performing these tests.
- To avoid unexpected changes in pressure and to establish a baseline, all doors in the sterile facility must be closed and no traffic is to be allowed through the facility during the test.
- Pressure readings are taken with the high and low pressure tubing at the specified following locations. The following stress conditions (Table 2) should be simulated while monitoring pressure.

Table 2

	Test 1	*Test 2*	*Test 3*	*Test 4*
Gowning	Closed	Open	Closed	Open
Ancillary	Closed	Open	Closed	Open
Primary room	Closed	Open	Closed	Open
Corridor	Closed	Open	Closed	Open

Acceptance criteria

- Pressure differentials should be as indicated in the design conditions at all times under static conditions.
- Pressure differentials should be maintained as indicated in the design conditions under standard simulated operating conditions.
- Pressure differentials should be above 0.02 at the primary environments when stress conditions occur.
- The system will not be acceptable if, at any time during normal dynamic, static, or stress conditions, the pressure in the primary environments becomes less than zero or negative.

Frequency

Initial validation: once

Revalidation: annually

9. Airborn Particle Count Test

Purpose

To establish that, at critical work locations within clean rooms, a count of less than 100 particles per cubic foot of air, 0.5 μm in diameter or larger, is maintained. The other critical areas of class 10,000 and class 100,000 are also maintained.

Equipment

CI-500 laser particulate counter with printer

Method

- The measurement should be performed at a height of 1.5 m above the floor level.
- These tests are performed after the HEPA filter leak tests and air velocity tests are completed.

SOP No. Val. 600.30 **Effective date: mm/dd/yyyy**

Approved by:

- To obtain baseline data with the room in static conditions, perform the following tests with operational personnel absent and the equipment at rest:
  1. Using the particle analyzer, count particles greater than or equal to 0.5 μm in diameter at heights of 40 in. in the center of each grid.
  2. If the particle count in the 0.5 μm range is less than 50 per cubic foot of air, four additional counts at this location are taken to place these particle counts within a 50% confidence interval.
- After completion of these tests, if the absolute air filtration modules are operating within accepted limits, repeat steps 1 and 2 with operational personnel present and the fill equipment running. If at any time there is a deviation from accepted parameters, the various components of the systems in operation are reviewed.

The minimum volume of air to be sampled can be read from Table 3:

Table 3

Testing for particles	*Air volume required*
Š 0.1 µm	0.1 cft or 2.8 l
Š 0.3 µm	0.1 cft or 2.8 l
Š 0.5 µm	0.2 cft or 5.6 l
Š 5 µm	0.3 cft or 8.4 l

The minimum number of sampling points can be read from the Table 4:

Table 4

Square feet	*Square meter*	*Sampling points*
100	9.2	4
200	18.4	8
400	36.8	16
1,000	92	40
2,000	184	80
4,000	368	160
10,000	920	400

Table 5 shows room air classification based on Federal Standard 209 E:

Acceptance criteria

- The air system can be considered validated when the results of three consecutive sets of tests are within accepted operational parameters.
- At any of the designated critical locations (where any sterilized product or material is exposed to the working environment), the particulate count shall not exceed 100 particles 0.5 µm in diameter and larger per cubic foot of air.

Table 5 Federal Standard 209 E class limits in particles per cubic foot of size equal to or greater than particle size shown

	Measured Particles size (μm)				
Class	*0.1*	*0.2*	*0.3*	*0.5*	*5.0*
1	35	7.5	3	1	NA
10	350	75	30	10	NA
100	NA	750	300	100	NA
1,000	NA	NA	NA	1,000	7
10,000	NA	NA	NA	10,000	70
100,00 0	NA	NA	NA	100,00 0	700

- The same test should be repeated at ancillary environments. Ancillary environments shall not exceed a particle count of 100,000 particles 0.5 μm in diameter and larger per cubic foot of air, in order to be considered acceptable by current regulations. It is common practice to design and operate ancillary environments at levels not exceeding 10,000 particles of 0.5 μm per cubic foot of air, in order to provide additional protection to the final product while it is processed at the critical area.

SOP No. Val. 600.30 **Effective date: mm/dd/yyyy**
Approved by:

Frequency

Initial validation: once
Revalidation: annually

10. Induction Leak Test

Purpose

- To determine if there is intrusion of unfiltered air into the clean work areas from outside the clean room enclosure through joints and cracks in the walls, ceiling, etc., other than from the pressurized air supply system
- To determine unfiltered air intrusion into the clean room through open entrance doorways

Equipment

Optical particle counter

Method

- Measure the concentration outside the clean room enclosure immediately adjacent to the surface or doorway to be evaluated. This concentration should be at least 100,000 particles per cubic foot of a size equal to greater then 0.5 μm. If the concentration is less, generate an aerosol to increase the concentration.
- To check for construction joint leakage, scan all joint areas from a distance of 6 in. at a speed of approximately 10 in./min.
- To check for intrusion of open doorways, measure the concentration inside the enclosure at 10 in. from the open door.
- Repeat the same test in front of any openings, i.e., pass-through, electrical outlets, and any openings connecting with the outside.
- Repeat this test while opening and closing clean room entrance doors.

SOP No. Val. 600.30 **Effective date: mm/dd/yyyy**

Approved by:

Acceptance criteria

No construction joint leaks or intrusion through open doors should exceed 0.1% of the measured external concentration. See Tables 6 and 7.

Table 6 Air Cleanliness Level: Definition of Classes

	Maximum number of particles			
	0.5 μm		*5 μm*	
Class	*Per cubic foot*	*Per cubic meter*	*Per cubic foot*	*Per cubic meter*
100	100	3.5	—	—
10,000	10,000	350	65	2.3
100,000	100,000	3500	700	25

Table 7 Guidelines for Cleanliness Levels Required during Manufacturing of a Parenteral Drug

Operation	*Class*	*Cleanliness level (particles 0.5 μm and larger)*
Warehousing	—	—
Preparation	100,000	No more than 100,000
Filtration	100,000	No more than 100,000
Filling area	100,000 or better	No more than 100,000
Filling line (point of use)	100	No more than 100

11. Air Flow Patterns Test

Purpose

- To determine air flow interaction with machinery and equipment in a critical area protected with a laminar flow clean air system
- To determine the air flow patterns during fill line operations
- To select and improve the flow pattern that generates the minimum turbulence and best washing capabilities

SOP No. Val. 600.30 **Effective date: mm/dd/yyyy**

Approved by:

Equipment

White visible or yellow smoke generator, anemometer, 35-mm camera or videotape recorder

Method

- Verify that the laminar flow devices in the sterile core are operational.
- Check air velocities at 6 in. from the filter face to ensure that the device is operating within the specified laminar flow velocity (90 ft/min or more).
- Verify that the ventilation and air conditioning systems are operating and balanced.
- If the system operates according to the specified operating parameter, begin to generate white visible smoke at the critical locations. A critical location is defined as any area where sterilized product or material is exposed to the working environment.
- Generate white smoke inside and over each component that forms part of the line (to avoid damage to the materials or equipment, cover them tightly with plastic). Film the smoke as it travels through each critical area of the machine.
- Smoke should flow through these critical areas. If the air returns (back-flows) due to turbulence, the system cannot be accepted and must be rebalanced or adjusted. Slight turbulence, due to equipment configuration, is not significant as long as the air does not return to the critical areas.
- If the air does not back-flow, continue to film. If the smoke back-flows to the critical working area at any point during this operation, procedures must be established to prevent cross-contamination and reentry into these areas. If the unit passes, proceed.
- Determine if the generated turbulence can carry contaminants from other areas to critical points of the line. If so, adjust the air flow to ensure a minimum of turbulence and rapid cleaning. If the turbulence cannot be stopped, a different aerodynamic pattern must be found (covers and diffusers can be used over the filling equipment). If turbulence carries contaminants from any area to the critical areas, the system should be reevaluated and analyzed in terms of the filling, capping, and laminar-flow equipment.

Acceptance criteria

- If the results of the test are unsatisfactory, the laminar flow system cannot be validated and the rest of the validation tests should not be carried out until a satisfactory operation has been reached. Otherwise, the system is valid and can be certified.
- Should corrective changes be necessary, the changes are made and recorded, and the validation process repeated.
- A turbulent air flow should not be present at each area location.

Frequency

Initial validation: once
Revalidation: annually

12. Recovery Test

Purpose

To determine the capabilities of the system to recover from internally generated contamination

Equipment

Visual smoke generator, particles counter, and hot wire anemometer

Method

- With smoke generation output tube located at a predesignated location, generate smoke for 1 to 2 min and shut off.
- Wait 2 min and then advance the sample tube of the particle counter to a point directly under the smoke source and at the level of the work zone. Record the particle count. If it is not 100 per cubic foot or less, repeat the test with the wait interval increased in increments of 0.5 min until counts are less than 100 per cubic foot.
- Repeat for all grid areas, recording recovery time for each area.

Acceptance criteria

The recovery time should be not more than 2 min.

Frequency

Initial validation: once
Revalidation: annually

13. Particle Dispersion Test

Purpose

To verify the parallelism of air flow through the work zone and the capability of the clean room to limit the dispersion

Equipment

Visual smoke generator, particle counter, and hot wire anemometer

Method

- Perform this test after completion of the air velocity uniformity tests.
- Divide the work zone into 2 × 2 ft grids of equal area.
- Set up the smoke generator, with outlet tube pointing in the direction of air flow and located at the center of a grid area at the work zone entrance plane.
- If smoke is introduced with air pressure, adjust it to provide a smoke outlet velocity equal to the room air velocity at that point.
- Operate the particle counter with the sample tube at the normal work level and at a point remote from the smoke source. Verify that the counter indicates particle concentrations less than 200 particles of 0.5 μm or greater.
- Move the sample tube in toward the smoke source from all directions at this level to the point where particle counts show a sudden and rapid rise to high levels (10^6 per cubic foot). This defines the envelope of dispersion away from the smoke source and demonstrates the airflow parallelism control of the room.
- Repeat for all grid areas. Prepare a diagram showing grid areas and corresponding dispersion envelopes.

Acceptance criteria

The degree to which dispersion away from the smoke source is confined and the regularity of the pattern (indication of directional drift in one direction) is a matter of the configuration of the line. It is recommended that dispersion should not extend beyond 2 ft rapidly from the point of smoke source, i.e., at 2 ft from the generation point, the particle count should be less than 100 per cubic foot of the 0.5 μm size and larger.

Frequency

Initial validation: once
Revalidation: annually

14. Airborn Microbial Test

Purpose

To determine the airborn microbial contamination level

Equipment

Solid surface impactor with a rotating collection surface or staged plates (Anderson-Slite)

Method

After proceeding with calibration and indications given in the operating manual, proceed as follows:

- Aseptically prepared collection plates are placed in the sampling apparatus. Petri dishes used must be sterilized prior to filling. Verify the adequacy of petri dish dimensions so that the operational characteristics are maintained according to the manufacturers specifications. Plastic petri dishes are not recommended because static changes are likely to be present in plastic that will reduce the collection efficiency.
- Any general purpose, solid bacteriological medium, such as trypticase soy agar or blood agar, can be used. Selective media are not recommended, since they inhibit the repair and growth of injured or stressed cells.

- Verify the air sample rate, time, and location of the plate before starting the sampling. Sampling time should be 20 min at every location. After the sampling is complete, remove the collection plates, cover, and identify them. Identification should include date, sampling instrument number, location, and plate number.
- Plates are then taken to an incubator and maintained inverted, to prevent condensation drop for a period of 18 to 24 h at 35°C.
- After incubation, the number of colonies on each plate is counted, using a standard bacterial colony counter.

Acceptance criteria

The following table provides the Federal Standard 209 E for cleanliness level:

Table 8 Air Cleanliness Guidelines in Colony-Forming Units (cfu) in Controlled Environments (Using a Slite-to-Agar Sampler or Equivalent)

Class			
SI	*U.S. Customary*	*cfu per cubic meter of air*	*cfu per cubic feet of air*
M3.5	100	Less than 3	Less than 0.1
M5.5	10,000	Less than 20	Less than 0.5
M6.5	100,000	Less than 100	Less than 2.5

Establishment of sampling plan and sites

- During initial start-up or commissioning of a clean room or other controlled environment, specific locations for air and surface sampling should be determined. Consideration should be given to the proximity to the product and whether air and surfaces might be in contact with a product or sensitive surfaces of the container-closure system. Such areas should be considered critical areas requiring more monitoring than nonproduct-contact areas. In a parenteral vial filling operation, areas of operation would typically include the container-closure supply paths of opened containers and other inanimate objects (e.g., fomites) that personnel routinely handle.
- The frequency of sampling will depend on the criticality of specified sites and the subsequent treatment received by the product after it has been

aseptically processed. Table 9 shows suggested frequencies of sampling in decreasing order of frequency of sampling and in relation to the criticality of the area of the controlled environment sampled.

Table 9 Suggested Frequency of Sampling on the Basis of Criticality of Controlled Environment

Sampling Area	*Frequency of Sampling*
Class 100 or better room designations	Each operating shift
Supporting areas immediately adjacent to Class 100 (e.g., class 10,000)	Each operating shift
Other support areas (class 100,000)	Twice/week
Potential product/container contact areas	Twice/week
Other support areas to aseptic processing areas but nonproduct contact (class 100,000 or lower)	Once/week

Frequency

Initial validation: once
Revalidation: annually

15. Surface Bioburden Test

Purpose

To determine the microbial contamination level on surfaces

Equipment

Cotton swabs or RODAC plate (nutrient agar culture medium)

Method

Take the swab stick from the tube and gently swab 25 cm^2 of area (walls, floor, equipment, etc.) and place back in tube containing 5 mL sterile buffer and test or incubate per official procedure.

This technique is to be used after decontamination procedures. Agar media left on the surface could represent a problem. Therefore, immediate decontamination procedures should follow sampling. Identify every plate, indicating the exact location where the sample was taken. Room landmarks should be noted for present and future reference.

Acceptance criteria

The maximum number of colonies per square foot should not exceed the limits in Tables 10 and 11.

Table 10 Surface Cleanliness Guidelines of Equipment and Facilities in cfu Controlled Environment

Class		*cfu per Contact Plate**
S.I	*U.S Customary*	*Gloves*
M3.5	100	3
M5.5	10,000	5
		10 (floor)

* Contact plate areas vary from 24 to 30 cm^2. When swabbing is used in sampling, the area covered should be greater than or equal to 24 cm^2 but no larger than 30 cm^2.

Table 11 Surface Cleanliness Guidelines in Controlled Environments of Operating Personnel Gear in cfu

Class		*cfu per Contact Plate**	
S.I.	*U.S. Customary*	*Gloves*	*Personnel clothing and garb*
M3.5	100	3	5
M5.5	10,000	10	20

* See Table 10 above (*).

Frequency

Initial validation: once
Revalidate: annually

16. Air Pressure Control Test

Purpose

To demonstrate that air pressure is maintained in critical and adjacent areas as specified in the HVAC design according to the specification limits

Equipment

Inclines pressure gauge with resolution of 0.01 in. water

Method

- All HVAC and laminar flow systems are to be in continuous operation when performing these tests.
- To avoid unexpected changes in pressure and to establish a baseline, all doors in the sterile facility must be closed and no traffic is to be allowed through the facility during the test.
- Pressure readings are taken with the high and low pressure tubing at the following locations: (refer to each room's diagram).

Acceptance criteria

- The minimum positive pressure differential between the room and any adjacent area of less clean requirement should be 0.05 in. water (12 Pa), with all entryways closed. When the entryways are open, the blower capacity should be adequate to maintain an outward flow of air to minimize contamination migrating into the room.
- A filtered air supply should maintain a positive pressure relative to surrounding areas under all operational conditions and flush the area effectively. Final filtration should be at or as close as possible to the point of input to the area. A warning system should be included to indicate failure

in the air supply and an indicator of pressure difference should be fitted between areas where the difference is critical.

- Aseptic processing areas should have a positive pressure differential relative to adjacent less than clean areas. A pressure differential of 0.05 in. water (12 Pa) is acceptable.
- The sterile filling and sealing rooms are kept under higher air pressure than adjacent rooms, while the remaining clean rooms (in which containers, raw materials, or other parts of the finished product are processed) are under greater air pressure than the surrounding nonsterile environment. Such pressure differentials help minimize the inward flow of airborn contaminants.

17. Air Changes

Purpose

To demonstrate that an adequate number of air changes are maintained within the classified rooms per HVAC design

Method

Determine the number of air changes per hour in the aseptic area by calculation from the inlet air flow and the area volume.

Requirements

More than 20 air changes per h should be achieved.

Frequency

Initial validation: once
Revalidation: annually

REASONS FOR REVISION

Effective date: mm/dd/yy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.40 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Microbiological Monitoring of Areas Used for Production of Solids, Semi-Solids, and Liquids**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

SUBJECT: Microbiological Monitoring of Areas Used for

No.	Section	Pages	Initials/Date

SOP No. Val. 600.40 **Effective date: mm/dd/yyyy**

Approved by:

Production of Solids, Semi-Solids, and Liquids

PURPOSE

To define the procedure for the monitoring of surfaces

RESPONSIBILITY

The quality control manager is responsible for following the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Monitoring Surfaces

Surfaces in areas of production of solids and liquid for oral use are tested periodically to indicate the adequacy of cleaning and sanitizing procedures, and to detect contamination caused by personnel. The samples are taken routinely under normal working conditions. The techniques used are as follows:

Contact plates

The test is performed with RODAC plates (replicate organisms detecting and counting). These plates contain a solid culture medium in a specially designed petri dish (diameter 65 mm). The convex surface extends above the walls of the plate. The surface of the medium is pressed against the test surface, transferring the microorganisms to the nutrient agar. Incubation colonies are formed wherever microorganisms were present on the tested surface. Disinfect the area of contact after sampling.

Swabbing

Swabs (sterile, moistened, alginate wool tips) are used for sampling discrete surfaces areas or difficult-to-reach locations. Subsequent direct inoculation on solid media or membrane filtration of the swab rinsing fluid can be used to cultivate the microorganisms.

SOP No. Val. 600.40 **Effective date: mm/dd/yyyy**

Approved by:

The use of contact plates is the recommended technique. The RODAC plate method is the simplest, but it is useful only for flat surfaces. Swab samples afford examination of corners, crevices, and other area inaccessible to RODAC plates.

Materials

RODAC dish (Falcon) code No. 1034, containing a culture medium made to the formula as indicated in the USP should be used. This medium contains approximately 0.7 g/1 lecithin and 5.0 g/1 polysorbate 80, two commonly used neutralizers, to inactivate residual disinfectants on the spot where the sample is collected.

Normal petri dishes are not suitable because the lid will make contact with the convex surface of the agar, which for this test must protrude above the brim of the dish.

Alcohol 70%, sterile (0.2 μm filtered) should be used.

Technique

- All handlings should be performed in a way as aseptic as possible.
- Prepare the culture medium according to the USP and fill the medium into sterile RODAC dishes to the brim to obtain a convex surface. Extreme care should be taken to prevent the formation of air bubbles and to prevent the medium from overflowing (if either occurs, these plates should be discarded). Allow the plates to solidify. Preincubate the plates at 35°C for 24 h and then at 25°C for 24 to 48 h.
- Carefully introduce the RODAC dish at the area to be tested and remove the lid. Carefully but firmly press the plate with a slight rolling movement onto the surface being examined and hold for a few seconds without moving it. Remove the dish and replace the lid immediately. The tested area is then to be cleaned and disinfected with 70% alcohol.

- First, incubate the plates at 35°C for 48 h and subsequently at 25°C for another 5 days. Count the formed colonies.

  Sampling locations and number of samples: per room, 1 to 3 representative samples from the walls in a height of 1 to 2 m.

SOP No. Val. 600.40 **Effective date: mm/dd/yyyy**
Approved by:

Interpretation of results

The contamination rate of the area is stated as the number of viable microorganisms per 100 cm^2. The area of a standard RODAC dish is 25cm^2.

Requirements

ð 200 CFU/100 cm^2 under working conditions

Actions in case of defect

An evaluation of the reasons for the contamination and the performance of the cleaning procedure should take place. Furthermore, an additional cleaning may be necessary.

Frequency

Twice a year

1.1 Monitoring equipment surfaces

For the procedure, requirements, actions in case of defect, and frequency, see Section 1.1. Sampling locations and sample number: the locations have to be established in-house, three samples per equipment.

1.2 Monitoring floors

For procedure, action in case of defect, and frequency, see Section 1. Sampling locations and number of samples: per room, one to three representative samples scattered over the total floor space.

Requirements

ð 500 CFU/100 cm^2 under working conditions

2. Monitoring Air

Procedure

Although the microbiological quality of the air can be estimated by various methods, the RCS method is recommended. The biotest RCS (centrifugal air sampler) collects

viable airborn particles in combination with the principle of agar impaction.

As air is drawn towards the impeller blades, it is subjected to centrifugal acceleration. Viable microorganisms in the sampled air are impacted at high velocity onto the surface of the agar strip. After sampling, the strip containing the nutrient is incubated at 30 to 35°C for days. The colonies can be enumerated by visual examination and the results should be recorded. Sampling time with the RCS should be 2 min (= 80 1 air).

Sampling locations and number of samples: per room, one sample taken in the middle of the room in a height of between 1 and 2 m.

Requirements

ð 200 CFU/m^3 under rest conditions
ð 400 CFU/m^3 under working conditions

Actions in case of defect

An evaluation of the reasons for the contamination should occur. A discussion of the results with the technical services department should take place.

Frequency

Twice a year

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.50 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Efficiency Testing for Disinfectants**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.50 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Efficiency Testing for Disinfectants

PURPOSE

To ensure that disinfectants used to clean the facility are effective

RESPONSIBILITY

It is the responsibility of the quality control manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

Definitions

Sanitizer is specifically defined as any chemical that kills microbial contamination in the form of vegetative cells.

Frequency

The *membrane filtration technique* is used once, prior to the introduction of a new disinfectant within the production department.

The s*urface testing technique* is used prior to any changes in the recommended procedure for evaluating its effectiveness on surfaces to be treated and demonstrating activity against contaminated for various contact times.

Equipment

Incubator 23°C and 32°C,

Standard loop

Membrane filtration unit

Vortex

Cultures

- *P. aeruginosa* ATCC 9027
- *E. coli* ATCC 8739
- *S. aureus* ATCC 6538
- *C. albicans* ATCC 10231
- *B. subtilis* var. *niger* ATCC 9372
- *A. niger* ATCC 16404
- Organisms recovered from plant environment

Sterile distilled water

Sterile screw-cap test tubes
Sterile buffer (dilution blanks)
Poured, sterile soybean casein digest agar (SCDA) petri plates
Poured, sterile potato dextrose agar (PDA)
Sterile pipettes, 25 ml, 10 ml, and 1 ml sizes
Sterile forceps
Sterile membrane filtration unit with 47 mm diameter
0.45 μm pore size
Solvent resistant membrane
Sterile, empty petri plates
Sterile, empty containers of ≈ 200 ml volume
Sterile Ca alignate swabs
Brushed stainless steel strips

PROCEDURE

1. Preparation of Challenge Inocula

Except for *B. subtilis,* streak slants (one or more) of appropriate agar (PDA for *C. albicans* and *A. niger,* SCDA for all others) with specific microorganisms from stock culture. Incubate at 30 ± 1°C for 48 to 72 h, except *A. niger*, which may need extended incubation for good sporulation.

Harvest cells by withdrawing Ý 3 ml of buffer from a 10 ml tube and pipetting onto a slant. Using a pipette, gently scrape the slant to suspend the cells. Withdraw the suspension and transfer it back into the tube for buffer.

Do a microbial plate count of suspensions as necessary and dilute with appropriate buffer to obtain final working suspensions of 10^4 to 10^5 CFU/ml.

1.1 Sample preparation

Dilute the tested sanitizer to the use dilution (according to the recommendations of the manufacturer). Prepare further dilutions of the use dilution (10^{-1} or 10^{-2}). Adjust pH to 6.8 to 7 and attempted at 30°C.

Membrane filtration technique

In duplicate, pipette 10 ml of each of the dilutions into separate sterile test tubes (changing pipettes after each transfer). Provide 12 tubes for each dilution and time interval, as there are six challenge organisms. Using a calibrated pipette, inoculate each separate complement of dilution tubes with different challenge microorgan-

isms, using an inoculum volume of 0.1 ml. Shake well and let stand at 30°C. For positive controls, inoculate appropriate duplicate dilution blanks with challenge microorganisms.

Assay at 5, 10, and 15 min intervals. Perform the entire operation in a laminar-flow hood. At the conclusion of each challenge time interval, pass the contents of each tube through a separate membrane filter unit. Wash each membrane with 3 × 100 ml portions of neutralizer solution. Remove each membrane from its filter unit and place face up on the surface of appropriate poured agar plate. Positive controls must be tested last.

Incubate all plates at 30 ± 1°C for 48 to 72 h. Examine each day for signs of growth of the inocula. Count and record.

Growth promotion controls: control membranes must show confluent growth of each of the challenge microorganisms.

Surface testing technique

Clean each polished stainless steel strip (or any surface to be treated) with detergent and rinse well with distilled water. Spot-inoculate four steel strips with a known volume of a culture for each dilution of sanitizer. Each strip should contain approximately 100 organisms. Allow drying for 30 min at room temperature. After drying, immerse two strips in sanitizer solution to be tested. Allow the contact for 5, 10, or 15 min.

Repeat this for each test organism. For positive control use sterile DW instead of sanitizer solution. For negative control use sterile strips. Swab each strip thoroughly with a premoistened Ca alginate swab and place in *Lecithin broth* (or other suitable neutralizer). Vortex for 30 sec, then perform the usual pour plate method.

Acceptance criteria

The recommended disinfectant solution must be able to establish a 5-log reduction of each of the inoculated microorganisms within 5 min.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.60 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Drinking Water**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.60 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Drinking Water

PURPOSE

To describe the acceptable standard of drinking water

RESPONSIBILITY

It is the responsibility of the validation manager and concerned departmental managers to maintain consistent quality of drinking water. The QA manager is responsible for SOP compliance.

PROCEDURE

Drinking water serves as the starting material from most forms of water covered by compendial monographs and plays an important role. The source of drinking water is either municipality or privately drilled wells. According to the USP, "Drinking water may be used in the preparation of USP drug substances but not in the preparation of dosage forms, or in the preparation of reagents or test solution." The major concern is the microbial content of drinking water.

1. Microbiological Investigation

1.1 Total aerobic viable count

Procedure

Method:	Pour plate
Minimum sample size:	1 mL
Culture media:	Plate count agar
Incubation time:	47 to 72 h
Incubation temp.:	30 to 35°C

Requirements

Total aerobic microbial count: ð 500 CFU/ml (grown at 30°C)

1.2 E. coli *and coliforms*

Test for the presence of *E. coli* and coliforms:

Sample volume:	At least 100 ml
Test method:	Membrane filtration, place the membrane filter into 50 ml of lactose broth 1%
Incubation temperature:	35 to 37°C
Incubation time:	20 to 28 h
Observation time:	40 to 48 h
Provisional inspection:	Suspension for *E. coli* and coliforms if gas or acid formation is observed.
Further identification:	Transfer to Endo agar
Incubation temperature:	35 to 37°C
Incubation time:	20 to 28 h

Requirements

Total *E. coli*	Not detectable in 100 ml
Total coliforms	Not detectable in 100 ml

Frequency of microbiological investigation

The drinking water quality shall be monitored and the results should be evaluated to establish a routine monitoring program.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.70 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Purified Water**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.70 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Purified Water

PURPOSE

To describe the acceptable standard for purified water USP

PROCEDURE

1. Definition

Purified water is water obtained by a suitable process. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or comparable regulations of the European Union or Japan. It contains no added substances.

2. Complying with Monograph (e.g., USP XXIV) Requirements

Since no added substances are allowed, if chloride and ozone are applied in the preparation of purified water, the following should be ensured: tests for total organic carbon and conductivity apply to purified water produced on site for use in manufacturing. Purified water packaged in bulk for commercial use elsewhere shall meet requirements of all tests under sterile purified water, except labeling and sterility, per USP XXIV.

Frequency

In continuous production facilities (minimum 10 working days), water should be sampled at least weekly.

From noncontinuous production facilities water must be sampled from each production batch.

Acceptance criteria

Conductivity:1.3 ms/cm at 25°C
TOC:<500 ppb

3. Microbiological Investigations

Requirements

Total aerobic viable count: Establish in-house requirements

Action limit:	100 CFU/ml
Total *E. coli*:	Not detectable
Total coliforms:	Not detectable

Frequency

Samples for microbiological investigations must be tested within 6 hours of sample collection. For continuous production facilities (minimum 10 working days) water should be sampled at least weekly. For noncontinuous production facilities, water must be sampled prior to each production batch.

Acceptance criteria

The requirements of USP XXIV are met.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.80 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Water for Injection**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.80 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Water for Injection

PURPOSE

To provide the guideline for the validation of water for injection (WFI) to be maintained in compliance with USP 24 monograph

RESPONSIBILITY

It is the responsibility of the quality control, validation, and technical services managers to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Definition

The USP 24 monograph states, "Water for injection is water purified by distillation or reverse osmosis. It contains no added substance."

The British Pharmacopia states, "Water for injections is sterilized, distilled water, free from pyrogens. It is obtained by distilling potable water, purified water or distilled water.…"

Although the USP allows generation of water for injections by use of reverse osmosis, this is not in line with the FDA opinion. Therefore, water for injections should always be generated by distillation.

To fulfill the monograph requirements with respect to the maximum allowed pyrogen content of about 0.25 endotoxin units per ml, the water used for distillation must be of very high microbial quality.

Prerequirement for water used for generation of water for injection is that it must comply with the microbiological requirements stated under Drinking Water, SOP No. Val. 600.60.

2. Chemical Investigation

Requirements

Complying with the monograph requirements (USP 24)

Frequency

Once per week

SOP No. Val. 600.80 **Effective date: mm/dd/yyyy**
Approved by:

Acceptance criteria

Conductivity: <1.3 ms/cm at 25°C
TOC: <500 ppb

3. Microbiological Investigation

3.1 Pyrogens

Requirements

Endotoxin content: ð 0.25 EU/ml

3.2 Total aerobic viable count

Requirements

- ð 10, CFU/100ml, plus a complete absence of pseudomonas and *e. coli*. Frequency of microbiological investigations. Samples for endotoxins and total aerobic viable count should be investigated within 8 hours after collection.
- Water for injection used for other purposes (e.g., washing and rinsing product components and equipment) should be tested for pyrogens and aerobic viable count at least weekly.
- Water for injection used for product compounding should be tested each day for pyrogens and aerobic viable count.

4. Storage of Water for Injection

Water for injection is not allowed to be retained in the system for longer than 24 h unless it is maintained at a minimum temperature of 85°C in a continuously circulating loop.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.90 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Validation of a Water System**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.90 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Validation of a Water System

PURPOSE

To provide the guideline to validate the water system for the pharmaceutical industry

PROCEDURE

The following types of water systems are preferable for use in the pharmaceutical industry:

Purified Water — Purified water is described in the USP 24 as "water obtained by distillation, ion-exchange treatment, reverse osmosis, or other suitable process. It is prepared from water complying with the regulations of the Federal Environmental Protection Agency with respect to drinking water. It contains no added substances."

Water for Injection — Water for injection is described in the USP 24 as "water purified by distillation or reverse osmosis. It contains no added substances." See Tables 1 and 2.

Table 1 USP 24 Chemical Requirements for Purified Water and Water for Injection

Component	*Purified Water*	*Water for Injection*
Conductivity	< 1.3 µS/cm at 25°C	< 1.3 µS/cm at 25°C
TOC	< 500 ppb	< 500 ppb
Pyrogens (EU/ml by LAL)	—	< 0.25 EU/ml

The validation process is divided into the following stages:

- Prevalidation of the full system
- Construction validation
- Start-up validation
  - Functional operation
  - Procedures verification

Table 2 Microbiological Levels for Compendial Waters in CFU/ml

	Purified Water	*Water for Injection*
Pyrogen	—	< 0.25 EU/mL
Sterility	< 100 cfu/mL	< 10 cfu/100mL
Pathogens	Absent	Absent

  - Quality limits
- System qualification
- Approval of the system for use

After finishing the above stages, a monitoring program should be established.

1. Prevalidation of the Total System Design

- Flow schematics for the designed (layouts) water system showing all of the instrumentation valves, controls, and monitors, numbered serially
- Complete description of the features and function of the system
- Specifications for the equipment (storage tanks, heat exchangers, pumps, valves and piping components) to be used for water treatment and pre-treatment
- Detailed specifications for sanitary system controls
- Procedures for cleaning the system, both after construction and ongoing
- Sampling procedures to monitor water quality and the operation of the equipment

2. Construction Validation

Construction validation shall be conducted to avoid irreparable damage due to the use of unsuitable techniques.

- System components and construction materials

Major equipment, such as distillation unit and WFI storage tanks, should be inspected before it is shipped from the supplier to verify operational function and compliance with specifications.
Equipment should be examined immediately upon arrival.

- Verification of construction procedures
  List of procedures should be established and reviewed.
- Construction completion
  - As-built drawing completed and approved
  - Checking of dead legs
  - Checking for proper slope for draining
- Pressure testing of the system
  During construction it is impossible to avoid contamination of the piping with airborn ferrous particles from installation of structural steel and carbon steel piping components. If the stainless steel is kept dry, this may not be a problem. If the stainless steel piping is allowed to become wet, e.g., from a hydrostatic pressure test, the system should be tested with dry, oil-free air. If water is used, then provision must be made to thoroughly clean the system immediately after the hydrostatic pressure test.
- Post-construction cleaning
  Flush the system to remove dust and major debris. Recirculate detergent or alkali cleaner at elevated temperatures to remove grease or oil. Flush and recirculate an acid at elevated temperatures to dissolve any ferrous particles in the system. Flush with water of the same quality as will be used in service. The cleaning procedure shall be validated by making chemical analysis of surface residues.
- System functional checkout
  The instrumentation and controls should be adjusted and calibrated to ensure proper monitoring and control of functions.

3. Start-Up Validation

- Functional operation:
- Verify consistency of operation of equipment and controls by repeated cycles of start-up and shutdown of all equipment and controls. Simulate manual, automatic, and emergency conditions. Verify suitability of design under all conditions.
- Establish preliminary monitoring program to ensure validation conditions, specificity, and calibration maintenance.

- Equipment logs, filter logs, and monitoring records must be properly documented.

SOP No. Val. 600.90 **Effective date: mm/dd/yyyy**

Approved by:

4. Quality Limits

- Verify that the water produced by the system meets all the predefined chemical, microbiological, and pyrogenecity specifications.
- Verify sanitization temperature and pressure by steam.
- Establish target and alert limits for chemical and microbial quality.

5. System Qualification

Once the validation report is completed and approved, a qualification run should be made with the system to verify that validations will be duplicated in normal operation.

6. Approval for Use

If all requirements have been satisfied and all validation documents have been approved, the quality assurance managers may release the water system for production use.

7. Microbiological Investigations: Water for Injection

7.1 Viable count

Procedure

Take 100 ml sample from each tap point, one before the start of the production, and the second at the middle of the working day. An equivalent sample taken from the last sample point of the generating device and from the first sample point of the returning water should be used as a reference.

Requirements

Viable count ð 10 CFU/100 ml for each sample

SOP No. Val. 600.90 **Effective date: mm/dd/yyyy**
Approved by:

Frequency

Preproduction and concurrent validation: three working days a week (e.g., Monday, Wednesday, Friday)
Ongoing validation: each tap point once a week
Reference sample each working day

7.2 Pseudomonads and coliform

Procedure

Take 300 ml sample from the last sample point of the generating device and from the first sample point of the returning water.

Requirements

Pseudomonads/Coliform: 0 CFU/100 ml for each sample

Frequency

Each last day in the work week.

7.3 Pyrogens

Procedure

Take 10 ml sample from each tap point. An equivalent sample taken from the last sample point of the generating device and from the first sample point of the returning water should be used as a reference.

Requirements

ð 0.25 EU/ml for each sample

Frequency

Preproduction and concurrent validation: each tap point, once a week
Ongoing validation: each tap point, once a month

SOP No. Val. 600.90 **Effective date: mm/dd/yyyy**
Approved by:

8. Chemical Investigation

8.1 Investigation according to the pharmocopias (USP 24)

Procedure

From the last sample point of the generating system and from the first sample point of the returning water a sample of 1 l from each must be taken, at the same time, at the beginning of the working week and at the moment when water is first pumped through the distribution network circuit.

Requirements

Fulfilling of the pharmcopia requirements (USP 24)

Frequency

Prevalidation and concurrent validation: once a week
Ongoing validation: once a month

8.2 Quick limit-test for an indicator ion

Chemical investigations are rather time consuming. Therefore an indicative test, in which the indicator ion is the chloride ion (Cl^-), to get information about the status of the water system quickly.

Procedure

After 3 min of prerinsing, a sample of 50 ml is taken from the last sample point of the generating device and from the first sample point of the returning water.

Limit Test

To 10 ml of the water sample, 1 ml of dilute nitric acid and 0.2 ml of silver nitrate solution are added.

SOP No. Val. 600.90 **Effective date: mm/dd/yyyy**
Approved by:

Used reagents: Dilute nitric acid
Contains about 12.5% M/V of HNO3
Silver nitrate solution
A 1.7% M/V solution

Requirements

The test solution should show no change in appearance for at least 15 min.

Frequency

Concurrent validation: Daily
Ongoing validation: At the first working day of the week

9. Physical Investigation

9.1 Conductivity

For monitoring system performance, a conductivity meter should be present or built in the water system for continuous measurement of the conductivity. If this device is not available, samples must be taken manually and measured respectively.

Procedure

After prerinsing for 3 min, samples of about 50 ml should be taken.

Requirements

Normally, for pharmaceuticals, the requirement is ð 1 µS/cm, but this depends on the local terms of reference.

Frequency

Concurrent validation: at the start and in the middle of each working day
Ongoing validation: at the start of each working day

9.2 pH

In purified water it is hardly possible to measure the pH.

Procedure

After prerinsing for 5 min, samples of about 50 ml should be taken from the sample point of the returning water, after which a few drops of a saturated potassium chloride solution should be added. Then pH can be measured.

Requirements

The pH for each sample should be between 5 and 7 (for information only).

Frequency

Concurrent validation: at the start and in the middle of each working day
Ongoing validation: at the start of each working day

9.3 Temperature

The temperature within the system plays an important role from a microbiological point of view.

Requirements

For water prepared by distillation and to be used as water for injection, the requirement is > 80°C. Systems with built-in reverse osmosis modules and ultrafiltration devices must comply with the supplier specification.

9.4 Pressure testing

The pressure within the system is an essential factor for functioning of the water generating and distribution system. Therefore pressure prior to and after subunits of the system should be registered continuously.

SOP No. Val. 600.90 **Effective date: mm/dd/yyyy**
Approved by:

Requirements

Should meet supplier specification

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.100 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Oil-Free Compressed Air System**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.100 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Oil-Free Compressed Air System

PURPOSE

To describe guideline for the validation of the oil-free compressed air system

RESPONSIBILITY

It is the responsibility of the technical service manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Types of Compressed Air Systems

Two types of compressed air systems are found in an aseptic manufacturing facility:

- An instrument air system normally consists of conventional oil-lubricated compressors and is used for operating instruments and machinery where no contact with the product or product environment exists.
- An oil-free compressed air system is normally used in aseptic areas and often may be involved with product contact.

The system consists of an oil-free compressor, drier, storage tank, and distribution system. The validation process consists of installation qualification, operational qualifications, and actual validation testing of the operational system.

2. Installation Qualification of Oil-Free Compressor

- Verify and document specifications on purchase order against actual delivery.
- Check and document that no oil or other lubricant is used in the compressor.
- Verify and document that all required utilities are connected properly.
- Verify prestartup procedures.
- Document calibration performed.

3. Installation Qualification of Compressed Air Storage Tank

- Check and document that the materials of construction are as specified.
- Check storage tank for adequate capacity.
- Perform and document pressure hold test to determine that the leak rate is within specification.
- Perform and document the cleaning procedures after installation.
- Check and document all pressure ratings.
- Calibrate all critical pressure gauges and control sensors on the storage tank.

4. Installation Qualification Distribution System

- Check and document that the materials of construction are as specified.
- Follow the drawings of the system to trace the actual constructed system and make an "as built" drawing.
- Pressure test the system and document.
- Clean the system with detergent or solvent and document the procedures.
- Label all piping and components.

5. Operational qualification

5.1 Chemical investigation

Sampling procedure

Materials: Gas bag, 3.8 liter capacity (rubber bladder), with stopcock
Rubber tubing of appropriate size
Aluminium foil squares (10 × 10 cm)

Sampling: Use method as recommended by the manufacturer with all safety precautions.

6. Identification

Procedure

Use gas chromatograph for the identification of compressed air. For comparison, an air standard should be used.

Requirements

The identity test for oil-free compressed air must show a chromatogram with no additional peaks other than those obtained with the air standard.

Frequency

Initial validation: once at all critical supply points
Revalidation: once at all critical supply points

7. Moisture Content

Procedure

Use dew-point meter to determine moisture content from critical supply point

Requirements

Moisture content measurements at supply point should not be greater than in-house specification

Frequency

Initial validation: one test per day for the first 30 days of the operation of the system from a different location each day. The test program should cover all critical supply points.
Revalidation: one test from each critical supply point per month.

8. Oil Content

Procedure

Use oil indicators.

Requirements

Oil content of oil-free compressed air should be not more than 0.01 ppm.

Frequency

Initial validation: one test per day for the first 30 days of the operation of the system from all critical supply point locations each day.

Revalidation: one test from each critical supply point

9. Nonviable Particle Count

Procedure

The outlet of the supply point is opened and purged for 5 min. Adjust to a volume flow of about 30 l/min. The particle counter is connected to the outlet; at the maintained flow a minimum volume of 90 liters is monitored. Each supply point should be investigated in the same way.

Requirements

No requirements; for information only

Frequency

Initial validation: once for each supply point.
Revalidation: every 3 months

9.1 System supply reliability test

Document the system pressure twice a day over a period of about 30 working days. The data generated should be compared with the specifications of the system.

10. Certification

The system can be certified after successful execution and documentation of above tests.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.110 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Nitrogen Distribution System**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.110 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Nitrogen Distribution System

PURPOSE

To describe the procedure for validation of the nitrogen distribution system to be installed and operated per specification

RESPONSIBILITY

The technical services manager is responsible for following the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification of Gas Generator

- Check availability of electrical supply (voltage, amperage, frequency).
- Chilled water (supply volume, temperature)
- Compressed air (pressure, cubic feet per minute, oil-free)

2. Prestart-up Procedures

- Clean out system to remove construction debris, lubricants, and residue from manufacture.
- Fill all lubricant reservoirs.
- Check all utility connections.
- Test safety device (automatic shutdown and general safety equipment) for proper operation.

3. Calibration of All Critical Gauges and Instrumentation

- Identify and write standard operating procedures for calibration.
- Perform calibration of critical gauges.

4. Operational Qualification

- Verify alarm control.
- Perform calibration requirements identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify all switched and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for the relevant staff.

5. Storage Tank

- Check the storage tank for capacity per specification.
- Check that material and construction conform to specification.
- Conduct a pressure hold test and determine that the leak rate is within specifications.
- Document cleaning procedures done on the tank after installation.
- Calibrate and document all pressure gauges and sensors, both monitoring and controlling.

6. Distribution

- Confirm that the materials of construction and design parameters are per specification.
- Verify the as-built drawings.
- The system should be pressure tested and documented to confirm its integrity.

7. Chemical Investigation

For sampling procedure see SOP No. Val. 600.100, step 5.1, of the guideline for an oil-free compressed air system.

7.1 Compliance with pharmacopial monograph

Procedure

Samples for analysis should be taken from each critical supply point, and meet the official monographic requirement.

Requirements

Results should be in compliance with pharmacopial monograph

USP: 99% pure (nitrogen)
0.001 or less (carbon monoxide content)

Frequency

Initial validation and revalidation: one test from each supply point
Revalidation: every 3 months

7.2 Moisture content

Procedure

Determine the moisture content at critical points. Use dew-point meter.

Requirements

No requirements; for information only (or per in-house specification)

Frequency

Initial validation and revalidation: one test from each critical supply point

8. Physical Investigation

8.1 Nonviable particle count

Procedure

Purge the outlet of the supply point for 5 min. Adjust to a volume flow of about 30 l/min. Connect particle counter to the outlet for sampling. All supply points should be investigated in the same way.

Requirements

No requirements; for information only (per in-house specification)

Frequency

Initial validation: once for each supply point
Revalidation: every 3 months

System supply reliability test

Verify the system pressure twice a day over a period of about 30 working days.

Acceptance criteria

System should meet the specification requirement.

9. Microbiological Investigation

9.1 Viable particle count

Procedure

Purge the outlet of the supply point for 5 min. Adjust to a flow volume of about 30 l/min. Pass the nitrogen through an air sampler provided with a 0.22 μm filter. Sampling time is about 5 min. Perform the procedure twice. One filter should be incubated for anaerobic, the other for aerobic viable count.

Filters used in the system (commonly at point of use) should be included in a routine filter integrity testing program. Establish the life cycle of the filters to maintain the system.

Requirements

No requirements; for information only (per in-house requirements)

Frequency

Initial validation and revalidation: once for each supply point

SOP No. Val. 600.110 **Effective date: mm/dd/yyyy**
Approved by:

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.120 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Clean Steam**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.120 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Clean Steam

PURPOSE

To describe the validation guideline for clean steam

RESPONSIBILITY

It is the responsibility of the utilities manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Steam System

The following types of steam systems are normally found in modern aseptic manufacturing facilities:

- "House steam" consists of a steam generator and distribution system made of either iron or steel, which are both subject to rusting. This system is normally used in applications where contact with product or product contact surfaces does not occur.
- "Clean steam" systems are normally constructed of nonrusting (stainless steel) materials and typically use either distilled or deionized water as feed water; no additives are allowed to be used due to contact with products.

2. Types of Steam Systems

	Plant steam	*Clean steam*
Feed water	Portable, softened, or deionized water	Water for injection (distilled, reverse osmosis) or purified water
Material system construction	Iron or steel or stainless steel	Stainless steel
Use of additives	Yes — hydrazines, amines, etc.	None
Condensate	Commonly reused	May or may not be reused

3. Major Pieces of Equipment

- Deionizer
- Distillation equipment (optional)
- Holding tank
- Steam generator
- Distribution system

3.1 Installation qualification deionizer

- Check unit for conformance to purchase specifications.
- Connect unit to required utilities and verify the correctness of utilities connected.
- Check and document all plumbing connections.
- Calibrate and document that all instrumentation is operating correctly.

3.2 Operational qualification deionizer

- Test that water of appropriate quality (conductivity) is produced by the system using written standard operating procedures.
- Verify that the regeneration system works satisfactorily.
- Verify the adequacy of the ultraviolet light device used for maintaining deionized systems in a sanitary condition.

3.3 Installation qualification distillation equipment

- Document that the distillation equipment received conforms to the purchase specifications.
- Verify the correctness of utilities connections.
- Complete all required prestart-up maintenance procedures (including cleaning).
- Calibrate, check, and document all critical process instrumentation.

3.4 Operational qualification distillation equipment

- Using the written standard operating procedure, start up and run the distillation equipment.

- Check and verify that the water produced by the still conforms to specifications (quality and quantity).

3.5 Installation qualification holding tanks

- Verify and document that the tank conforms to purchase specifications.
- Pressure test the vessel to determine that the leak rate conforms to specifications, then document.
- Ensure that the pressure rating of the vessel conforms to specifications.
- Perform all required cleanout procedures for start-up.
- Calibrate, check, and document all instrumentation systems.

3.6 Operation qualification holding tanks

- Check all instrumentation systems during actual operation and document.
- Check heating system (control) for correct operation.
- Fill tank with distilled water and hold for typical production cycle to determine that the water quality does not change adversely during storage.

3.7 Installation qualification clean steam generator

- Verify and document that the steam generator conforms to purchase specifications.
- Connect the generator to the required utilities; verify and document that they are correctly connected.
- Passivate generator after installation.
- Calibrate, check, and document all critical process instrumentation.

3.8 Operational qualification clean steam generator

- Determine the normal operating parameters of the system.
- Verify and document that all instrumentation and alarms are working correctly.
- Check and document that the steam produced meets quantitative and qualitative specifications. (The steam output should be condensed and then tested against current USP WFI).

3.9 Installation qualification distribution system

- Check and document that materials of construction conform to specifications.
- Using design drawings, verify distribution system to determine that specifications have been met.
- Complete and document the cleaning of the system prior to start-up.
- Pressure test the system under actual production conditions and document the results.

3.10 Operational qualification distribution system

- Test and verify all use points of the system for adequate supply of steam under maximum load or production conditions.
- Steam quality should be tested at use points by condensing steam and condensing current USP, WFI, on the condensate.
- Use points should also be checked to determine that excess condensate is not present under operating conditions.

4. General Sampling Procedure

A condenser is connected to the clean steam supply point. Allow the clean steam to flow through the condenser without coolant flowing through the condenser for approximately 30 min. This will sterilize the condenser and allow it to be cleaned. The sampling bottles, condenser tubing, and fittings must be depyrogenated prior to use. After turning on the coolant, sampling from the lowest point of the condenser can be started. Caution should be observed during the sampling of clean steam, as it is dangerous.

5. Chemical Investigation

Procedure

Chemical investigation is performed according to the pharmacopial monograph, Water for Injection. Take a minimum of three condensate samples (sample volume 1 l each) from each supply point.

Requirements

The acceptance criteria of USP monographs should be met.

6. Microbiological Investigation

6.1 Viable count

Procedure

Take a minimum of three condensate samples (sample volume 300 ml each) from each supply point.

Requirements

ð 10 CFU/100 ml

6.2 Pyrogen test

Procedure

Endotoxin determination is performed according to the bacterial endotoxins test of the USP. Take a minimum of three condensate samples (sample volume 100 ml each) from each supply point.

Requirements

No endotoxins detectable

Frequency

The investigations should be performed at the initial validation and should be repeated after maintenance and repair work on the clean steam system.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.130 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Vacuum System**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.130 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Vacuum System

PURPOSE

To describe the procedure for validation of the vacuum system

RESPONSIBILITY

It is the responsibility of the utilities manager to follow the procedure. The quality assurance manager is responsible for SOP compliance

PROCEDURE

1. Vacuum Systems

Three vacuum systems are commonly used in modern aseptic manufacturing facilities: (1) house vacuum systems, (2) vacuum systems dedicated to lyophilization equipment, and (3) vacuum systems dedicated to autoclaves or other sterilization equipment.

2. Installation Qualification of Vacuum Pump

2.1 Documentation

As-built drawings of the vacuum system within the plant should be available. The vacuum system should be installed in accordance with the set specifications. Records about maintenance repairs and modifications should be filed.

Check and document that the pumps conform to purchase specifications. Connect the pumps to the required utilities and document that the utilities are correct. Tighten flanges and mounts. Fill pumps with oil (if required). Check shock mountings and remove shipping restraints. Calibrate. Check and document all critical process instrumentation.

3. Operational Qualification of Vacuum Pumps

The following tests should be executed with disconnected vacuum-consuming equipment

3.1 Maximum obtainable vacuum

Procedure

Evacuate the system and determine the maximum obtainable vacuum.

Requirements

No requirements; for information only

Frequency

Initial validation and revalidation once. The test should be repeated after maintenance, repairs, and modifications of the system.

3.2 Vacuum hold test

Procedure

Evacuate the system to its maximum obtainable vacuum and then isolate the pump from the system. Monitor the vacuum over a period of 45 min.

Requirements

A closed system should not lose more than 3 to 7 KPa within 45 min of testing. The actual performance of the system will vary depending on the length of the system and the number of valves. Establish acceptance criteria for each individual system under test.

Frequency

Initial validation and revalidation once. The test should be repeated after maintenance, repairs, and modifications of the system.

3.3 Time required for reaching the maximum obtainable vacuum

Procedure

Evacuate the system to its maximum obtainable vacuum and record the time needed for this.

Requirements

No requirements; for information only

Frequency

Initial validation and revalidation once. The test should be repeated after maintenance, repairs, and modifications of the system. Following trials should be performed with connected vacuum-consuming equipment.

3.4 Determination of the worst case load

Procedure

Testing should also be performed using maximum demands on the system to determine the worst case load.

Requirements

No requirements; for information only

Frequency

Initial validation and revalidation once. The test should be repeated when new, additional equipment is connected to the vacuum system.

4. Installation Qualification of Reservoir Tank

4.1 Documentation

Document that the reservoir conforms to purchase specification and invoice. Verify and document that the vessel meets or exceeds the pressure rating (vacuum) specified in the purchase specifications. Perform vacuum hold tests on the tank and document. Acceptance ID tests will vary with the size of the system. A positive pressure test is often done in order to find leaks. Perform and document cleaning procedures used prior to placing the vessel in service. This completes the normal testing done on the tank prior to joining it to the vacuum system.

5. Installation Qualification Distribution System

Check and document that distribution system materials of construction conform to specifications. Using design drawings, determine dimensions and all design features such as filters, strainers, check valves, etc. An as-built drawing should then be created to document the system. All branches of the system should be labeled. Pressure test the system using positive and negative pressure testing (pressure and vacuum hold tests). Complete and document cleaning procedures prior to system start-up. Calibrate all critical gauges, alarms, and automatic controllers.

6. Vacuum System Certification Testing

Test the system under production conditions to determine that it can reproducibly reach the vacuum required within the normal time constraints. The results of the testing should then be documented for future reference.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 600.140 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Validation of an HVAC System**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 600.140 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Validation of an HVAC System

PURPOSE

To provide the guideline for validation of the HVAC system to meet the design qualification requirement and to be capable of operating within established limits and tolerances

RESPONSIBILITY

It is the responsibility of the technical service manager and contractors to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Documentation

Check the quality of materials received against purchasing specifications.

1.1 Scope

The HVAC system, in general, comprises the following elements:

- Design
- Calculation
- Airflow
- HVAC P and ID
- HVAC ductwork and equipment arrangement
- Control P and ID
- Air handling units
- Reheat coils
- Ductwork
- Insulation for HVAC ductwork
- Sound attenuators
- Humidifiers
- Air distribution
- Supply air grills
- Exhaust air grills
- Sand trap

- Motorized dampers
- Round duct dampers
- Diffusers
- Programmable logic controller panel with control unit
- Chillers
- Recirculation pumps
- Valves
- Pressurization unit

The controls involved are generally as follows:

- Air velocity sensor
- Room pressure sensor
- Duct-mounted temperature sensor
- Duct-mounted combined temperature and RH sensor
- Differential pressure switch
- Airflow switch
- On/Off motorized damper actuator
- Two-way modulating valve
- Three-way modulating valve
- Actuator for modulating valve
- Damper actuator

1.2 Documentation

Check that the approved layout is available for reference; verify the intended purpose of the rooms against the standard requirement. For technical information (rooms, activity cleanness class, pressure, temperature, RH, number of air changes and AHUs), prepare a table for reference.

2. Characteristics Checks Performed

The following checks may be performed to assure that the HVAC system meets the requirements specified in the contract.

2.1 General

Verify that formal design criteria have been developed and approved and that the document being checked conforms in all respects to the approved design criteria.

2.2 Specific

Design

1. Duct hangers and supports, in clean areas, are designed to prevent dust collection.
2. Outside intake and exhaust points are filtered with bird screens.
3. Access doors are provided at all in-line devices requiring access (coils, vanes, etc.).
4. Duct work materials are in accordance with design criteria.
5. Air intakes are located as far away as possible from any upwind air exhaust.
6. Process equipment heat loads have been established and reviewed.
7. Locations of laminar flow hoods, biosafety hoods, and exhaust hoods are noted.
8. Directional airflow based on pressure differential is noted along with special exhaust requirements.
9. Pressurization is noted in the form of actual room pressure levels from a common reference point. Reference point is not outdoors (affected by wind).
10. Filtration addresses final filter efficiency and location.
11. Temperature and humidity are listed as design set points with plus and minus tolerances.
12. Inside design criteria include, but are not limited to, temperature, relative humidity, filtration level, minimum air change rate, and pressurization requirements.

Calculations

1. Heating calculations include heat required to raise supply air temperature from summer design point to room temperature plus sufficient heat to offset winter heat loss.
2. Cooling load calculations have been performed on a room-by-room basis. Considerations include motor load, radiation from heated vessels, radiation

from thinly insulated process and utility piping and equipment, electrical loads, and AHU supply fan motors for air handling units.
3. The calculation for the airflow leakage rate for each room is based on the pressure differential established on the design criteria sheet and not on a percentage of supply air.
4. Fan static pressure is calculated.

Air flow diagrams

1. Supply, return, exhaust, infiltration, and exfiltration airflow from each room are shown on airflow diagrams
2. Air flow diagrams for air handling unit components show, in proper sequence, flow measuring stations, reheat coils, location of each filtration level, humidifiers, exhaust fans and other system components.

HVAC P and IDs

1. HVAC, chilled water, and hot water P and IDs are generated independently of process-related systems and have been checked using a P and ID checklist.

HVAC ductwork and equipment arrangement drawings

1. All ducts identify materials of construction, insulation type, and pressure classification.
2. Duct center-line locations are shown from column lines.
3. Sections are provided at any design point not clearly defined.
4. Ductwork is coordinated with other disciplines, especially piping and electrical.
5. Duct work is drawn as double-lined and fully dimensioned duct (including center-line elevation for round duct and bottom-of-duct elevation for rectangular duct).
6. HVAC drawings are detailed.

Control P and IDs

1. Separate control diagrams have been generated for each air handling unit, showing all control devices individually.
2. Control diagrams have been supplemented with sequences of operation and a control valve schedule showing the size and specification for each valve.
3. Control diagrams show coil piping, including valves and line number.

Air handling units

1. Insulation
   - Double-wall construction sandwiching insulation between two metal panels or single-wall construction with external insulation is used.
   - Insulation has not been placed on the inside of the air supply ducts.
   - Check compliance with all relevant drawings.
   - Check physical appearance.
   - Check positioning.
   - Check leveling.
   - Check piping connection with pump and valve.
   - Check bolt tightness in section joints.
   - Check denting on coil fin.
   - Check free rotation of impeller.
   - Check that all components of AHU have been installed per manufacturer instruction.
   - Check belt drive alignment.
2. Filters
   - Air handling unit has been provided with prefilters two inches thick at a minimum and medium efficiency cartridge or bag filters.
   - Check compliance with all relevant drawings and check physical appearance.
   - Check complete cleanliness of filter casing.
   - Check gasket and clamp.
   - Check correct air flow direction.
   - Check proper mounting.
   - Check the serial number and relevant test certificate.
3. Fans

- Fans are belt drive with variable-pitch drives for 25 HP or less and fixed-pitch drives for drives above 25 HP.
- Air handling unit fans are able to modulate air flow by using inlet vanes, discharge dampers, or variable speed drives.
- Fan motors are sized 25% above brake horsepower.

4. Sand traps

   If the sand traps are used due to the climatic conditions of the area, the following checks shall be performed on fan:
   - Check overall cleanliness.
   - Check all components, bolts, and fixing, and secure.
   - Check physical damage to casings, impeller, drives.
   - Check alignment of pulleys and couplings.
   - Check belt tension and match.
   - Check inlet guide vanes over full range of movement.
   - Check anti-vibration mountings, free to vibrate.
   - Check impeller, free to rotate.
   - Check for abnormal noise in bearings on free rotation.
   - Check for grease nipples on fan and motor bearings.
   - Check blanked off temperature nipple on bearings.
   - Check drive guards with speed measuring openings.
   - Check inlet protection guard.
   - Check flexible connections.
   - Reinstall drive guard.
   - Check motor type to specification.
   - Check power wiring of motor.
   - Check air flow direction.
   - Check tag number and manufacturer's ID plate.
5. Coils
   - Handling unit coils have no more than eight fins per in. and are no more than six rows in depth.
   - Coils are properly oriented.
   - Fins are continuous and flat (noncorrugated).
   - Coils are piped to achieve air and water counterflow.
   - Coils are spaced a minimum of 24 in. apart.
   - If cooling capacity requires more than six rows, two coils are to be placed in series.
   - Water connections and manifolds are mounted.
   - Updated FID is available.

- Check visual damage on casings.
- Check damage on fins and tubes.
- Check bolting air side.
- Check bolting flanges or threaded connection.
- Check clearance.
- Check vents.
- Check drains and drain pipes.
- Check water traps, siphons, and condensate pipe.
- Verify water trap height against design under pressure on cooling coils.
- Check stress-free connection to manifolds.
- Check for venting possibilities of pipe work to coil.
- Check for draining possibilities of pipe work to coil.
- Check air flow direction through coil.
- Check water flow direction through coil.
- Check painting quality of steel parts.
- Check configuration of control station, pumps, and valves.
- Check adequate supporting and hangers.
- Check for correct tag number and manufacturer's ID plate.

6. Reheat coils
   - Maximum fin spacing on reheat coils does not exceed eight fins per in. (more than two rows are rarely required).
   - Smaller reheat coils are not sized for a large water-side temperature difference.
   - Reheat coils are electric (multistage or SCR controlled) or hot water.
7. Duct work
   - Materials
     Duct work should be constructed of lock forming quality aluminum, galvanized steel, or stainless steel.
   - Specifications
     Specific tables are generated for each pressure classification and each duct system pressure class is clearly defined.
   - Flexible ductwork
     - Round, flexible duct contains aluminum foil liner in lieu of a vinyl liner.
     - The helix of flexible ductwork has formed on the outside of duct's surface.
     - Flexible ductwork complies with NEPA 90A and 90B.
     - Check compliance with all relevant drawings.
     - Check physical appearance.

- Check cleaning of ducts.
- Check flange joints.
- Check fixings of damper.
- Check continuity of insulation and vapor sealing.
- Check fixing of inspection door.

- Elbows
  - All vaned elbows have an excess door located nearby for cleaning the vanes.
  - Either elbows of the radius type and without turning vanes or square mitered elbows equipped with single-thickness, extended-edge turning vanes are used.
- Dampers
  - Balancing dampers have a self-locking regulator suitable for securing the damper at the desired setting and making adjustments.
  - Manual balancing dampers are installed where required and shown clearly on design drawings.
  - End switches and wiring are completed. Perform the following checks on motorized damages:
    - Check overall cleanliness.
    - Check damages on casing, blades, spindels, and seats.
    - Check clearance.
    - Check free movement of blades.
    - Check relative position of blades in multileaf dampers.
    - Check pinning to damper spindles.
    - Check position of blades to quadrant indication.
    - Check fixation of damper bearings.
    - Check control linkages for alignment, rigidity free movement without slop
    - Check position of end switches and adjust.
    - Check wiring of motor and switches.
    - Check coupling of damper with other dampers and mode of operation.
    - Check fail position, e.g., fail open, fail closed, fail as is.
    - Check direction of low (if relevant).
    - Check open/closed indication.
    - Check manufacturer's ID plate.
- System shut off checks for motorized dampers
  - Check position of damper and system shutoff.
  - Check fail position at loss of power (simulate).

- Check working of end switches.
- Check free movement of blades.
- Check controlling movement of damper.
- Check stressless operation of control linkages.
- Check mode of operation of linked dampers.
- Check and adjust course of servomotor.
- Check control linkages for alignment, rigidity-free movement without slop

- System running checks for motorized dampers
  - Check the position of the damper with the system on.
  - Check fail position at loss of power (simulate).
  - Check working of end switches.
  - Check free movement of blades.
  - Check controlling movement of damper.
  - Check stressless operation of control linkages.
  - Check mode of operation of linked dampers.
  - Check and adjust course of servomotor.
  - Check control linkages for alignment, rigidity-free movement without slop
  - Verify deformation, due to (under) pressure.

8. Access doors
   - Hinged access doors have not been used.
   - Access doors are large enough for a person to clean obstructions from the interior of the duct and are provided with extension collars and sash locks.
   - Access doors are clearly indicated on the drawings.
   - Access doors are located at reheat coils and at any other surface that could collect material within the duct.
9. Hangers and supports
   Exposed duct work has smooth rod hangers threaded only at the end.
10. Diffusers
    The following checks are recommended on diffusers:
    - Check the cleanliness of the diffuser and connection box.
    - Check for any damage.
    - Verify correct type in correct location.
    - Check connection to box and duct.
    - Check rigid suspension.
    - Check open position of regulating damper.

- Check and adjust deflection vanes.
- Check correct sealing to ceiling.

11. Insulation for HVAC ductwork
    - Rigid duct insulation is used in mechanical rooms.
    - Jacketed ductwork is dense enough to minimize dimpling.
    - Exposed duct work in clean spaces is insulated with rigid board-type insulation and jacketed with a washable metallic or PVC jacket
    - No internal duct insulation has been used.
    - Check complete mounting of units, correctly fitted in link.
    - Check air handling units.
    - Check supply and exhaust fans.
    - Check supply, return, and exhaust air duct work.
    - Check motorized, regulating, and nonreturn dampers.
    - Check fire and smoke exhaust dampers.
    - Check filter units.
    - Check diffusers.
    - Check control instruments and apparatus.
    - Check electrical and pneumatic connections to apparatus.
    - Check clearance for fans, coils, and filters.
    - Check that air leakage test is complete.
    - Check that duct work is cleaned and flushed.
    - Check that terminal units are cleaned.
    - Check that fire dampers are in open position.
    - Check that smoke exhaust dampers are in closed position.
    - Check that measurement point is identified and holes drilled.
    - Check that access to measurement is points free.
    - Check that prefilters are installed.
    - Check that HEPA filters are available and installed.
12. Sound attenuators
    - Sound attenuators are not used in systems requiring periodic sanitizing.
13. Electrical power and control system
    - Power supply to electrical panels is cut off.
    - Transit package is removed from equipment.
    - Panels and switch gears are clean and undamaged.
    - Connections are tight on busbars and wiring.
    - Fuse rating is correct.
    - Starter overloads are correctly set according to circuit diagrams.
    - Thermal cut-outs are correctly set.

- Internal links on starters are correct.
- All contractors, etc. are correctly fixed.
- Dash pots are correctly charged; time adjustments and levels are identified.
- There is no loose wiring.
- All cover plates are fixed.
- Power and control wiring is complete and in accordance with circuit diagram.

14. Humidifiers
    - Stainless steel (316L grade) has been used for piping, headers, and all humidifier components.
    - Humidifiers use lean steam for humidification.
    - Check physical appearance.
    - Check location.
    - Check leveling.
    - Denting on condenser fins should be removed, if any.
    - Remove transit fixture from compressor floating mounting.
15. Air distribution
    - All returns and exhaust are the louvered, removable core type.
    - Class 100 areas are protected with plastic curtain sheets.
    - Class 10,000 or cleaner areas have low wall returns.
    - Class 100,000 areas have ceiling returns.
    - Return and exhaust air
    - Class 10,000 or cleaner areas have terminal HEPA filters in the ceiling.
16. Terminal filters (HEPA) internal
    - Preinstallation condition
        - Check compliance with all relative drawings.
        - Check physical appearance.
    - Inspection during installation
        - Check complete compliance of filter casing.
        - Check gasket and clamps.
        - Check correct airflow direction.
        - Check proper mounting.
        - Check the serial number of relevant test certificate.
17. Chiller
    - Check compliance with all relevant drawings.
    - Check physical appearance.
    - Check foundation.

- Check positioning.
- Check leveling.
- Check bolt tightness.
- Check free rotation of impeller.
- Check that flow directions are correct.
- Check that pump has been installed per manufacturer instruction.

a. Visual inspection, observations, and adjustments:
   - Check visual damages and external cleanliness.
   - Check bolting and tightness.
   - Belt drive and coupling are securely aligned and tensioned.
   - Belt drive and coupling are a matched set.
   - Bellows are correctly mounted.
   - Drive guards are installed.
   - Tachometer access is available.
   - Positioning of pump shaft is correct.
   - Measuring gauges are installed.
   - Antivibration mounting is in concrete base.
   - Impeller is free to rotate.
   - Flow direction is correct.
   - Glands are packed and adjusted for correct drip rate.
   - Gland drains are fitted and free of dirt.
   - Pumps and motor are correctly lubricated.
   - Tag number and manufacturer's ID plate are correct.
   - Power supply and controls are connected and correct.
   - Starter overload and fuse ratings are correctly set.

b. Pretest condition checks for chiller pumps:
   - Visual inspection report is available.
   - System is pressurized and completely vented.
   - All normally open valves are fully open.
   - All bypass and normally closed valves are closed.
   - All thermostatically controlled valves are (blocked) open.
   - Motorized valves are set to manual override.
   - Automatic control valves are set to full flow.
   - Standby pumps are isolated.
   - Pump casing is vented.
   - Direction and rotation speed is correct.
   - Motor, pump, and drive are free of vibration.
   - Motor, pump, and drive are free of undue noise.

- Motor starting current is correct.
- Motor running current is equal between phases.
- Motor and bearings are not overheating.
- No water sea page of lubrication from housing is detected.
- Pressure in the system keeps stable.

c. Preinstallation condition chiller piping:
- Check compliance with all relevant drawings.
- Check physical appearance.

d. Inspection during installation:
- Check finishing of joints.
- Fix valves and accessories per drawing.
- Supporting
- Hydraulic test at 1.5 times working pressure (1 hour)
- Check continuity of insulation.

e. Pressure testing (hydraulic) procedure for water piping system:
Procedure No: 210029/PTA/PIPINGS, REV O
After completion of all hot jobs like welding and grinding, the pipeline is subject to pressure tests to ensure leak tightness of the system. Before starting the pressure test, it must be ensured that all instrument mounting sockets and connections are in suitable arrangement. At the topmost point of the piping system, two numbers of pressure gauge must be fixed with suitable isolation valves. Water should be filled with a hose connection and air should be vented from all high points of the system. When all air is vented out, water will come out from all vent points, then the vent point should be closed properly to prevent any leakage of water. Now, by means of a small hand pump, the system pressure should be increased by means of introducing a suitable quantum of water. The test pressure should be 1.25 to 1.5 times the working pressure of the system.

When the desired pressure is developed, isolate the system by closing the isolation valve and ensure no physical leakage takes place from all welding joints as well as bolted joints. If any leakage is identified, then release the pressure. After rectification of the leakage, repeat the same

SECTION

VAL 700.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Validation of a Steam Sterilizer**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.10 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Validation of a Steam Sterilizer

PURPOSE

To provide a written procedure to be used as a guideline for the certification/validation of a steam sterilizer

RESPONSIBILITY

It is the responsibility of the production manager, validation manager, and concerned departmental managers to follow the procedure. The QA manager is responsible for SOP compliance.

PROCEDURE

Different types of sterilizers are used in the pharmaceutical industry. However, the following criteria are generally considered common.

- A thermostatic steam trap to efficiently remove condensate from the chamber. This is open when cool and closed when in contact with steam. As condensate collects, the trap opens due to the slight temperature reduction, and the condensate is discharged. There is also a trap to remove condensate from the steam jacket.
- A safety door mechanism to prevent opening while the unit is under pressure. The locking device may be actuated directly by internal pressure or indirectly through an automatic switch. The door itself may be the swing-out or sliding type.
- A pressure vessel constructed according to the American Society of Mechanical Engineers (ASME) code to withstand the required internal steam pressures
- A steam jacket and insulation to conserve energy designed primarily to heat the metal mass of the vessel and to limit heat loss from within the vessel. Some laboratory and small special–use sterilizers are unjacketed.
- A chamber pressure indicator
- A microbial retentive vent filter (optional)
- A cycle timer and (usually) a sequencing controller
- A temperature control system. Although operating under pressure, temperature is the controlling factor in steam sterilization. The modern tem-

perature controller is made up of several key elements to sense, record, and react. These are discussed in a later section.

1. Prevalidation Protocol

The documentation of prevalidation protocols should be as follows:

- A brief description or scope. This is a basic but complete explanation of the sterilizer and its ancillary equipment, including physical characteristics and function.
- Detailed specifications list
- A list of pertinent drawings
- System installation check sheet
- Calibration records of all instrumentation
- Listing of key devices and brief description of each
- Operational record that compares actual operating parameters to specifications

2. Preparing for Validation

A critical part of the validation study is the temperature measurement. Several items will be required to measure and record temperature effectively.

Type T (copper-constant) thermocouples are most applicable in steam sterilizer validation work. Their working temperature range is wide and they are resistant to corrosion in moist environments. A high grade of thermocouple wire should be chosen. Premium grades of wire accurate to as close as 0.1°C at 121°C are recommended. These must then be calibrated against a temperature standard traceable to the National Bureau of Standards (NBS).

The acceptable error should be no greater than the sum of the thermocouple wire accuracy (e.g., +0.1 to 0.3°C) and the degree of traceability of the NBS reference instrument (i.e., ±0.2°C). Thermocouples that do not meet this criterion should be replaced.

Calibration of thermocouples should be carried out at two temperatures. One of these is an ice-point reference at 0.0°C. The other should be a hot point slightly higher than the expected sterilization temperature. Correction factors are applied at both temperatures and the response of the thermocouple over the temperature range can be linearized. The corrected temperature measurements are used to calculate F_O.

3. Validation Protocol

The documentation (installation qualification, operational qualification, etc.) established prior to initiating validation studies provides the foundation for the subsequent validation. A comprehensive steam sterilization protocol should include the following items:

- Description of objectives of the validation study
- Responsibilities of validation personnel
- Identification and description of the sterilizer and its process controls
- Identification of standard operating procedures
- Description of or SOP for instrument calibration procedures
- Identification of calibration procedures for temperature-monitoring equipment (thermocouples, data loggers, etc.)
- Description of the studies to be conducted as under
  - Bioburden determination
  - Microbiological challenge
  - Empty chamber heat distribution
  - Loaded chamber heat penetration
  - Container mapping
  - Evaluation of drug product cooling water (where applicable)
  - Integrity testing of vent filter membranes associated with the sterilizer
- Process parameter acceptance criteria

The review process may initiate supportive changes in the experimental design resulting in protocol revision. Once the protocol is approved, the validation study may begin.

4. Empty Chamber Testing

The initial testing is performed on an empty chamber to measure temperature distribution. The thermodynamic characteristics of the empty sterilizer are depicted in a temperature distribution profile, which will serve to locate hot or cold areas in the sterilizer by mapping the temperatures at various points in the chamber.

The temperature profile is obtained by placing at least 10 thermocouples distributed in the empty tunnel or batch sterilizer in such a way as to determine heat profiles. In the flames sterilizer the thermocouples should be placed at the level of

the ampules. The thermocouple tips should be suspended to avoid contacting any solid surfaces (wall, ceiling, support rods, etc.). A good profile should demonstrate uniform temperatures across the sterilizer.

The temperature range must conform to the protocol requirements. All environmental factors should closely represent actual manufacturing conditions (relative humidity, room temperatures, static air pressure, and balance). All control settings are recorded, including any variable that will affect the cycle (key process variables such as temperature set points, heating elements settings, cycle-timer set point, belt speed, etc.). The cycle timer (batch), belt speed (tunnel or flame), controller operating temperature span, and production charts can be verified by a multipoint temperature recorder with an integral timer.

5. Container Mapping and Container Cool Point

Prior to initiating loaded chamber heat penetration studies, a container mapping study should be conducted. The intent of this study is to determine the coolest point within a liquid-filled container.

In general, the smaller the container volume, the less likely the detection of a discernible cold spot. Nevertheless, temperature mapping should be conducted on all the different container types, sizes, and fill volumes that will be subject to validation.

The number of thermocouples positioned within the container will be dependent on the container volume. A sufficient number of thermocouples should be positioned in areas representing the upper, middle, and lower portions of the container. Error in cold spot determinations may be introduced by employing an excessive number of thermocouples within the container. The error may be attributed to thermocouple mass and the resulting baffling effects may influence the normal convection currents of the liquid.

It is also possible to use a single thermocouple at different positions in multiple runs. This requires careful control of autoclave temperature to reduce error caused by run-to-run variation. Repeat studies are required to establish reproducible cold

points and temperature profiles of the liquid in the container. The profile point having the lowest temperature or lowest F_O is designated as the cold spot.

In subsequent loaded chamber heat penetration studies, penetration thermocouples should be positioned within the container at the previously determined cold spot. The temperature profile of the container should remain constant among different sterilizing chambers, utilizing steam heat as the sterilizing medium.

6. Heat Distribution Studies

The intent of this study is to demonstrate the temperature uniformity and stability of the sterilizing medium throughout the sterilizer. Temperature distribution studies should be conducted on both empty and loaded chambers with maximum and minimum load configurations. Temperature uniformity may be influenced by the type, size, design, and installation of the sterilizer. The manufacturer of the vessel, based on the variables mentioned, should determine a satisfactory empty chamber temperature uniformity.

A narrow range is required and is generally acceptable if the variation is less than ±10°C (±2°F) of the mean chamber temperature. Significant temperature deviations greater than ±2.5°C (~±4.5°F) of the mean chamber temperature may indicate equipment malfunction. Stratified or entrapped air may also cause significant temperature variations within the sterilizer chamber. Initially, a temperature distribution profile should be established from studies conducted on the empty chamber. Confidence may be gained through repetition, and therefore empty chamber studies should be conducted in triplicate in order to obtain satisfactory assurance of consistent results.

Subsequent to the empty chamber studies, maximum load temperature distribution studies should be conducted to determine if the load configuration influences the temperature distribution profile obtained from the empty chamber studies. The thermocouples utilized in the heat distribution studies are distributed geometrically in representative horizontal and vertical planes throughout the sterilizer. The geometric center and corners of the sterilizer should also be represented. An additional thermocouple should be placed in the exhaust drain adjacent to the sensor that controls vessel temperature, if possible.

The number of thermocouples utilized in the heat distribution study will be dependent on sterilizer size. In a production-size sterilizer, 15 to 20 thermocouples should be adequate. The thermocouples utilized for loaded chamber heat distri-

bution studies should be positioned in the same locations used for empty chamber heat distribution studies. The uniformity and stability of the sterilizing medium are monitored in the distribution studies; consequently, the temperature probes should be suspended to avoid contacting solid surfaces and should not be placed within any containers. Temperatures must be obtained at regular intervals (e.g., each minute) throughout the time duration specified for a normal production cycle.

7. Loaded Chamber Heat Penetration Study — Load Cool Point

The intent of this study is to determine the coolest points within a specified load and configuration. Cool points originate because of the varied rate of heat transfer throughout the load. It is therefore imperative that heat penetration studies be conducted to determine cool points within a loading pattern and ensure that they are consistently exposed to sufficient heat lethality.

Load cool points are dependent on load configurations and the types of items that comprise the load (liquid-filled containers, process equipment, etc.). Prior to conducting heat penetration studies, maximum and minimum load configurations must be established. The penetration thermocouples are positioned within liquid-filled containers at the cool point previously determined by container mapping studies. The probed containers should be distributed uniformly throughout the load. When the load consists of multiple layers or pallets, a sufficient number of thermocouple-probed containers should be employed to provide an equal representation among layers.

Heat penetration studies conducted on maximum and minimum loads should be repeated until temperature data are obtained for all representative areas of the load. It may be necessary to reposition thermocouples in order to study different areas. Several runs, usually three of each thermocouple configuration, will provide confidence in the repeatability of the temperature profile.

A heat penetration study defining load cool points is not limited to load configurations composed of liquid-filled vials. The same principles can be applied to process equipment loads (filters, hoses, etc.) subject to steam sterilization. Penetration thermocouples are positioned at points within the process equipment suspected to be the most difficult for steam heat penetration. Temperature data

are obtained from representative maximum and minimum loads in order to establish

temperature profiles depicting load cool points. Equipment load configurations may be designed to allow reasonable flexibility for the operating department by permitting the use of partial loads. In this case partial loads would be defined as a portion of the established maximum validating load.

Heat penetration studies are also employed to determine points within a load configuration that achieve higher temperatures and consequently greater F_O values. The temperature data obtained may be significant when heatable products are involved in the sterilization process and the potential for product degradation exists. The cool points established for a specified load and configuration will eventually be utilized to control the exposure time in subsequent routine production runs. The temperature sensors that control sterilization–cycle–exposure time at process temperature may be positioned within the load at the previously detected cool point. Consequently the entire load is exposed to sufficient heat lethality and achieves the desired F_0 value.

Lethal rates can be determined from the temperature data obtained from the heat penetration studies. The temperature data are converted by the following formula:

$$L = \log^{-1} \frac{T_0 - T_b}{Z} = 10^{\left(T_0 - T_b\right)/Z}$$

where
T_0 = temperature within the container
T_b = process temperature (121°C)
Z = temperature required to change the D value by a factor of 10
L = lethality.
F_O is then determined by integrating the lethal rates throughout the heating process:

$$F_O = \square 10^{(T-121)/10_{dt}}$$

or

$$F_O = \sum 10^{(T-121)/10_{\Delta t}}$$

where
Δt = time interval between temperature measurements
T = product temperature at time t in °C.
When the sterilization process temperature deviates from 121°C, the amount of time providing equivalent lethality can be determined by the following formula:

$$F_t^Z = \frac{F_{121}^Z}{L}$$

where
F_t^Z = the equivalent time at temperature T delivered to a container for the purpose of sterilization with a specific value of Z
F_{121}^Z = the equivalent time at 121°C delivered to a container for the purpose of sterilization with a specific value of Z (if Z = 10°C, then $F_{121}^Z = F_O$).

8. Microbiological Challenge Studies

Biological castles are employed during heat penetration situations in order to demonstrate the degree of process lethality provided by the sterilization cycle. Calibrated biological indicators utilized for this purpose function as bioburden models providing data that can be utilized to calculate F_O or substantiate and supplement physical temperature measurements obtained from thermocouples.

The most frequently utilized to challenge moist heat sterilization cycles are Bacillus stearothermophilus and Clostridium sporogenes, spore-forming bacteria are selected because of their relatively high heat resistance. In addition to the selection of an appropriate organism for use as a biological indicator, the concentration and resistance of the indigenous microbial population is established.

The biological indicator can be prepared to adequately challenge a sterilization cycle designed to provide a 10:6 probability of microbial survival with respect to indigenous bioburden. The concentration of spores utilized as the biological indicator can be determined from the following formula:

$$D_S (\log N_i + 6) = D_{bi} (\log N_0 + 1)$$

where
N_i = the load of microorganisms on the product to be sterilized
D_S = D value of the most resistant isolate
N_0 = number of organisms on the biological indicator
D_{bi} = D value of biological indicator.

9. The Validation Report

Record keeping is a prime requirement of current good manufacturing practices. The records required for a validated steam sterilization cycle are listed below:

- Qualification reference documents (specifications, drawings, and calibration records)
- Operational qualification protocol and record
- Approved validation protocol
- Raw calibration and validation data
- Approved validation report

Frequency

Initial validation: three times
Revalidation: once in a year

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.20 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Hot Air Sterilization Tunnel Certification and Validation Guideline**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.20 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Hot Air Sterilization Tunnel Certification and Validation Guideline

PURPOSE

To provide a written procedure to be used as a guideline for the certification and validation of a dry heat sterilizer

RESPONSIBILITY

It is the responsibility of production manager, validation manager and concerned departmental managers to follow the procedure. The quality assurance manager is responsible for SOP compliance.

Introduction

Laminar flow sterilization tunnels are widely used in high-speed aseptic manufacturing. Typically, laminar flow tunnels contain three sections: 1. preheating, 2. heating, and 3. cooling.

Sterilization occurs at temperatures higher than 300°C in the heating section. After sterilization, cooling is necessary before container filling. It is therefore very important to keep conditions sterile in the cooling section (up to the filling station) by keeping the cooling section at a slight positive pressure towards the tunnel room (2 to 3 Pa). A higher overpressure would result in cooling the heating section with cooling air, decreasing the sterilization efficiency of the heating section.

The certification activities include a series of process documentation and qualification studies that start with the initial installation of a sterilization system and continue as process engineering changes or new or revised product introductions are required. Qualification activities comprise installation, operational, change, and performance phases.

SOP No. Val. 700.20 **Effective date: mm/dd/yyyy**

Approved by:

PROCEDURE

1. Installation Qualification (IQ)

The initial IQ hot air sterilizer tunnel certification shall consist of the development of the following information package:

- Hot air sterilizer tunnel dimensions
- Product carrier description
- Utility support system description
- Sterilizer equipment description
- Equipment control system description

2. Process Description

- Description of the sterilization medium employed
- Description of the cycle steps and process functions initiated during the sterilization process
- Type of process control employed, i.e., time and temperature or product container control
- System operating procedures and system flow diagrams

3. Product Safety

To confirm that product safety considerations have been addressed, review of tunnel construction and operation materials for product contact potential or suitability shall be documented. Tunnel construction materials, which contact the sterilization medium, shall be identified. This would include:

- Product carriers
- All exposed potential medium contact surfaces including heating and cooling sections
- Heat generating, cooling, and conveying system

Equipment lubricants with potential product contact implications must be verified as not jeopardizing product integrity. Lubricants should be identified.

4. Critical Process Instrumentation List

- Temperature control and monitoring systems
- Pressure control and monitoring systems
- Carrier drive monitoring systems
- Critical system alarms

The following equipment installation qualification checks shall be performed:

4.1 DOP tests of HEPA filters

Test objective

To demonstrate that HEPA filters are properly installed by verifying the absence of bypass leakage and other defects such as tears and pinhole leaks

Test method

This test is performed only by certified or previously trained personnel who introduce DOP aerosol upstream of the filter through a test port and search for leaks downstream with an aerosol photometer. Filter testing is performed after operational air velocities have been verified and adjusted where necessary.

Align the aerosol photometer as follows:

1. Position the smoke generator so the DOP aerosol will be introduced into the air stream ahead of the HEPA filters.
2. Open the appropriate number of nozzles until a DOP challenge concentration of 100 mg/l of air is reached. This challenge concentration is measured upstream of the HEPA filter, and is evidenced by a reading of between 4 and 5 on the logarithmic scale of the aerosol photometer.
3. Scan each filter by holding the photometer probe approximately 1 in. from the filter face and passing the probe in slightly overlapping strokes at a traverse rate of not more than 10 ft/min, so that the entire face is sampled.

4. Make separate passes with the photometer probe around the entire periphery of the filter, along the bond between the filter medium and the frame, and along all other joints in the installation through which leakage might bypass the filter medium.

Acceptance criteria

- Entrance section filters and cooling section filters
- Local DOP penetration ð 0.01% of the upstream concentration
- Heating section filters
- Local DOP penetration ð 0.1% of the upstream concentration provided that local results of hot tunnel particle counting air cleanliness classification are within specifications (particle counts at any location of the heating section ð 100 particles Š 0.5 μm/ft³ and zero particle Š 5 μm/ft³)

Equipment

DOP polydisperse aerosol is generated by blowing air through liquid dioctylphthalate (DOP) at room temperature. The approximate light scattering mean droplet size distribution of the aerosol is 99% + less than 3.0 μm and 95% + less than 1.5 μm.

The DOP aerosol generator is compressed-air operated, equipped with Laskin–type nozzles. The aerosol photometer is a light-scattering type with a threshold sensitivity of at least 10^{-3} mg/l, capable of measuring concentrations in the range of 80 to 120 mg/l, and with air sample flow rate of 1 ft³ + 10% per min. This instrument is to be calibrated per manufacturer recommendation.

4.2 Air velocity and homogeneity at the exit of HEPA filters

Test objective

To demonstrate that air speed is homogeneous in each section of the tunnel (entrance, heating, cooling). The air speed values and homogeneity are important for uniform heating (sterilization) and uniform cooling of glass containers.

Test method

- Draw a grid on the floor of tunnel.
- Measure and record the velocity at the center of each grid at the specified heights.
- Allow no objects near the anemometer, except for built-in equipment.
- Measurements should be taken for a minimum of 15 sec.

- Record the pressure readings (in in.) from the manometer connected to the module's plenum.

Equipment

Hot-wire anemometer and stand

Acceptance criteria

From left to right, speed variation should not be more than 30% around the mean. From each filter the speed uniformity must be greater than ± 20% relative to the mean, per filter not more than one location out of this limit.

4.3 Air velocity and uniformity on the tunnel conveyor

Test objective

To demonstrate that air flow is continuous from top to bottom along the whole surface of the conveyor (air flow from bottom to top would contaminate glassware with particles from the conveyor and machinery)

Test method

- Draw a grid on the floor of tunnel.
- Measure and record the velocity at the center of each grid at the specified heights.
- Allow no objects near the anemometer, except for built-in equipment.
- Measurements should be taken for a minimum of 15 sec.
- Record the pressure readings (in in.) from the manometer connected to the module's plenum.

Equipment

Hot-wire anemometer and stand

Acceptance criteria

There should be no measured speed at any point from the bottom to the top (anemometer). No opposite flow should be visualized with the Drager tube and pump. It is preferable that left to right speed variation be lower than 30% around the mean. The number of points out of this limit is to be minimized.

4.4 Hot tunnel particle countings

Test objective

To demonstrate that the air handling system of the tunnel (hardware and software) is able to produce at the level of the top of the container a class 100 air on all the surface of the conveyor.

Test method

- These tests are performed after the HEPA filter leak tests and air velocity tests are completed.
- To obtain baseline data with the room in static conditions, perform the following tests with operational personnel absent and the equipment at rest:
  1. Using the particle analyzer, count particles greater than or equal to 0.5 μm in diameter at heights of 40 in. in the center of each grid.
  2. If the particle count in the 0.5 μm range is less than 50 per ft^3 of air, four additional counts at this location are taken to place these particle counts within a 50% confidence interval.
- After completion of these tests, if the absolute air filtration modules are operating within accepted limits, repeat steps 1 and 2 with operational personnel present and the fill equipment running. If at any time there is a deviation from accepted parameters, the various components of the systems in operation are reviewed, repaired, or adjusted until the desired conditions are achieved.

Equipment

Laser particulate counter

Acceptance criteria

All locations with particle counts:

ð 100 particle Š 0.5 μm/ft^3
zero particle Š 5 μm/ft^3

4.5 Empty tunnel heat distribution

Test objective

The objective of the empty distribution runs will be to evaluate:

- Heating characteristics of the sterilizer, product carrier system, and the sterilization medium employed
- Ability of the sterilizer to hold the required sterilization parameters
- Ability of the sterilization cycle control mechanisms to operate as intended

Test method

A review of all sterilization specifications assigned to the sterilizer under consideration shall be made, with the specifications cycle requiring the maximum peak dwell temperature and heating rate to be selected for the empty sterilizer heat distribution runs. During the empty sterilizer heat distribution runs, sterilizer parameters and equipment component status shall be visually monitored to confirm applicable control operations.

Technical criteria

- Fixed thermocouples shall be located at key sterilizer positions, as justified by the sterilizer operation and control characteristics (i.e., at exhaust or vent line, in recirculation heating medium line, next to controller sensor, as applicable).
- Distribution thermocouples for sterilizer shall be located throughout the chamber per plan and traceable location diagram. Sufficient functional thermocouples shall be used during distribution runs conducted in sterilizer to assure adequate distribution determination.
- Traveling temperature sensors for continuous sterilizer shall be located throughout the conveyor system per plan and traceable placement diagram.

The temperature sensors shall be placed in various locations within each distribution run.

- Heat distribution data shall include evaluation of the coldest and hottest sterilizer zones, the mean distribution temperature observed, the range of distribution temperatures observed, and the heat-up and cool-down times obtained.

Acceptance criteria

- The distribution runs must meet the time and temperature requirements of the corresponding specifications or operating procedures.
- All function initiations required during the operating modes must have occurred as specified.

4.6 System alarm and safeguard checks

Test objective

To confirm that all alarm feature input and output loops function as intended

Test method

All alarm features available on the sterilizer system under consideration, both program controlled or separately wired, shall be challenged to confirm appropriate functionality.

Technical criteria

- Where possible, each alarm and safeguard feature should be challenged by simulation of actual alarm conditions within the sterilizer equipment system. Where simulation of physical alarm conditions would be impractical, alarm circuitry may be challenged by use of electrical input signals.
- The following alarm and safeguard systems should be checked, as applicable:
  - Power or electrical system interruption alarms
  - Chamber door-open alarms
  - Cycle sequence alarms
  - Timer system alarms

- High or low temperature alarms
- Chain speed and R.P.M. alarms
- Fan-on alarms
- Computer or controller data entry safeguard system alarms

Acceptance criteria

All alarm and safeguard features shall respond to their corresponding system condition signal as specified.

Support documentation

The following documents shall be included in the IQ certification package:

- Sterilizer engineering drawings
- Sterilizer operation procedure
- Sterilizer sanitization procedure
- Sterilizer maintenance procedures
- Sterilizer specification utilization list
- Distribution thermocouple location diagrams
- Temperature sensing unit location diagram (continuous sterilizers)
- Sterilizer process log sheets
- Empty chamber heat distribution test data summaries
- Copy of appropriate specifications used
- Test data summary sheets for each function evaluation
- Test and equipment pre- and postcalibration status listings

5. Operational Qualification (OQ)

5.1 Background

The intent of sterilizer OQ studies will be to:

- Confirm that sterilizers are capable of processing at established time and temperature ranges that assure conformance with respective specification requirements
- Confirm that established sterilization cycles deliver a uniform and reproducible heat input to products assigned to each cycle

The sterilization test functions required to qualify or validate the sterilizer will include process heat distribution, process heat penetration, and process microbial and depyrogenation validation, as applicable.

The OQ phase of sterilizer validation shall consist of the development of an information package fulfilling the documentation requirements of the generic equipment operational qualification. The following sterilizer-specific documentation shall be incorporated in the operation qualification:

- Brief sterilizer equipment or process description shall be included for initial certification.
- The products utilized for testing subsection shall include a listing of the items used for OQ test function runs and items utilized for sterilizer bulking during test function runs.
- The sterilizer utilization list subsection shall include a listing of the sterilization cycles being validated and the corresponding product list numbers assigned to each specification.

The sterilizer utilization list and the following OQ test requirements summary will be utilized to determine the products assigned to the sterilizer that shall be subjected to the type and number of test function runs required to establish overall sterilizer qualification or validation. The test function subsections shall include test objectives, test methods and acceptance criteria, as follows.

5.2 Heat distribution

Test objective

To evaluate the heating characteristics of the tunnel, carrier system, and sterilization medium employed under loaded conditions

Test method

- Distribution thermocouples shall be located in each run as described in IQ empty tunnel heat distribution runs.
- All distribution runs shall be performed, monitored, and documented in accordance with the respective sterilizer operating procedure.

Acceptance criteria

All distribution runs must meet the parameter requirements of the corresponding specification and established production sterilization cycle.

5.3 Heat penetration

Test objective

- To evaluate the heating characteristics of items within the tunnel when subjected to the sterilization medium
- To evaluate the relative heating characteristics of items and reference thermocouples where applicable
- To establish production work order sterilization parameters

Test method

- Heat penetration runs may be conducted in conjunction with required heat distribution runs.
- Thermocouple or temperature sensor probes shall be placed within the penetration test containers in accordance with established written container preparation procedures. Test containers may be trays, pans, commodities, etc., depending upon the testing required.
  - Thermocouple and temperature sensor probe placement within the containers shall be documented.
  - Where applicable, thermocouple placement shall be in the container cold zone, as determined from generated container mapping studies.
- Each heat penetration run shall include thermocouple temperature sensor probe containers distributed throughout the tunnel, per planned and traceable location diagram.
- The number of heat penetration test containers per run shall agree with that required for heat distribution thermocouples.

- If previous empty tunnel heat distribution test runs have identified hot or cold zones, at least one of the penetration test containers must be placed in each of these zones per run.
- The heat penetration sample containers shall be loaded into the tunnel carrier in an orientation consistent with planned production run loading and the corresponding container heat mapping study loading method.

Acceptance criteria

- All heat penetration data collected during each run must meet the requirements for the corresponding specification.
- The production operating ranges and windows established from the heat penetration runs must assure all products in the test runs will meet the calculated requirements for the corresponding specification. If a satisfactory operating range is not established using minimum and maximum loading parameters, intermediate loading conditions must be tested.
- Where tunnel peak dwell temperature and time are to be used for routine production cycle control, or as back-up control, correlation of sterilizer peak dwell time and temperature with the hottest and coldest profile container must be shown for each run, where applicable.

5.4 Componentry microbial or pyrogen challenges

Test objective

To confirm the biological relationship between parametrically determined process lethalities, by demonstrating the ability of the sterilizer to effectively reduce the challenge material to an acceptable level

Test method

1. Componentry microbial challenges
   - The number of challenge containers, preparation methods, spore crop type, and inoculation levels described in the appropriate documentation shall be followed in the production of test items for each run.
   - Heat penetration test containers of corresponding container size and type and fill volume shall be placed adjacent to the challenge test items in each run.
   - At least one set of microbial challenge or penetration test containers shall be placed in the sterilizer cold zone per run (where applicable).
   - Test container placement shall be defined per planned and traceable location diagrams.
   - Maximum sterilizer loading configurations shall be used when conducting challenge test runs.

- The corresponding production cycle time and temperature control parameters that deliver subminimal specification conditions shall be utilized when conducting the challenge runs.
- If absolute minimum time and minimal temperature parameters are not used during the componentry challenge runs, manufacturing order parameter limits must reflect the parameters used during these runs.

2. Componentry pyrogen challenges
   - The number of challenge containers, preparation methods, endotoxin identification, and inoculation levels described in the appropriate documentation shall be followed in the production of test items for each run.
   - Heat penetration test containers of corresponding container size and type and fill volume shall be placed adjacent to the challenge test items in each run.
   - At least one set of pyrogen challenge or penetration test containers shall be placed in the sterilizer cold zone per run where applicable.
   - Test container placement shall be defined per planned and traceable location diagrams.
   - Maximum sterilizer loading configuration shall be used when conducting challenge test runs in all other sterilizers.
   - The corresponding production cycle time and temperature control parameters that deliver subminimal specification conditions shall be utilized when conducting the challenge runs.

Acceptance criteria

- A minimum microbial challenge spore log reduction of equal to or greater than six must be shown for each run.
- A minimum pyrogen challenge must be equal to or greater than three log reductions for each run.

- At least 15% of the required functional container time and temperature values must show subminimal process conditions, per run.
- Cold zone temperature correction must be used where applicable.

5.5 Support documentation

The following documents shall be included in each operational qualification certification package, as applicable:

- Sterilizer operating procedure
- Current sterilizer utilization list
- Copies of the specifications used during the OQ function test runs
- Copies of all penetration distribution and challenge thermocouple placement diagrams
- Description of the bulking items used, where applicable
- Copies of all microbial challenge protocols, which should include identification of the types, crop numbers, and D values for the biological indicators used
- Copies of all pyrogen challenge protocols, which should include materials used, lot number, sensitivity, and inoculation levels
- Key test and equipment instrumentation pre- and postcalibration status supporting each function
- Test data summaries

The temperature data collected during each operational qualification run shall be summarized so that the following information, as applicable, can be readily determined for each run:

- Sterilizer heat-up time
- Duration of sterilizer peak dwell
- Minimum and maximum sterilizer temperatures during peak dwell
- Sterilizer cool-down time
- Commodity or component heat-up time
- Peak dwell residence time or carrier speed
- Minimum and maximum item temperature during peak dwell
- Item cool-down time

Process Engineering Change Qualification

Modifications to sterilizer equipment systems shall be accompanied by initiation and completion of a formal engineering change request and authorization documentation package. Plant engineering, manufacturing and quality assurance shall be responsible for determining whether a change impacts the certified functions of the sterilizer. Changes involving the modification of the sterilizer, carrier design, sterilization medium supply or distribution systems, or sterilizer operation or control mode will require the performance of heat distribution and penetration runs with items bracketing thermal mass characteristics represented by the sterilizer utilization list.

All packages shall address the IQ and OQ documentation requirements affected by the change and shall include:

- Description of the proposed change
- Documented reason or rationale for the proposed change
- Description of the test functions required to qualify and validate the sterilization process after the change is made, as applicable
- Confirmation that documentation affected has been updated after the change takes place

Frequency

Initial validation: three times
Revalidation: twice per year

REASONS FOR REVISION

Effective date: mm/dd/yy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.30 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Freeze Drier**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.30 **Effective date: mm/dd/yyyy**
Approved by:

SUBJECT: Freeze Drier

PURPOSE

To describe the procedure for validation of the freeze drier to ensure it meets the installation, operational, and performance qualification criteria

RESPONSIBILITY

It is the responsibility of the production manager, quality control manager, and technical services manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Vacuum Leak Testing

Procedure

Perform the vacuum leak test with an empty freeze drier and condenser. After reaching the maximum available vacuum, the vacuum pump is switched off after a delay time and the valves are closed. Monitor the vacuum decrease for a period of 24 h. Let the condenser cool to avoid water evaporation and vacuum decrease.

Requirements

Maximum available vacuum: meet manufacturing specification
Vacuum decrease: meet specification requirements

2. Shelf Temperature Study

Uniformity of temperature distribution across the shelves is important in order to maintain product uniformity.

Procedure

To study the temperature distribution and differences compared with the set values of each shelf, a temperature evaluation study of each shelf in a complete cooling-down and warming-up cycle should be performed as follows:

Distribute Š 15 thermocouples over the shelf surface, and at the refrigerant fluid inlet and outlet.

Run following cycle:

Start point	End Point	Time period
1) +20°C	+50°C	minimum time
2) –50°C	–50°C	hold for 30 min
3) –50°C	+50°C	minimum time
4) +50°C	+50°C	hold for 30 min

Requirements

Average refrigerant temperature should be ± 3°C during the holding period compared with set temperature Cooling down velocity, warming up velocity, temperature distribution among the different shelves, and average shelf temperature should be in compliance with the manufacturer specifications.

Frequency

Initial validation: once
Revalidation: once per year

3. Temperature Distribution Study

Simulate the freeze drying process to perform an empty chamber temperature distribution study.

Procedure

Establish the minimum quantity of thermocouples to be used for temperature distribution study. The thermocouples should preferably be placed in recognized cold spots during the shelf temperature study.

Requirements

The temperature distribution within the different shelves compared with the average temperature measured within the stable phase of the process and the average shelf temperature must comply with supplier specifications.

Frequency

Initial validation: once
Revalidation: once per year

4. Pressure Testing

Procedure

During simulated lyophilization processes, the pressure inside the freeze drier should be measured and compared with the set values.

Requirements

Average pressure should be no more than ± 1 Pa compared with the set values.

Frequency

Initial validation: three times
Revalidation: once per year

5. Sterilization

Steam sterilization technique is commonly used for this purpose.

Procedure

Perform temperature distribution study. Determine the quantity of thermocouples to be used during the investigation using the following formula:

Number of thermocouples = usable chamber volume (liters)/100 liters + 1

The minimum number of thermocouples recommended to conduct the study is 5. Additional thermocouples shall be placed in these condensate drains and condenser of the freeze drying chamber, of the condenser and of the steam inlet.

The F_o value of the cold curve should be calculated from all run processes. Following these data the worst case can be recognized.

Requirements

F_o Š 12 min

Frequency

Initial validation:once for the whole chamber and afterwards three times repeated for recognized cold spots
Revalidation:once per year

6. Microbiological Investigation

Procedure

Use spore strips for microbiological investigation:

Bacillus stearothermophilus
D-value Š 1.0 min
Population between 10^4 and 10^7

The cold spots recognized during the temperature investigation (worst case) are investigated again by placing a spore strip near each thermocouple location which has been proved to be a cold spot. Besides, the two spore strips shall be used as a positive control.

Frequency

Initial validation: two times at the identified cold spot
Revalidation: once per year

Requirements

Sterilized spore strips: no growth
Growth of the positive control strips: show growth

7. Pressure Testing during Sterilization Process

Procedure

The pressure profile during the sterilization cycle should be monitored and compared with the theoretical pressure calculated from sterilization temperatures.

Requirements

Measured pressure = theoretical pressure ± 5 kPa (refer to specification)
Measured temperature = theoretical temperature ± 3°C (refer to specification)

Frequency

Initial validation: three times
Revalidation: once per year

8. Media Fills

The verification of aseptic processes entails the use of media to assess the suitability of the handling procedures.

Procedure

Media-filled vials (soybean casein digest broth or fluid thioglycollate medium) are filled on the filling line, transported to the freeze drier, loaded into the chamber, subjected to a simulated lyophilization process, stoppered, sealed, and incubated for 14 days at 25°C. The minimum number of vials to be used is 5000.

Requirements

Infection rate ð 0.1% (PDA)

Frequency

Initial validation: three times
Revalidation: every 6 months

9. Oil Contamination

To assess the possibility of contamination of the freeze drying chamber with oil during the final drying process by diffusion of oil out of the vacuum pump.

Procedure

Place silica gel thin layer chromatogram plates on the shelves and run the normal process cycle. The TLCs are analyzed on their content of pump oil and refrigerant oil.

Requirements

Content pump oil: $< 1.00\ \mu g/cm^2 \times h$

Frequency

Initial validation: three times with different locations of the TLCs during the three runs
Revalidation: once per year

10. Cross-contamination Test after Cleaning the Device

Cross-contamination test must be performed for freezers not dedicated to one process.

Procedure

Prepare vials containing an inert material (e.g., 5% w/v mannitol solution) and run the freeze drying process after the actual product run. Analyze the vials with inert material for the active content of the previous product.

Requirements

The cross-contamination rate should meet the in-house criteria.

Frequency

For the product with the most serious active or the highest content of active: once
Revalidation: once every 5 years

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.40 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Ampule and Vial Washing Machine**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.40 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Ampule and Vial Washing Machine

PURPOSE

To describe the procedure for validation of an ampule and vial washing machine to maintain microbiological quality

RESPONSIBILITY

It is the responsibility of the production manager and technical service manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturers.
- Verify that the utilities required are available.
- Installation shall be conducted per the instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Medical drawings

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

3. Cleaning Process Efficiency

Procedure

Wash ampule and vials using different available washing programs. Determine the efficiency of the process by comparing the quantity of present sticking particles (particle size classes: > 50 μm and 2 to 50 μm) prior to and after washing the glassware.

Fill washed and dried glassware with sterile filtered water, sonicate for 5 minutes and test with a particle counter.

Requirements

Sticking particles: 90% reduction

4. Microbiological Quality of Water Used for Glassware Washing

4.1 Recirculating water

Test the water used for prewashing in ampule and vial washing machine for viable count.

Procedure

Perform hourly sampling for a 3-day period.

4.2 Purified water supply system

Procedure

Perform sampling for a period of 2 weeks each day from each needle outlet and test for microbial count.

Requirements

Total aerobic microbial count: < 100 cfu/ml

5. Water Filter Integrity

Procedure

Perform pressure hold test or a forward flow test.

Requirements

The filters should meet the integrity test as proposed by the filter supplier. The allowed usage time of a filter must be fixed (e.g., maximum pressure differences between water inlet and outlet).

Frequency

Initial validation: at the time of installation
Revalidation: each filter change

REASONS FOR REVISIONS

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.50 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Washing, Sterilizing, and Drying Machine for Stoppers**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.50 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Washing, Sterilizing, and Drying Machine for Stoppers

PURPOSE

To provide the guideline for validation of the washing, sterilizing and drying machine for stoppers to meet the cGMP requirement

RESPONSIBILITY

It is the responsibility of the technical service and quality control managers to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturers.
- Verify that the utilities required are available.
- Installation to be conducted per instructions provided in the manual.
- Ensure all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Medical drawings

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

3. Performance Qualification

3.1 Cleaning efficiency

3.1.1 Reduction of sticking visible particles

Procedure

The number of stoppers should be chosen according to a total stopper- surface of 200 cm^2. Place the stoppers to be tested into a particle-free container with a pair of tweezers. Shake the stoppers for about 30 sec with a filtered and dilute detergent solution. Filter the obtained solution through a 0.45 μm filter, as reference. Repeat the same procedure without stoppers.

Perform the test and reference test three times. Inspect the filter afterwards visually, using microscope using lateral incident light with an enlargement of 40x.

Frequency

Initial validation: each stopper type should be tested once prior to and once after running the standard process with a loading of 100%.
Revalidation: once every 3 years

Requirements

Reduction of particles should be 80% compared with unwashed stoppers.

3.1.2 Reduction of sticking subvisible particles

Procedure

Transfer the stoppers into a particle-free container with a pair of tweezers. Fill eight stoppers in each container, add 10 ml of sterile filtered water, sonicate for 5 minutes.

Measure the particle load with a particle counter in the measuring ranges (92 to 5, 5 to 10, 10 to 25, 25 to 50, and > 50 μm). From each container perform 20 measurements in the different ranges. As a reference test, perform the same procedure without stoppers.

Frequency

Initial validation: each stopper type should be tested once prior to and after running the standard process with a loading of 100%.
Revalidation: once every 3 years

3.1.3 Reduction of pyrogen content

Procedure

Prepare five stoppers covered with 1000 endotoxin units each. Place the stoppers in a net and place them in the process vessel during a standard run with a 100% loading. Determine the endotoxin quantity present on the five stoppers

Frequency

Perform the test three times.

Requirements

A 3-log reduction

3.1.4 Content of silicone

Procedure

After processing with 50 and 100% loading, the silicone content on the stoppers should be determined. The unprocessed stoppers' silicone content shall also be determined as a reference value.

Frequency

Validation: initial for each stopper type and loading rate one time
Revalidation: once every 3 years

Requirements

Content processing of the stoppers
Silicone content: 5 to 20 µm/cm²

3.1.5 Sterilization

3.1.6 Determination of the F_o

Procedure

With loading rates of 0, 50, and 100% using each stopper type, place thermocouples in the process vessel with predetermined location.

Frequency

Validation: each loading rate one time
The worst case loading identified from the initial testing should be repeated three times.
Revalidation: every 6 months

Requirements

F_o Š 12 min

3.1.7 Microbiological investigation

Procedure

- Bacillus stearothermophilus
- D–value Š 1 min
- Viable count Š 10^3 bacteria/ampule

The ampules should be sterilized together with the stoppers; three ampules must be used.

Frequency

Three times at the worst case loading rate as determined above.

Requirements

No growth of the test organism after the sterilization

3.1.8 Drying process

Procedure

Run the standard process with 100% loading rate. Collect the dried stoppers in predried glass vessels. The stoppers are afterward cut into pieces of ± 80 mg and analyzed using the Karl Fischer moisture determination method. The moisture out of the stoppers is obtained at increased temperature and blown over with nitrogen into the reaction vessel.

Frequency

Once for each stopper type

Requirements

Moisture content equal to or lower than that of unprocessed stoppers

3.1.9 Feedwater

Procedure

Monitor pyrogen and microbial content of feed water as the cleaning and depyrogenation effects are dependent from the water quality used during processing of the stoppers.

Requirements

pyrogen content ð 0.25 EU/ml
viable count ð 10 CFU/ml

3.1.10 Rework procedure

If the reprocessing of stoppers that already passed the whole process is unavoidable, the whole process should be revalidated.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.60 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Ampule and Vial Filling Machine**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.60 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Ampule and Vial Filling Machine

PURPOSE

To describe the validation guideline for the ampule and vial filling machine to be free from contamination during the filling cycle

RESPONSIBILITY

It is the responsibility of the production manager and technical service manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturers.
- Verify that the utilities required are available.
- Installation shall be conducted per instructions provided in the manual.
- Ensure all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Medical drawings

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

3. Classification at Filling Point

Procedure

The particle load should be examined at the location near the filling points with a particle counter.

Requirements

- ð 100 particles Š 0.5 µm/cft or ð 3000 particles Š 0.5 µm/m^3
- 0 particles Š 5 µm/cft or m^3

4. Particle Contamination of Ampules and Vials during Filling Procedure

Ampules and vials should be filled with water for injection and afterward be inspected on the contamination with particles (particle classes: ð 10 µm and ð 25 µm). The inspection can be performed with a particle counter.

Requirements

The USP 24 requirements for "particulate matter in injections, small-volume injections" must be fulfilled. The contamination with particles during the filling step should be equivalent at all available machines.

5. Filling Trials (Media Fill Run)

Procedure and requirements

Refer to SOP No. Val. 700.70.

6. Filling Volume Accuracy

The filling accuracy should be within ± % of the adjusted and desired filling volume in accordance with the machine specification, etc.
Attention limit: ± 1%
Action limit: ± 2%

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.70 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Media Fill Run**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.70 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Media Fill Run

PURPOSE

To describe the media fill procedure to qualify the aseptic following lines

RESPONSIBILITY

It is the responsibility of the production manager and technical service manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Documentation

The document should include at least the following:

- Identification of the process to be simulated and a copy of the batch record to be used
- Identification of the rooms to be used
- Identification of the filling line and equipment to be used
- Type of container and closure to be used
- Line speeds (low, normal, and high)
- Number of units to be filled
- Number and type of interventions to be included in the test
- Number of personnel participating
- Media or placebo materials to be used
- Volume of medium to be filled into the containers
- Incubator identification, and incubation time and temperature for the filled units
- Environmental monitoring to be performed
- Growth promotion test
- Box and tray number and time, especially of any positive units
- Verification of medium sterility

Procedure

All the process should be videotaped or observed to gain further insight into problem resolution. The test should be performed under worst case approach.

Units to be filled

The probability of detection of nonsterility in a media fill = $1 - (1 - x)^n$, where x = acceptable contamination rate and n = the number of vials filled. It should be the same as a normal production run, but not less than 3000 units.

2. Solutions

2.1 Media to be used

Soybean casein digest broth shall be used for normal media runs but thioglycolate broth shall be used for the detection of anaerobic organisms, especially when a filtered nitrogen purge is used to ensure anaerobic conditions.

2.2 Compounding operations

A suitable holding tank is sterilized in place by steam. The following sterilized parts are aseptically connected to the tank: a blender valve, a safety relief valve, and a vent filter assembly containing a 0.2 μm filter. Prepare the media according to manufacturer instruction. Adjust pH.

The medium is sterilized by autoclaving it to 121°C for 30 min, after which it is rapidly cooled to 25 to 30°C. Growth media is handled in a manner similar to the production process being simulated. The medium is passed through the run as though it were an actual product batch, and all routine procedures used in manufacture of a batch are performed (i.e., filter integrity testing, sampling, etc.).

Once the medium has been processed, it is held for a period of time at least equal to that for aseptically produced materials. Any aseptic manipulations performed during and at the end of the hold period should be simulated as well (i.e., sampling, refiltration, hold times, and product recalculation).

2.3 Verification of medium sterility

Perform sterility test for the bulk media.

2.4 Filling operations

The containers and closures, if necessary, are cleaned and sterilized using SOPs. It is preferable to use materials, components, and closures that have remained in the aseptic processing area for extended periods.

The filling machine is operated at the predetermined fill rate for the container size utilized, as well as at the fastest speed (handling difficulty) and the slowest speed (maximizing).

The containers are sealed and the medium-filled units are collected in sequentially numbered trays or boxes (notified to the filling time). It is preferable to use materials, components, and closures which have remained in the aseptic processing area for extended periods.

The filled units should be briefly inverted and swirled after filling to assure closure contact with the medium. Increase the size of filling crew to more than the number necessary to fill the batch. All routine activities which take place on the filling line should be a part of the test (i.e., weight adjustments, replenishment of containers, addition of components, change of filling pump, change filter, etc.). Increase the size of filling crew to more than the number necessary to fill the batch.

3. Lyophilized products

3.1 Compounding and filling operations

3.2 Lyophilization operations

The method employed for lyophilization process simulation testing generally is similar to those used for solution fills with the addition of the transport and freeze-drying steps. However, it should focus on loading and sealing activities, which are presumed to be the greatest source of potential contamination.

Containers are filled with medium, and stoppers are partially inserted. The containers are loaded into the lyophilizer. A partial vacuum is drawn on the chamber and this level is held for a predetermined time. The vacuum must not be so low as to permit the medium in the containers to boil out.

The chamber is then vented and the stoppers are seated within the chamber. The stopper units are removed from the aseptic processing area and sealed.

An anaerobic condition exists if there is need for sterile inert gas to break the vacuum on the chamber and remain in the container after sealing. The use of anaerobic medium (e.g., alternative fluid thioglycolate medium) would be appropriate where the presence of anaerobic organisms has been confirmed in either environmental monitoring or, more likely, during end product sterility testing.

Where anaerobic organisms have not been detected in the environmental monitoring or sterility testing, lyophilizer process simulation tests should utilize TSB and air.

Alternatively, an appropriate number of glass vials are filled to the proper level with sterilized WFI, following which the filled bottles are subjected to the lyophilization process. The processed bottles are then filled with a known volume of a sterile liquid medium, sealed, and incubated as described above.

4. Powders

Selection of placebo powder

The chosen material must be easily sterilizable, dispersible, or dissolvable in the chosen medium. The principal sterile placebo materials (irradiated in a final container) are lactose, mannitol, polyethylene glycol 6000, and sodium chloride. The material should pass solubility testing at the desired concentration with suitable amount and time of agitation.

4.1 Compounding operations

A quantity of an appropriate sterilized placebo powder is blended with sterile excipients prior to filling (if needed) in a manner similar to the production process being simulated. The medium is passed through the run as though it were an actual product batch, and all routine procedures used in manufacture of a batch are performed. Once the medium has been processed, it is held for a period of time at least equal to that for aseptically produced materials. Any aseptic manipulations performed during and at the end of the hold period should be simulated hold times and product recalculation.

4.2 Filling operations

The containers and closures are cleaned and sterilized using SOPs. The filling machine is operated at the predetermined fill rate for the container size utilized, as well as at the fastest speed (handling difficulty) and the slowest speed (maximizing). The containers are sealed and the medium-filled units are collected in sequentially numbered trays or boxes (notified to the filling time).

All routine activities which take place on the filling line should be a part of the test (i.e., weight adjustments, replenishment of containers, addition of components, change of filling pump, change filter, etc.). Increase the size of filling crew to more than the number necessary to fill the batch.

4.3 Powder reconstitution

Before incubation of the vials, powder should be reconstituted with adapted media (TSB or thioglycolate broth) using aseptic technique under laminar flow. The reconstitution volume is according to the volume described in the original formula. Strict environmental monitoring should be followed through this step.

Incubation Conditions

The incubation period should be not less than 14 days per procedure. An incubation temperature in the range of 20 to 35°C may be used depending upon information gained from the environmental monitoring (during routine production, sterility testing, and media filling).

Inspection

It may be advisable to inspect containers midway through the incubation period. The filled units should be briefly inverted and swirled after filling to assure closure contact with the medium. Personnel who have had specific training in the visual inspection of media-filled units should perform these incubator checks.

SOP No. Val. 700.70 **Effective date: mm/dd/yyyy**

Approved by:

Growth promotion test

The medium in the final containers should be tested for growth promotion method according to the in-house or official monograph. The units used for growth testing

must subject to the same processing steps (e.g., cleaning, depyrogenation, sterilization, filtration, filling, lyophilization, reconstitution) up to the point at which they are placed into incubation.

Container inspection

The containers should be inspected for any breach of integrity which may have gone undiscovered during release inspection prior to incubation, or could have occurred during post-inspection handling (e.g., transport to incubator, microbiological inspections).

Damaged containers should not be considered in the evaluation (acceptance) of the aseptic processing.

An identification of the organism may be performed, but the information will most likely be of little value for damaged containers.

Acceptance criteria

Number of vials with microbial growth × 100

$$\text{The \% of contamination} = \frac{\text{Number of vials filled} - \text{Number of damaged vials}}{\text{The acceptable percentage of contamination is } \leq 0.1\%}$$

Failure investigation and corrective action

A contaminated container should be examined carefully for any breach in the container system. All positives (from integral containers) should be identified to at least genus, and to species whenever possible. The identification of contaminant should be compared to the database of the organisms recently identified.

The biochemical profile of the contaminant can then be compared to that of microorganisms obtained from the sterility tests and bioburden and environmental monitoring programs, in order to help identify the potential sources of the contaminant.

SOP No. Val. 700.70 **Effective date: mm/dd/yyyy**

Approved by:

- If media fill contaminant is the same as sterility test contaminant:

- Increase media fill vial quantities and routine filling environmental monitoring to identify the source of contamination.
- Review environmental data obtained during line setup.

- If media fill contaminant is the same as media fills environmental contaminant:
  - Increase routine environmental monitoring to determine if the contamination potential exists during routine filling operation.
- If media fill contaminant is the same as routine environmental contaminant:
  - Increase media fill environmental monitoring (in the same location) to confirm the contaminant source.
- If sterility test contaminant is the same as media fill environmental contaminant:
  - Increase routine environmental monitoring (in the same location) and number of media fill vial to conform.
- If sterility test contaminant is the same as routine environmental contaminant:
  - The sterility test is voided.
  - Investigate sterility test procedures and room sanitation and sterilization methods to eliminate cause.
- If media fill environmental contaminant is the same as routine environmental contaminant:
  - Increase the number of media fills vial in media fill in order to determine the product risk potential.
  - Review monitoring technique for possible problem.
  - Review personnel practices, gowning, sanitation, and sterilization.
- If media fill environmental contaminant is the same as sterility test contaminant and if routine environmental contaminant is the same as sterility test contaminant:
  - Check environmental monitoring methods and techniques closely for problems.
  - Review personnel practices, gowning, sanitation, and sterilization.

If the failure repeated represents a potential for product concern, a corrective action system should be activated. This system should contain provision for the following:

- Critical systems (HVAC, compressed air and gas, water, steam) should be reviewed for documented changes.
- Calibration records should be checked.
- All HEPA filters in the filling area should be inspected and rectified, if warranted.
- Training records for all individuals (production, maintenance, cleaning) involved in the fill should be reviewed to assure proper training was provided.

If the root cause is assignable, corrective action needs to be taken and documented. If three consecutive runs over action levels occur, a problem analysis corrective action report (PACAR) must be issued.

Frequency

Initial validation: three successful consecutive media fill runs required
Revalidation: twice per year, and additional tests should be performed in response to adverse trends or failures in the ongoing monitoring of the facilities or process such as:

- Continued critical area environmental monitoring results above the action levels
- Increased incidence of product sterility test failures
- Break of asepsis in the aseptic processing area, or to evaluate changes to procedures, practices or equipment configuration

Examples of such changes include:

- Major modification to the equipment or immediate product containers or closure
- Modification to equipment or facilities, which potentially affects the quality of air flow in the aseptic environment
- Major changes in the number of the production personnel or initiation of second (or third) shift production when the facility has been qualified only for single shift operations
- Major changes to the aseptic production process or procedures

The process should be requalified when production line is not in operation for 3 months. In case of one run failure, three consecutive runs should be performed.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.80 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Half-Automatic Inspection Machine**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.80 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Half-Automatic Inspection Machine

PURPOSE

To describe the procedure for validation of the half-automatic inspection machine to ensure that it meets installation, operational, and performance qualification requirements

RESPONSIBILITY

It is the responsibility of the production manager and technical services manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturers.
- Verify that the utilities required are available.
- Installation shall be conducted per instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual.
  - Maintenance manual.
  - List of change parts.
  - Electrical drawings.
  - Mechanical drawings.

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

3. Performance Qualification

The following parameters shall be evaluated for product to be inspected:

- Rotation velocity of ampules and vials prior entering the inspection cabin
- Rotation velocity of ampules and vials during visual inspection
- Setting of background illumination
- Setting of Tyndall lamps
- Coordination of brake moment, chain speed, and dropout position

After finishing these evaluations, the inspection efficiency of the machine should be compared with the visual inspection method.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.90 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Ampule Crack Detection Machine**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.90 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Ampule Crack Detection Machine

PURPOSE

To describe the procedure for validation of the ampule crack detection machine to meet the specification; other machines available shall be validated accordingly.

RESPONSIBILITY

It is the responsibility of the production manager and technical services manager to follow the procedure. The quality assurance manager is responsible for SOP compliance

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturers.
- Verify that the utilities required are available.
- Installation shall be conducted per the instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Mechanical drawings

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

3. Performance Qualification

Mix 50 ampules rejected by the dye vacuum with 50 accepted ampules to produce a calibration set. Each calibration set should contain a representative sample of ampules with different sizes of holes and cracks as shown by the intensity of the dye in the ampule. Number the bad ampules on the base depending on the intensity of the dye, from 1 to 50.

Pass the ampule sets through the machine at the manufacturer-recommended setting.

Requirements

All ampules rejected by the dye-vacuum method must also be rejected on the ampule crack detection machine.

Frequency

Initial validation: three test runs
Revalidation: after maintenance on the machine yearly (per company frequency)

4. Comparisons with the Dye-vacuum Method on Actual Product Lots

Procedure

To compare the effectiveness of the machine with the dye-vacuum method, production batches are passed through the crack detection machine and then through the dye-vacuum chamber. The final check after that is carried out again on the crack detection machine.

The scheme of documentation and evaluation of the results is shown below.

Requirements

The crack detection machine shall recognize more bad ampules than the dye-vacuum method and shall reject an equivalent number of good ampules as the dye-vacuum method.

Frequency

Initial validation: three production batches of each product
Revalidation: one production batch of each product once every 3 years

5. Effect of Solution or Dried Product on the Outside of Ampules

To determine the effect of wet or dry product on the outside of the ampule, select 100 good ampules and pass through the machine. The ampules are then wetted (with water) and passed through the machine again. Rewet the ampules (with product solution); allow solution to dry on the outside of the ampules. Pass the ampules again through the crack detection machine.

Requirements

No requirements; for information only

Frequency

Initial validation: once per product
Revalidation: once every 2 years

6. Checking of Counting Device Accuracy

During the comparisons, three ampule trays shall be removed every hour and the count checked for accuracy over one working shift.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

SOP No. Val. 700.90 **Effective date: mm/dd/yyyy**
Approved by:

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.100 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Laminar Flow Installations**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.100 **Effective date: mm/dd/yyyy**
Approved by:

SUBJECT: Laminar Flow Installations

PURPOSE

To ensure that laminar flow meets the specification

RESPONSIBILITY

The quality control manager is responsible for following the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Integrity Test of HEPA Filters

Procedure and requirements are according to SOP No. Val. 600.30.

Frequency

Initial validation: at the time of installation
Revalidation: once per year

2. Air Stream Profile and Air Velocity

Procedure

Use smoke cartridges to determine the air stream profile of the used laminar flow system. Measure the air velocity of at least 15 different locations below the LAF installation with the help of an anemometer.

Requirements

There should be undisturbed laminar air flow above the machinery and exhaust of the air. The average air velocities should be as follows: 0.4 to 0.5 m/s with a lower limit of 0.4 m/s at each measure point.

Frequency

Initial validation and revalidation once per year

3. Surface Contamination

Procedure and requirements are according to SOP No. Val. 600.30.

Frequency

Initial validation and revalidation: once per year

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.110 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Sterile Filtration Validation**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.110 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Sterile Filtration Validation

PURPOSE

To describe the procedure for validation of the sterile filtration to ensure filter integrity before and after the filtration

RESPONSIBILITY

The production manager is responsible for following the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Product Compatibility

Perform a test filtration with the selected product samples prior to and after filtration. Results should be examined with regard to chemical stability (i.e., active content, physical, color, etc.).

Requirements

Unfiltered and filtered product: no chemical and physical difference

2. Filter Integrity Test prior to and after Sterilization

Perform a pressure hold test with the nonsterilized filter. Expose the filter to the chosen sterilization conditions. Repeat the pressure hold test with the sterilized filter. For pressure hold test conditions, follow the recommendations of the filter supplier.

Requirements

Filter shall meet the pressure hold test prior to and after sterilization successfully per supplier specification.

Frequency

Repeat the procedure three times for each filter type.

3. Filter Integrity Test after Product Filtration

Perform a pressure hold test with the sterilized filter. Perform the filtration of the product to be sterile filtered using normal production conditions. After the filtration step, the filter should be tested again with the bubble point test.

The filter shall meet the recommendation of filter supplier for pressure hold test.

Requirements

The filter must indicate integrity after undergoing a filtration at full production scale.

Frequency

For the largest batch size of each product: three times

4. Microbial Effectiveness (Bioburden)

The product bioburden must comply with the microbial retention capacity of the filter.

Frequency

For each product and each filter type: three times

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 700.120 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Cleaning Efficiency of Production Equipment for Parenterals**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 700.120 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Cleaning Efficiency of Production Equipment for Parenterals

PURPOSE

To describe the procedure to ensure effective cleaning of parenteral manufacturing equipment to minimize the chances of cross-contamination and unacceptable viable count

RESPONSIBILITY

The validation manager and quality control manager are responsible for following the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Aqueous Products

1.1 Chemical cleanliness

Procedure

At the end of approval cleaning, the equipment should be rinsed with sterile water for injection. The water for final rinse shall be tested for its conductivity. As an alternative, run a placebo batch after a production batch and subsequent cleaning. Analyze the samples of placebo batch for the active ingredients of the previous run batch to ensure that there is no cross-contamination.

Requirements

Conductivity: <1.3ms/cm at 25°C

Frequency

Three times for each piece of equipment and each different product

1.2 Microbiological cleanliness

Procedure

After cleaning, the equipment should be rinsed with sterile water for injection. This water should be collected and tested for its viable count.

Requirements

Viable count: ð 10 CFU/100 ml

Frequency

Three times for each piece of equipment and product

2. Oily Products (Arachis Oil)

Procedure

Rinse the equipment with acetone after the cleaning. Analyze the rinsing using a UV spectrophotometer (sample size 20 ml). Wipe at each selected location a surface area of between 100 and 800 cm^2 or alternatively rinse the equipment with a suitable liquid and check.

Requirements

The residues found should not exceed the method's detection limit for the relevant active detergent.

Frequency

Initial validation: once at different equipment locations
Revalidation: once every 3 years

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates and contract manufacturers

SECTION

VAL 800.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 800.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Kneading Machine**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 800.10 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Kneading Machine

PURPOSE

To describe the procedure for validation of the kneading machine to ensure product homogenization and that equipment meets installation, operational, and performance qualifications

RESPONSIBILITY

It is the responsibility of the validation manager, quality control manger and concerned departmental managers to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturers.
- Verify that the utilities required are available.
- Installation shall be conducted per the instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Mechanical drawings

1.1 Net capacity of the granulating chamber

Fill the granulating chamber with preweighed quantities of water.

Requirements

The available net capacity should be equal to the manufacturer specification.

1.2 Velocity of the granulating device

Determine the velocity of the granulating device with an empty and a loaded granulator.

Requirements

Shall meet the manufacturer specification

1.3 Liquid dosing pump

1.3.1 Dead volume determination of the dosing system

Prepare a sample of the granulating liquid and pump it into a separate vessel. Determine the percentage of granulating liquid transferred. Determine the pump losses.

1.3.2 Dosing speed

Determine the effective liquid flow per minute by pumping a normal production granulating liquid at fixed dosing speeds.

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

2.1 End point determination of granulation

Determine procedure to establish end of granulation process for each product (for instance, by particle size distribution of granulate).

3. Performance Qualification

Manufacture one batch of the product, dry it and take samples for the analysis of the contents.

3.1 Compressing capabilities and tablet characteristics evaluation

The material obtained from the kneading process should be, after drying and blending, compressed to tablets. The compressing capabilities and the tablet characteristics (content uniformity, thickness, hardness, friability, weight variances, and disintegration time) should meet the finished product specification for the compressed tablets.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 800.20 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Oscillating Granulator**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 800.20 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Oscillating Granulator

PURPOSE

To describe the procedure to ensure that the oscillating granulator meets installation, operational, and performance qualifications

RESPONSIBILITY

The validation manager and respective departmental managers are responsible for following the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturer.
- Verify that the utilities required are available.
- Installation shall be conducted per the instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings

1.1 Calibration of recording equipment

Check the product flow vibrator and the oscillating rotor.

Procedure

Evaluate the effective frequency of the product flow vibrator and the oscillating rotor at the different possible adjustments; develop history and date.

2. Operational Qualification

- Verify alarm control,
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

2.1 Evaluation of equipment capacity

Procedure

Verify the capacity of the equipment.

Requirements

Shall meet the manufacturer's specifications

3. Performance Qualification

Influence of machine variables on particle sizes and moisture content of the granulations:

- Speed of product flow through the granulator
- Flow vibrator frequency
- Product filling level in the granulating chamber
- Sieve mesh sizes
- Oscillating rotor frequency

Procedure

Determine the moisture content of the nongranulated product with the granulated product.

Requirements

Product shall meet the product specification per SOP.

3.2 Compressing capabilities and tablet characteristics evaluation

After establishing the process variables for the granulation step, compressing capabilities and tablet characteristics (thickness, hardness, friability, weight variances, and disintegration time) should be reviewed.

Requirements

Product shall meet the specification per SOP for individual products.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 800.30 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Milling Machine**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 800.30 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Milling Machine

PURPOSE

To describe the procedure to ensure that the milling machine meets installation, operational, and performance qualifications

RESPONSIBILITIES

It is the responsibility of the validation manager, technical services manager and respective departmental managers to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturer.
- Verify that the required utilities are available.
- Installation shall be conducted per the instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Mechanical drawings

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

3. Performance Qualification

Influence of machine variables on granulation properties:

- Speed of product flow through the mill
- Rotation speed of the milling unit
- Influence of sieve mesh sizes (if sieves are used) on the granulation properties (e.g., particle size distribution, moisture content, poured density, tap density, and flow capacity)

3.1 Compressing capabilities and tablet characteristics evaluation

After fixing the process variables for the milling step, compressing capabilities and tablet characteristics (thickness, hardness, friability, weight variances, and disintegration time) should be investigated.

Requirements

The product shall meet the specification per SOP.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 800.40 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Fluid Bed Drier**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 800.40 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Fluid Bed Drier

PURPOSE

To describe the procedure for validation of the fluid bed drier to ensure that it meets installation, operation, and performance qualification requirements

RESPONSIBILITY

It is the responsibility of the production manager and technical services manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturer.
- Verify that the utilities required are available.
- Installation shall be conducted per instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings

Instruments for measuring temperature, humidity, time, air volume and pressure, as well as recording devices for these variables, should be calibrated.

1.1 Air temperature distribution

Place several thermocouples at different locations in an empty fluid bed drier, e.g.:

- Inlet air channel below product container mesh bottom
- Product container
- Below filter bag
- Above filter bag
- Exhaust air channel

Measure the temperatures, letting in air of a constant temperature (e.g., 60°C).

1.3 Inlet air installation

1.3.1 Delay time for achieving constant air conditions

Determine, by use of a thermocouple and hygrometer, the necessary delay time required at an adjusted inlet air temperature (in relation to drying processes) for reaching constant air conditions. Determine these figures for the first use of the equipment at the working day, as well as for further use of the equipment at the same working day.

Also calculate from the obtained data the water content of the inlet air (g water per kg air) and compare with the previously fixed requirements.

1.3.2 Microbiological quality of the inlet air

Determine, by use of a biotest RCS centrifugal air sampler, the microbiological quality of the inlet air.

Sampling time 5 min = 8:1 air

Requirements

ð 200 CFU/m^3 inlet air

1.3.3 Influence of weather on inlet air conditions

1.3.4 Inlet air installation

1.3.5 Delay time for achieving constant air conditions

Procedure

Determine, by use of a thermocouple and a hygrometer, the necessary delay time required at an adjusted inlet air temperature (in relation to granulating processes)

for reaching constant air conditions. Determine these figures for first use of the equipment at the working day, as well as for further use of the equipment at the same working day.

Also calculate from the obtained data the water content of the inlet air (g water/kg air) and compare to the requirements.

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

Procedure

Run three batches of each product and analyze for:

- Active ingredient homogeneity
- Moisture content
- Particle size distribution
- Percentage fines
- Tap density

Based on these data try to fix a drying end point of the process (e.g., correlation between moisture content of the product and the product bed temperature).

3. Performance Qualification

Run each product type.

Requirements

Each product shall meet the product characteristics per SOP.

REASONS FOR REVISION

Effective date: mm/dd/yy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 800.50 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Blender**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 800.50 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Blender

PURPOSE

To describe the procedure for validation of the blender to ensure that it meets installation, operational, and performance qualification requirements

RESPONSIBILITY

It is the responsibility of the production manager and technical services manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturer.
- Verify that the required utilities are available.
- Installation shall be conducted per the instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Mechanical drawings

1.1 Calibration of the control and recording equipment

Instruments for measuring temperature, pressure, time, mixing chamber slope, and mixing velocity, as well as recording devices for these variables, should be calibrated.

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

2.1 Net capacity of the mixing chamber

Procedure

Fill the mixing chamber with preweighed quantities of water.

Requirements

The available net capacity should be equal to the supplier specification.

2.2 Mixing or stirring velocity

Measure velocity three times at low, medium, and high speed and compare the average and deviation from the average of the single measurements with the supplier specification.

Requirements

Compliance with the supplier specification

3. Performance Qualification

3.1 Product homogeneity

3.1.1 Mixing process

Procedure

Fix the mixing or stirring velocity, load the mixer with the product and switch the mixer on. After previously fixed intervals, the mixer should be switched off and samples should be taken from different locations of the product surface. The samples should be analyzed for their active content.

3.1.2 Unloading

Procedure

After determination of the suitable mixing time to achieve product homogeneity, the influence of the unloading process on the homogeneity should be evaluated. Samples should be taken and sent to QC for analysis.

Requirements

Homogeneity should remain consistent.

3.2 Water content of the product

Take samples of the product prior to mixing, after mixing, and after unloading (begin, mid, end). Determine the water content of all samples.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 800.60

Effective date: mm/dd/yyyy
Approved by:

TITLE: **Tablet Press**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 800.60 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Tablet Press

PURPOSE

To describe the procedure for validation of the tablet press to ensure that it meets installation, operational, and performance qualification requirements

RESPONSIBILITY

It is the responsibility of the production manager, validation manager, and technical services manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturers.
- Verify that the utilities required are available.
- Installation shall be conducted per the instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Mechanical drawings

1.1 Calibration

The following meters should be calibrated:

- Revolution speed of the tableting table
- Counterpressure at the precompression station
- Counterpressure at the main compression station

1.2 Adjustment of compression forces of the precompression and main compression stations

Use adequate pressure meter to adjust the compression forces.

1.3. Control of the product feeding unit

Determine the rotation speed of the product feeding unit at the variable adjustments per manufacturer specification.

1.4 Adjustment of the tablet outlet station

Prepare for each tablet diameter a test set of two upper punches (shorter and longer) as the standard punches (e.g., using a plaster layer). Build in the one punch and run the tablet machine with a placebo product. Then perform the same test with the other punch.

Requirements

All tablets compressed with manipulated punches should be discharged by the machine for 100%.

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.

- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for the relevant staff.

Run one pilot batch for each product on the tablet press and investigate the items detailed next.

2.1 Loading of granulation

Requirements

No sticking of the granulations in the feeding system

2.2 Segregation of granulation

Take samples from the granulation prior to tableting and during tableting (beginning, middle, and end of the pilot batch); analyze the particle size distribution of the samples taken.

Requirements

No significant deviations in particle size distribution should be found.

2.3 In-Process controls

In-charge the sample quantity of tablets to be taken at routine intervals to the available number of punches in the tableting table.

2.4 Control of the tablet outlet station

To evaluate the self-adjusting properties, collect all tablets discharged by the machine and evaluate them for their weight.

3. Performance Qualification

Evaluation of the compressing capabilities and tablet characteristics

SOP No. Val. 800.60 **Effective date: mm/dd/yyyy**
Approved by:

Procedure

The compressing capabilities and tablet characteristics (i.e., content uniformity, thickness, hardness, friability, weight variation, and disintegration time) should be investigated.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 800.70 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Metal Check Device for Tablets**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 800.70 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Metal Check Device for Tablets

PURPOSE

To describe the procedure to ensure that the metal check device meets installation, operational, and performance qualifications to detect metal parts accidentally added into the powder blend during and after sieving

RESPONSIBILITIES

It is the responsibility of the production manager, validation manager, and technical services manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturer.
- Verify that the utilities required are available.
- Installation shall be conducted per the instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Mechanical drawings

2. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

3. Performance Qualification

3.1 Sensitivity determination

Prepare a test set of tablets with known contamination with stainless steel or iron wires or balls (e.g., used as sieve material for an oscillating granulator or a milling machine). Pass these tablets (falling free, directed through the center of the detector area, or directed along the side of the detector area) at the different adjustable sensitivity levels through the metal check device and document whether the device is approving or withdrawing the tablets. Determine the warm-up time of the device necessary to receive a constant device sensitivity.

Requirements

The sensor should detect a tablet with an iron ball of 0.5 μm diameter at a medium sensitivity adjustment.

3.2 Determination of the pass-through time of the different products

Determine the pass-through time necessary for the different products available and compare the calculated speeds with the requirements fixed by the supplier.

3.3 Determination of the correct reaction time of the outlet mechanism for withdrawn tablets

Determine the minimum time necessary to ensure that test-set tablets will be sorted out in each case.

3.4 Determination of the pass-through capacity

Mix the tablet test set prepared for sensitivity determination with placebo tablets. Pass this mixture completely through the metal check sensor at a mass flow necessary to cover the output (kg tablets/min) of the connected tablet press.

Requirements

The number of manipulations of iron or stainless steel containing tablets withdrawn by the device should be determined and compared.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 800.80 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Tablet Coater**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 800.80 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Tablet Coater

PURPOSE

To describe the procedure for validation of the tablet coater to ensure that it meets installation, operational, and performance qualification requirements

RESPONSIBILITY

It is the responsibility of the production manager and technical services manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Installation Qualification

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Check for any physical damage.
- Confirm location and installation requirements per recommendation of manufacturers.
- Verify that the utilities required are available.
- Installation shall be conducted per the instructions provided in the manual.
- Ensure that all relevant documentation is received:
  - User manual
  - Maintenance manual
  - List of change parts
  - Electrical drawings
  - Mechanical drawings

1.1 Calibration

Instruments for measuring time, temperature, pressure, pressure differences, revolution speed, flow rate, air volume, and converters, as well as recording devices for these variables, should be calibrated.

1.2 Air volume

Determine the achievable air volume flow (m^3/h) for the empty and the loaded coater and compare the results with the previous set requirements and the supplier specification.

1.3 Delay time for achieving constant inlet air conditions

Determine, by use of a thermocouple and a hygrometer, the necessary delay time required at an adjusted inlet air temperature (with regard to the coating process) for reaching constant air conditions. Determine these figures for first use of the equipment at the working day, as well as for further use of the equipment at the same working day.

Also calculate from the obtained data the water content of the inlet air (g water per kg air) and compare with the requirements.

1.4 Microbiological quality of the inlet air

Determine, by use of biotest RCS centrifugal air sampler, the microbiological quality of the inlet air.

Sampling time 2 min = 80:1 air.

Requirements

Viable count ð 200 CRU/m^3 inlet air

1.5 Microbiological quality of the compressed air system

The outlet of the compressed air supply point is opened and purged for 5 min. Adjust to a flow volume of about 30 l/min. Then the compressed air is passed through an air sampler equipped with a 0.22 μm filter. Sampling time should be about 5 min. This procedure should be performed three times. One filter should later be incubated for anaerobic, the other for aerobic viable count. Viable count should be ð 200 CFU/m^3.

1.6 Mixing properties of the coater

Load the coating pan for 90% of the determined usable capacity with product (e.g., white placebo tablets). Subsequently add additional 10% of a different product (e.g., colored placebo tablets). Measure the time necessary to achieve a homogenous mixture by visual examination.

2. Coating Solution Vessel

2.1 Capacity of the vessel

Fill the coating solution vessel with preweighed quantities of water.

Requirements

The available capacity should be equal to the manufacturer specification.

2.2 Mixing velocity of the stirring unit

Determine the effective stirring velocity at low, medium, and high speed stirring and compare it to the manufacturer specification.

3. Spraying Equipment

3.1 Spraying pattern

Establish the characteristics of the spraying pattern in relation to spraying pressure, spraying speed, viscosity of liquid to be sprayed, and nozzle sizes.

4. Operational Qualification

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operations manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

4.1 Optimization of process parameters

Optimization of process parameters should be based on use of placebo batches, environment equivalency factor, heat losses, or worst case simulation (too dry and too wet coating conditions).

5. Performance Qualification

Three production pilot batches shall be run and checked for:

- Physical attributes of inspection for coated tablets per SOP
- Thickness
- Diameter
- Weight
- Disintegration time
- Hardness
- Moisture content
- Actives content
- Dissolution time of actives

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

SECTION

VAL 1000.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 1000.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Installation Qualification of Computerized Equipment**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 1000.10 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Installation Qualification of Computerized Equipment

PURPOSE

To describe validation guideline for the computerized equipment to meet the installation qualification

RESPONSIBILITY

It is the responsibility of the production manager, technical service manager, and computer engineer to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

Installation qualification shall include the verification that user manuals, technical manuals, and instrument calibration reports of the computerized system are available, complete, appropriate, relevant, and up to date.

1. IQ Approach

The installation qualification of automatic control systems shall consist of a logical panoply of tests. The tests are carried out step-by-step on each component. The structure of the installation qualification shall be standardized for all installation qualifications of computerized pharmaceutical systems as follows.

2. Document Description

The documents description shall include a paragraph stating the objective of the document and a paragraph specifying the scope of the document, i.e., the exhaustive list of the concerned equipment, or categories of equipment.

3. IQ Summary

The goal here is to summarize the installation qualification document. This includes:

- An abbreviated description of the computerized system analyzed

- For protocols, the preapproval of the document
- For IQ reports, the certification of the document
- For IQ reports, a summary of the deviations observed during the installation qualification

4. System Description

The purpose here is to describe the as-built installation and to compare the findings with system specifications. Components of the system are compared with those specified. Any detected discrepancy is mentioned for investigation, correction, justification, and approval. When components found are neither specified nor approved, they will be mentioned as not specified.

4.2 General characteristics

The general system characteristics are reported, including:

- Manufacturer, main contractor, customer
- Intended purpose
- System identification (serial number, inventory number, etc.)
- System location
- Technical characteristics
- Main system limits
- Required utilities

4.3 Hardware

The hardware of the system is described, including:

- Summary block diagram
- List of main components, processors and modules, memories, storage, signal converters, networking, communications, and peripherals, including model and serial numbers when applicable

- List of all fuses (type, rated current, location, protected items)
- Operating controls and alarms
- Central commands and overrides
- Manual downgraded controls

4.4 Software

The software of the system is described, including:

- Software identification (name, version, etc.)
- Operating system (name, version, etc.)
- Source code availability
- Language and tools used

5. Documentation

The purpose here is to verify the documentation of the system. This documentation must be appropriate, up to date, relevant, and complete. The analyzed documentation may include:

- User requirements
- System specifications
- Purchase orders and related information
- As-built drawings (block diagrams, mechanical drawings, electrical schematics, wiring, and interconnection diagrams)
- Technical documentation (input–output list, alarms and safety list, automatic and manual control listings, regulation loop descriptions, calibration guide, maintenance guide, troubleshooting guide, etc.)
- Software technical documentation (programmer's guide, reference guide, software diagrams, etc.)
- User manuals (user's guide, guide to operations, etc.)
- Instrumentation calibration certificates (not expired)
- Source code availability and storage arrangements

6. Structural Testing

6.1 Introduction

This structural testing section of the installation qualification consists of verifying the internal integrity of the equipment software and hardware and should be done separately for each.

6.2 Hardware structural testing

This testing consists of a panoply of verifications pertaining to the hardware of the equipment. Tests include:

- Cabling and wiring
- Labeling of wires and components
- Grounding of the system
- Hardware testing performed by the supplier (normal and stress testing)
- Electromagnetic interference compatibility

6.3 Software structural testing

This testing consists of assessing the quality of the development process, the produced code, and the testing process.

Verify quality of the development process by auditing the supplier's internal development process. The aspects analyzed cover:

- Specification methodology
- Diagramming techniques used
- Design verification
- Existence and adherence to production SOPs
- Enforced naming conventions

The method used to verify the quality of the produced source code consists of group reviews, called *structured walk-through* by experts in the field. In summary, these reviews consist of a presentation, made by the designers of the software, of source code sections selected by the reviewers according to their influence on the process or safety of the system. The acceptance criteria shall be based on existing internationally accepted engineering standards that the supplier must meet (delivery timing, budgets, personnel, methods used).

The aspects analyzed cover:

- Adherence of produced functions to system specifications
- Existence and quality of comments into the source code
- Code organization and structure
- Proper indentation
- Out-of-range or out-of-context input detection, including sensor fail detection

- Data edits
- Timeouts
- Abnormal conditions recovery
- Absence of dead code

The quality of the supplier testing process is verified by auditing the supplier's internal testing process. The aspects analyzed cover:

- Testing methodology, including stress testing
- Existence of and adherence to testing SOPs
- Testing reports

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 1000.20 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Operational Qualification of Computerized Equipment**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 1000.20 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Operational Qualification of Computerized Equipment

PURPOSE

To provide the guideline for the operational qualification of computerized equipment to ensure that it meets the equipment operational requirement

RESPONSIBILITY

It is the responsibility of the production manager, technical service manager, and computer manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Introduction

A specific operational qualification protocol shall be prepared for each piece of equipment undergoing operational qualification.

2. OQ Approach

The operational qualification of computerized systems consists of a group of tests, pooled in functional checks. The tests are carried out step by step on each component. The general approach used is of the gray-box type. More precisely, study the input and output data transmission at intermediate points. The structure of the operational qualification may be standardized for all operational qualification of computerized pharmaceutical equipment.

3. Document Description

The objective of the document and the scope of the document, i.e., the exhaustive list of the concerned equipment or categories of equipment, are the operational qualification documents to be included.

4. OQ Summary

This summary includes:

- An abbreviated description of the computerized system analyzed
- For protocols, the preapproval of the document
- For OQ reports, the certification of the document
- For OQ reports, a summary of the deviations observed during the operational qualification

5. Reporting the Initial Setpoint

Each user-accessible setpoint of the installation, equipment, or control system will be reported. Results shall be written in a report.

Most of these setpoints are fixed by the supplier, detailed in the purchase order, or are part of the installation qualification file. If the setpoints are fixed by the supplier, there are no acceptance criteria unless the supplier documents the setpoint in written form. When available from supplier's documents or when specified in the bill of order or the installation qualification report, the observed setpoints shall be compared with the documented ones. Any detected discrepancy is mentioned for investigation, justification, approval, or correction. When reported parameters are neither specified nor approved, they shall be mentioned as not specified.

Reporting the initial setpoints enables definition of the characteristics of the system as it is during qualification and will evidence any subsequent modifications of the setpoints.

6. Checking Digital Transmissions: Input

Qualification tests shall be carried out in order to check the transmission of one-bit binary information sent by sensors and safeties to the computerized control system or programmable logic controller.

Each sensor or safety tested is activated or deactivated a few times to visualize clearly the transmission. Signal visualization at the controller level is done either directly on the controller using an appropriate submenu or by using adequate validation measuring equipment.

7. Checking Digital Transmissions: Output

The qualifications tests consists of checking the transmission of the one-bit binary information sent by the controller to the contactors, relays, electrovalves, pilot lights, and other digital outputs of the system.

Each tested output is activated or deactivated a few times to visualize clearly the transmission. The visualization of the transmitted signals is made either on the activated system itself (mechanical indicators of electrovalves, start of motors or pumps) or by using an adequate validation measuring equipment.

8. Checking Analog Transmissions: Input

Tests shall be carried out to check the transmission of analog information sent by the sensors of the equipment or utilities to the system controller.

These tests check the integrity of measurement chains between the sensor and the equipment as well as along the measurement chain. For example, a temperature signal carried over by a current loop is checked against the exact temperature level and the exact conversion levels on the current loop. However, if the temperature sensor contains its own local temperature indicator, this indication will be compared to the temperature available on the control system.

Unless technically impossible, the accuracy and linearity of each measurement chain shall be checked at least at two different points of the measurement range. Visualization of values transmitted from the sensors to the system controller is made most often directly on the controller itself (screen or printer), using an appropriate submenu of the controller. The accuracy of the values read on the equipment or utilities instrumentation is checked by means of appropriate calibrated reference instrumentation traceable to national official standards.

9. Checking Analog Transmission: Output

Tests shall be performed to check the transmission of analog information sent by the system controller to analog peripheral systems (proportional valves, recorders, etc.). These tests check the integrity of the analog transmission chain equally between

the control system and the peripheral system as well as along the transmission chain. For example, the command of a proportional valve carried over by a current loop is checked both at the exact opening level and at the exact level of conversion on the current loop.

Unless technically impossible, accuracy and linearity of each output chain are checked. Visualization of values sent to the equipment is made either directly on the checked peripheral system or using appropriate equipment. Accuracy of values transmitted from the analog outputs is checked by using an appropriate calibrated reference instrumentation traceable to national official standards.

10. Data Entry and Boundary Testing

Tests shall be performed to check the data entry functions and the proper rejection of out-of-boundaries values. Where applicable, the mouse, graphic digitizer, or pen interface is checked for correct reaction to the user's commands. These tests include cursor movement checks, button verifications (simple- and double-click, left, right, and center, or special functions when applicable), and dragging operations.

The tests are conducted on critical data entry fields only. Each tested data entry field is challenged, including special key actions, control keys, invalid data type, out-of-range data, incorrect syntax or semantic, etc.

11. Access Control Testing

Tests shall be performed to check the computer system access control functions, including access level differentiation. The tests are conducted on critical functions only. Each tested function is verified against each access level.

For example, three different passwords are created to access the software system controlling lyophilizer. Each password is given a different access level. Using these passwords and an existing one, selected system functions requiring different authorization levels are initiated. The systems must refuse to start a tested function unless a proper password having correct access rights is supplied.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 1000.30 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Performance Qualification of Computerized Equipment**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 1000.30 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Performance Qualification of Computerized Equipment

PURPOSE

To describe the validation guideline for performance qualification of computerized equipment to ensure that it meets the performance requirement

RESPONSIBILITY

It is the responsibility of the production manager, technical service manager, and computer manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

1. Introduction

A specific performance qualification protocol shall be prepared for each piece of equipment undergoing performance qualification. The performance qualification of the computerized system consists of accumulating enough evidence that the computerized system is in compliance with its intended specifications, when functioning for the concerned process at the production premises.

2. Performance Qualification (PQ) Approach

The performance qualification of computerized control systems consists of a group of tests pooled in functional checks. The tests shall be carried out on the integrated system. The structure of the performance qualification shall be standardized for all performance qualification of computerized pharmaceutical equipment.

3. Document Description

Performance qualification documents shall include a paragraph stating the objective of the document and a paragraph specifying the scope of the document, i.e., the exhaustive list of the concerned equipment, or categories of equipment.

4. PQ Summary

The goal here is to summarize the performance qualification document. This includes:

- An abbreviated description of the computerized system analyzed
- For protocols, the preapproval of the document
- For PQ reports, the certification of the document
- For PQ reports, a summary of the deviations observed during the operational qualification

5. Standard Operating Procedure (SOP)

The purpose here is to verify the standard operating procedure at the user's premises. The procedures analyzed include:

- Installation operation SOPs
- Installation preventive maintenance SOPs, including virus checks
- Installation corrective maintenance SOPs
- Change control SOPs (planned and unplanned)
- SOPs for audits and on-going evaluations

These procedures must exist and be appropriate, up-to-date, relevant, and complete. They must be easily available to the users concerned.

6. Training

The purpose of the training section is to check that all people involved with the computerized equipment have received adequate training on operation of the computerized system.

The key aspects of this evaluation shall include checking:

- Existence of training programs for users, both technical and staff personnel
- Contents of training (basic, advanced, in-depth)
- Employee training history

7. System Recovery Procedures

The purpose of these procedures is to verify the system recovery procedures at the user's premises. The procedures analyzed include:

- Periodic backup and archival SOPs
- Data restoring SOPs
- Program restoring SOPs
- Disaster recovery SOPs

These procedure must exist and be appropriate, up-to-date, relevant, and complete. They must be easily available to the users concerned.

8. Computerized System Environment

The purpose here is to qualify the computerized system environment at the user's premises. The key aspects analyzed include:

- Quality of the electric power supplied to the equipment
- Efficiency of uninterruptible power supply (UPS) or safety power group (reaction delay, activity time)
- General environment: temperature, humidity, dust, etc.

9. Checking Process Control and Regulation Loops

The purpose here is to check the efficiency of process control and regulation loops critical to the process.

10. Checking Alarms and Safeties

Tests aim to check the alarm conditions and safeties available on the computerized equipment, even those with low activation probability. Each alarm or safety checked is activated between one and three times, possibly substituting some sensor with an appropriate calibrator simulator.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

SECTION

VAL 1100.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 1100.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Validation of Microbiological Methods**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SUBJECT: Validation of Microbiological Methods

PURPOSE

To provide the guideline for validation of the microbiological methods to ensure analytical accuracy and precision and that the methods are suitable for the intended use

RESPONSIBILITY

It is the responsibility of the quality control manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

The main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose. The procedures presented in this SOP provide basic guidelines for the validation of methods for microbiological assay, estimation of the number of microorganisms, detection of indicators of objectionable microorganisms, validation of preservative efficacy testing, and validation of the sterility testing and endotoxin test (LAL test).

Microbiological Assay of Antibiotics

It is an essential condition of biological assay methods that the tests on the standard preparation and on the sample whose potency is being determined should be carried out at the same time and, in all other respects, under strictly comparable conditions. The validation of microbiological assay method includes performance criteria (analytical parameters) such as linearity, range, accuracy, precision, specificity, etc.

Specificity is usually difficult to assess with microbial assay methods, because the tests measure the total activity and this will represent the synergetic action of all active components in the mixture under test.

1. Linearity

The correlation coefficient, y-intercept, and slope of the regression line should be included. A plot of the data should be included. For the establishment of linearity, a minimum of five concentrations are recommended. It may be demonstrated directly on the active substance (by dilution of a standard stock solution).

Acceptance criteria

A correlation coefficient Š 0.95 is acceptable.

2. Range

The specified range is derived normally from linearity studies. It is established by confirming that the analytical procedure provides an acceptable degree of linearity, accuracy, and precision when applied to samples containing amounts of analyzed material within or at the extremes of the specified range of the procedure.

Acceptance criteria

The minimum specified range considered for assay of an active substance or a finished product is normally from 80 to 120% of the test concentration.

3. Accuracy

Accuracy may be determined by application of the analytical procedure to synthetic mixtures of the product components to which known quantities of the substance to be analyzed have been added. The accuracy should be assessed by using a minimum of nine determinations over a minimum of three concentration levels covering the specified range (i.e., three concentrations and three replicates of each concentration).

Accuracy should be reported as percent recovery by the assay of known added amount of active ingredient in the sample.

Acceptance criteria

Accuracy within ± 10% of the true value is accepted.

4. Precision

The precision of an analytical method is usually expressed as the standard deviation or relative standard deviation (coefficient of variation) of a series of measurements. Precision represents repeatability or reproducibility of the analytical method under normal operating conditions. Precision determinations permit an estimate of the reliability of single determinations and are commonly in the range of ± 0.3 to 3% for dosage form assays.

Repeatability may be assessed using a minimum of nine determinations covering the specified range for the procedure (e.g., three concentrations and three replicates of each concentration) or a minimum of six determinations at 100% of the test concentration. (This can be determined by performing six replicate assays on six aliquots of the same homogeneous sample.)

Acceptance criteria

Relative standard deviation of ð 5% is acceptable.

Consider an assay as preliminary if its computed potency is less than 80% or more than 125% of assumed potency; adjust the assumed potency accordingly and repeat the assay. Overage should be taken into account when determining target assumed potency.

In routine use, the combined result of a series of independent assays spread over a number of days is a more reliable estimate of potency than that from a single assay. Minimum requirement for routine microbiological testing is duplicate assay.

Potency assays require comprehensive statistical packages and for a standard large plate assay this could include all the relevant statistical parameters. The *EP* (European Pharmacopoeia) or *BP* (British Pharmacopoeia) is recommended as a source of reference. For a high-precision large plate bioassay, the following parameters should be included: analysis of variance, tests of validity, estimation of potency and fiducial limits, missing values, and combination of potency estimates. Potency assays should not be performed using low-precision designs.

Bioassay may also be of low-precision design (multiple samples on large plates, i.e., >3 manual turbidimetric assays, small-plate assays). These types of assay are useful for trace analyses (cleaning validation), and are often used for the analysis of samples in body fluids as they are capable of dealing with the large numbers of samples that may be generated in these studies.

The amount of data generated by low-precision analyses is often insufficient for sophisticated statistical analysis. Even so, it is important to minimize manual data handling as this allows subjective interpretation to enter the interpretive stages.

All potency assays, from the simplest designs to the most complex Latin square design, necessitate potency estimation by computer. Low-precision assays employing plotting of zone sizes (response) against concentration of standards must be dealt with using computerized regression analysis, with the potency (standard equivalent) estimation calculated from the computed equation of the line. In this way, all opportunity for operator subjectivity is minimized.

For low-precision design the statistical package should include statistical rejection of outlying or aberrant observation. (EP makes no provision for this; USP has a test — USP 24, standard deviation, regression analysis, and potency estimation.)

The most important aspects of data handling for potency assays and low-precision assays are that the data is handled by validated computer programs and that the acceptance and rejection criteria incorporated are clear and based upon statistical or proven (at validation) limits.

All programs must be validated by comparison vs. manual calculation.

5. Validation of Microbial Recovery from Compendial Article

The antimicrobial properties of a product may be due to the presence of preservatives or its formulation. This antimicrobial property must be neutralized to recover viable microorganisms present. The neutralization of antimicrobial property of a pharmaceutical article can be achieved by:

- Using specific neutralizer (chemical inhibition)
  Table 1 shows known neutralizers for a variety of chemical antimicrobial agents and the reported toxicities of some chemical neutralizers to specific microorganisms. Antibiotics may not be susceptible to neutralization by chemical means, but rather by enzymatic treatment (e.g., penicillinase). These enzymes may be used where required (for β-lactum antibiotics).

Table 1 Some Common Neutralizers for Chemical Biocides

Neutralizer	*Biocide Class*	*Potential Action of Biocides*
Bisulfate	Glutaraldehyde, Mercurials	Non-sporing bacteria
Dilution	Phenolics, Alcohol, Aldehydes, Sorbate	—
Glycine	Aldehydes	Growing cells
Lecithin	Quaternary Ammonium Compounds (QACs), Parabens, *Bis*-biguanides	Bacteria
Mg^{+2} or Ca^{+2} ions	EDTA	—
Polysorbate	QACs, Iodine, Parabens	—
Thioglycollate	Mercurials	Staphylococci and spores
Thiosulfate	Mercurials, Halogens, Aldehydes	Staphylococci

- Dilution
  The relationship between concentration and antimicrobial effect differs among bactericidal agents but is constant for a particular antimicrobial agent. The relationship between concentration and antimicrobial effect is exponential in nature, with the general formula

$$C^{\eta}t = k$$

  where
  C = concentration
  t = time required to kill a standard inoculum
  k = constant
  η = the slope of the plot of log t vs. log C.
  Antimicrobial agents with high η values are rapidly neutralized by dilution, while those with low η values are not good candidates for neutralization by dilution.
- Filtration and washing
  This approach is used especially in sterility testing.
- Combination of washing and dilution
- Any combination of these methods

6. Validation of Neutralization Methods

The validation method for neutralizing the antimicrobial properties of a product must meet two criteria — neutralizer efficacy and neutralizer toxicity. The validation study documents that the neutralization method applied is effective in inhibiting the antimicrobial properties of the product (neutralizer efficacy) without impairing the recovery of viable microorganisms (neutralizer toxicity). Validation protocol may meet these two criteria by comparing recovery results for three treatment groups.

The following challenge organisms may be used as appropriate (*USP* 24, *BP* Vol. II, 1999, or *EP* 3rd edition, 1997):

- *Aspergillus niger* (ATCC 16404)
- *Candida albicans* (ATCC 10231, NCPF 3179)
- *Bacillus subtilis* (ATCC 6633, NCIMB 8054)
- *Escherichia coli* (ATCC 8739, NCIMB 8545)
- *Staphylococcus aureus* (ATCC 6538, NCTC 10788)
- *Pseudomonas aeruginosa* (ATCC 9027, NCIMB 8626)
- *Salmonella typhimurium* (or nonpathogenic strain, such as *Salmonella agona* NCTC 6017).

In a **test group** the product is subjected to the neutralization method, and then a low level of challenge microorganism (less than 100 cfu) is inoculated for recovery. In a **peptone control group** the neutralization method is used with peptone or diluting fluid A (Sterility test 71) as the test solution. In a **viability group** the actual inoculum is used without exposure to the neutralization method.

Similar recovery between the test group and peptone group demonstrates adequate neutralizer efficacy; similar recovery between the peptone group and the viability group demonstrates adequate neutralizer toxicity. In principle, the protocol must show that recovery of a low inoculum (less than 100 cfu) is not inhibited by the test sample and the neutralization method. Validation protocols may meet these two criteria by comparing recovery among three distinct test groups: neutralized product with inoculum, challenge inoculum control in buffered solution, and inoculum in the absence of product or neutralizer.

This can be established by directly comparing the result in the treated solution to the inoculum above. If the growth on the treated solution is not comparable to the growth on the inoculum group, it should be determined whether the neutralization method is toxic to the microorganisms.

7. Recovery on Agar Medium

At least three independent replicates of the experiment should be performed, and each should demonstrate that the average number of cfu recovered from the challenge product is not less than 70% of that recovered from the inoculum control.

In the event that a greater number of replicates is required in the validation study, the comparisons may be evaluated by transforming the numbers of cfu to their logarithmic values and analyzing the data statistically.

Acceptance criteria

- Similar recovery between the first and second group demonstrates adequate neutralizer efficacy
- Similar recovery between the second and third group demonstrates adequate neutralizer toxicity.
- At least three independent replicates of the experiment should be performed, and each should demonstrate that the average number of cfu recovered from the challenge product is not less than 70% of that recovered from the inoculum control.

8. Absence of Specified Organisms: (*S. aureus, P. aeruginosa, E. coli* and *Salmonella* spp.)

A similar approach to that employed in aerobic microbial count validation is employed but quantification is not possible. A low level (ð100 cells) of specified organism is added to various product and broth mixtures and recovery viewed on the resultant selective plates. For the method to be considered valid, growth on plates must be comparable to that derived from parallel control cultures containing no product. Parallel controls not only must be run at validation stage but also as a matter of routine to indicate acceptable preparation and performance of media.

pH checks on broth and product mixtures are important owing to the protracted period of contact. Failure to recover organisms from dilutions of product in broth in excess of 1:1000 is indicative of inability of that organism to contaminate the product; testing on a routine basis would not be recommended.

9. Recovery by Membrane Filtration

This validation follows the procedure described for validation tests for bacteriostasis and fungistasis under sterility tests in USP XXIV with the exception of plating on solid medium to quantitative recovery.

Three 100-ml rinses are assumed, but the volume and number of rinses are subject to validation. Each validation run should be performed independently at least three times.

1. In the test solution group, the product is filtered through the membrane filter, followed by two 100-ml portions of diluting-neutralizing fluid.
2. After the second rinse has been filtered, a final 100-ml portion containing less than 100 cfu of the specific challenge microorganism is passed through the filter. This filter is then transferred to the appropriate recovery agar medium and incubated for recovery.
3. The inoculum is directly plated onto the solid medium (to check viability).
4. Diluting fluid A is used as the dilution medium without exposing the filter to the product.
5. After addition of the low level of inoculum to the final rinse, the filter is plated as above.
6. Technique-specific loss of microorganisms can be estimated by comparing the recovery in the diluting fluid A group to the inoculum count.
7. If it is necessary to solubilize the test sample (in case of ointments, suspensions, etc.), the effects of the solubilization method on viable microorganisms must be determined.

Acceptance criteria

The method can be considered validated if the recovery rate in the three independent replicates is similar for the test solution and the diluting fluid A control.

10. Recovery in Liquid Medium

It is assumed in the direct transfer method under sterility tests that the recovery medium will allow for growth of all surviving microorganisms. The liquid medium in that test must serve to neutralize any antimicrobial properties of the test solution and to support the growth of the microorganisms. The treatment groups described above (antimicrobial neutralization for recovery on agar medium) can be used for validation of the recovery method, with the proportions of product and recovery medium varied to achieve adequate neutralization.

Acceptance criteria

The method can be considered validated if all groups show copious growth within 7 days for all microorganisms.

11. Estimating the Number of Colony-Forming Units

The accepted range for countable colonies on a standard agar plate is between 25 and 250 cfu for most bacteria and *Candida albicans*. It is not optimal for all environmental isolates. The recommended counting range for *Aspergillus niger* is between 8 and 80 cfu per plate. The use of membrane filtration to recover challenge microorganisms or the use of environmental isolates as challenge microorganisms in antimicrobial effectiveness testing requires validation of the countable range. This validation may be performed by statistical comparison of estimated cfu from successive pairs in a dilution series. Prepare a suspension so that plating will provide approximately 1000 cfu per plate, and then dilute two-fold to a theoretical concentration of approximately 1 cfu per plate. Plate all the dilutions in the series in duplicate, and incubate for recovery under the conditions of the antimicrobial effectiveness testing. Compare the estimates of cfu per ml from paired tubes in the dilution series by the formula:

$$\frac{\left[2L_{cfu} - H_{cfu}\right]}{\sqrt{2L_{cfu} + H_{cfu}}} \leq 1.96$$

where L_{cfu} = the number of colonies on the plate with the lower count (greater dilution) and H_{cfu} = the number of colonies on the plate with the higher count (lesser dilution). The estimates of the cfu per ml provided by L_{cfu} and H_{cfu} should agree within the limits of the formula with a critical value of 1.96. The upper limit of the plate counts is then defined as the number (H_{cfu}) that reproducibly passes this test.

This study should be independently repeated a sufficient number of times to establish an upper limit of cfu for the particular plating conditions. There is a lower limit at which the ability of the antimicrobial effectiveness test to recover microorganisms becomes unreasonable. If the first plating is performed with 1 ml of 10^{-1} dilution, cfu in the range of 1 to 10 per ml would not be seen. On this dilution plating, only the lower number of cfu may be reduced to three, allowing as few as 30 cfu/ml survivors to be reported.

Lower counting thresholds for the greatest dilution plating in series must be justified. Numbers of colonies on a plate follow the Poisson distribution, so the variance of the mean value equals the mean value of counts. Therefore, as the mean number of cfu per plate becomes lower, the percentage error of the estimate increases (Table 2). Three cfu per plate at the 10^{-1} dilution provide an estimate of 30 cfu per ml, with an error of 58% of the estimate.

12. Bacterial Endotoxin (LAL) Test

Validation is accomplished by performing the inhibition or enhancement test. Appropriate negative control should be included. Validation must be repeated if the LAL reagent source, method of manufacture, or formulation of the product is changed. Confirm the labeled sensitivity of each new lot of LAL reagent prior to use in the test.

Comprehensive tests described in USP 24, *BP* 1999 and *EP* 3rd edition, 1997 cover validation requirements.

See also U.S. Department of Health's "Guideline on Validation of the LAL Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices."

Specific guidance on the initial quality control procedure for a testing laboratory is available as an FDA addendum. The addendum and other practical guidelines are available from Associates of Cape Cod, Inc.

Table 2 Error as Percentage of Mean for Plate Counts

Cfu per Plate	*Standard Error*	*Error as % of Mean*
30	5.48	18.3%
29	5.39	18.6%
28	5.29	18.9%
27	5.20	19.2%
26	5.10	19.6%
25	5.00	20.0%
24	4.90	20.4%
23	4.80	20.9%
22	4.69	21.3%
21	4.58	21.8%
20	4.47	22.4%
19	4.36	22.9%
18	4.24	23.6%
17	4.12	24.3%
16	4.00	25.0%
15	3.87	25.8%
14	3.74	26.7%
13	3.61	27.7%
12	3.46	28.9%
11	3.32	30.2%
10	3.16	31.6%
9	3.00	33.3%
8	2.83	35.4%
7	2.65	37.8%
6	2.45	40.8%
5	2.24	44.7%
4	2.00	50.0%
3	1.73	57.7%
2	1.41	70.7%
1	1.00	100.0%

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 1100.20 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Validation of Analytical Methods**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 1100.20 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Validation of Analytical Methods

PURPOSE

To provide validation of analytical methods to ensure accuracy and reliability

RESPONSIBILITY

It is the responsibility of the quality control analyst and quality control manager to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

For detailed description, refer USP 24 (1225): Validation of Compendial Methods.

1. Validation

1.1 Definition of validation parameters

1.1.1 Precision

The precision of an analytical method can be defined as the pattern of variation of single assays on a uniform sample. The precision serves to identify random errors and is described by the repeatability (variability within a laboratory) and reproducibility (variation between different laboratories).

1.1.2 Accuracy

A procedure is accurate if — on the average — the method provides the true answer.

1.1.3 Selectivity

In providing evidence of selectivity, it must be shown that an analytical method exclusively determines the desired compound.

1.1.4 Linearity

Providing evidence of the linearity of an analytical method is necessary for quantitative determinations.

The direct proportional relation between the measured signal and the concentration of the sample has to be proven.

1.1.5 Limit of detection

The lowest value of a compound with which a defined statistical probability can be clearly identified for an analytical method is the limt of detection.

1.1.6 Limit of quantification

The limit of quantification is the concentration of a compound with which a defined precision and accuracy is only quantifiable.

1.1.7 Ruggedness

An analytical method is rugged when it shows, under different circumstances (different laboratory, different laboratory assistants, different times, etc.), the same results.

1.1.8 Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters; it provides an indication of its reliability during normal usage.

2. Validation Parameters to Be Realized

Overview

Compendial assay procedures vary from highly exacting analytical determinations to subjective evaluation of attributes. Considering this variety of assays, it is only logical that different test methods require different validation schemes. Only the most common categories of assays for which validation data should be required are covered. These categories are as follows (see also Table 1):

Table 1 Data Elements Required for Assay Validation

Analytical Performance Parameter	*Assay Category I*	*Assay Category II*		*Assay Category III*
		Quantitative	*Limit Tests*	
Accuracy	Yes	Yes	*	
Precision	Yes	Yes	No	Yes
Specificity	Yes	Yes	Yes	*
Limit of Detection	No	No	Yes	*
Limit of Quantitation	No	Yes	No	*
Linearity	Yes	Yes	No	*
Range	*	*	*	*
Ruggedness	Yes	Yes	Yes	Yes

* May be required, depending on the nature of the specific test.

Category I — Analytical methods for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products

Category II — Analytical methods for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These methods include quantitative assays and limit tests.

Category III — Analytical methods for determination of performance characteristics (e.g., dissolution, drug release)

Category IV — Identification tests

3. Precision

3.1 Precision of the system

Procedure

Perform the analysis based on one standard solution (with a concentration equal to the expected sample concentration) six consecutive times. Calculate the relative standard deviation of the obtained values.

Criteria

The relative standard deviation must be less than 1.5%; it is inevitably more than 1.5%, the reason has to be explained.

- Documentation
- Obtained values
- Calculation of the relative standard deviation (RSD)
- Justification for a higher RSD

3.2 Precision of the Method

3.2.1 Repeatability

The repeatability is the precision determined under equal conditions with one homogeneous sample. This sample should be analyzed in six-fold increments. Calculate the relative standard deviation of the obtained values.

Criteria

The RSD must be less than 2%; if it is more than 2%, the reason must be explained. The repeatability (r) can be calculated from the relative standard deviation, using the equation:

$$r = 2.83 \times \text{RSD}$$

The value thus found for r represents the difference between the results that is not exceeded more than once in every 20 cases.

3.2.2 Reproducibility

Reproducibility is the precision determined under different conditions (laboratory, reagents, analysts, days, equipment) with one homogeneous sample. Reproducibility may also be established retrospectively, using data obtained from earlier release procedures.

Criteria

The relative standard deviation should not exceed the 4% level.

Documentation

- Obtained values
- Calculation of the RSD
- Justification of exceedingly high RSD levels

3.2.3 Accuracy (addition and recovery)

Accuracy is a measure for the difference between the average value found in the analyses and the theoretical value. Accuracy studies should be performed at a level of active ingredient equal to 100% of the established label concentration of the product tested.

Prepare a series of six placebo mixtures to which the components are added in concentrations equal to the values expected for the sample. After the analysis of these mixtures, perform a statistical evaluation.

Criteria

1. The theoretical value should be within the 95% confidence limits of the average found.
2. The average found should be between 99 and 101% of the theoretical value.
3. The relative standard deviation should be less than 2%; if it is more than 2%, the reason must be explained.
4. The accuracy is acceptable if either criteria 1) and 3) or criteria 2) and 3) are fulfilled. If not, the reason must be given.

Documentation

- Method of the preparation of the placebo with the added components
- Obtained values
- Statistical evaluation
- Justification of a less accurate method

3.2.4 Selectivity

It must be ensured that the analytical method exclusively determines the desired compound.

The selectivity of an analytical method is determined by comparing test results from the analysis of samples containing impurities (related compound), degradation products (originated from samples submitted to stress conditions), or placebo ingredients with those obtained from the analysis of samples without impurities, degradation product, or placebo ingredients.

When impurities or degradation products are unidentified or unavailable, selectivity may be demonstrated by analysis by the method in question of samples containing impurities or degradation products and comparing the results to those from additional purity assays. The degree of agreement of test results is a measure of the selectivity.

3.2.5 Linearity

Procedure

Prepare by dilution from one solution five standard solutions with concentrations between 0 and 200% (e.g., 20%, 60%, 100%, 140%, 180%) of the expected sample concentration. Each solution must be tested at least twice.

Plot the average response against the quantity (or concentration) of the component and use linear regression analysis to calculate the calibration line. If an internal standard is used, the linearity of its curve has to be determined similarly.

Criteria

No lack of fit shall occur fitting a first order polynome through the measured points. The 95% confidence interval shall include zero. If the 95% confidence interval does not include zero, the 80% and 120% points on the calculated line shall not deviate more than 1% from a straight line through 0 and the calculated 100% point.

Calculation of the correlation coefficient

If the calibration curve is linear and the origin of the coordinate system lies within the 95% confidence limits of the curve, the use of one standard concentration (equal to the expected sample concentration) is allowed for the analysis.

If the deviation of the curve from the line 0.0 to 100% (at 80 and 120%) is less than 1% of the *y* value, the use of one standard concentration (equal to the expected sample concentration) is allowed.

If the curve is linear but does not comply with the criteria mentioned above, three standard concentrations around the expected sample value have to be used.

In all other cases, a second degree calibration curve has to be modified to five standard concentrations.

Documentation.

- All the data plots
- Statistical evaluation of the data
- Same procedure should be applied to an internal standard, if used

3.2.6 Limit of detection

If the objective of the analytical method is to detect trace components, the limit of detection (LOD) must be determined.

Procedure

Perform the standard analysis with a blank sample and calculate the standard deviation of the measured response at the position where the substance to be determined is expected. This has to be performed over a distance of 20 times the peak width at the middle of the peak height.

The detection limit is equal to two to three times the noise of the system.

Documentation

- Analysis results of the blank determination
- Calculation of the standard deviation

3.2.7 Limit of quantification

If the objective of the analytical method is to determine trace components, the limit of quantification (LOQ) must be determined.

Procedure

Perform the standard analysis with a blank sample and calculate the standard deviation of the measured response at the position the substance to be determined is expected. This has to be performed over a distance of 20 times the peak width at the middle of the peak height.

The quantification limit is equal to five to ten times the noise.

Criteria

The LOQ must be lower than the release requirement.

Documentation

- Analysis results of the blank determination
- Calculation of the standard deviation

3.2.8 Ruggedness

The ruggedness of an analytical method is determined by analysis of aliquots from homogeneous samples in different laboratories, by different analysts, using operational and environmental conditions that may differ but are still within the specified parameters of the assay. The degree of reproducibility of test results is then determined as a function of the assay variables. This reproducibility may be compared to the precision of the assay under normal conditions to obtain a measure of the ruggedness of the analytical method.

3.2.9 Stability indicating

Known degradation products — When the route of degradation is not known, or if samples of known or postulated degradation products are not available, the sample should be degraded artificially by heat, light, oxidation or reduction, acid or base, etc. Suitable conditions should be employed such that measurable, but not complete, degradation is induced, in order that the residual main component and likely levels of degradation are detected. It is important that the complete formu-

lation is degraded, in case components of the product matrix contribute to the degradation, or themselves degrade. One should also degrade a placebo (or mixture or excipients) as a control.

Example: stability indicating assay for product which is expected to be susceptible to hydrolysis and oxidation. Only one degradate (A) is readily available.

1. Demonstrate separation of A from major component.
2. To show that separation from other degradates is achieved, degrade the formulation and subject it to assay. Samples of the formulation should be stressed as follows:
   Heat — 105° for 24 h
   Light — high intensity UV for 24 h
   Hydrolysis — reflux an aqueous solution for 2 h
   Oxidation — reflux and aqueous solution containing hydrogen peroxide for 1 h
   Acid — reflux in 1M sodium hydroxide for 1 h
   Alkali — reflux in 1M sodium hydroxide for 1 h

Before testing, the solutions should be neutralized if necessary. If the method is suitable for stability studies, then the peak due to the major components will be reduced and other peaks will probably be represented. These degradation products should be resolved from the parent peak.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

SECTION

VAL 1200.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 1200.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Vendor Certification**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 1200.10 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Vendor Certification

PURPOSE

To describe the procedure for evaluation of suppliers to ensure that the materials purchased are of consistent quality

RESPONSIBILITY

It is the responsibility of the quality assurance manager to develop the vendor approval system and maintain SOP compliance.

PROCEDURE

After successful vendor auditing, it can be determined whether purchased ingredients and materials can be accepted on the basis of suppliers' certificates, with minimized inspections of incoming goods to a certain level.

Vendor certification leads to reduction of costs and release times.

VENDOR CERTIFICATION

The vendor certification procedure may include a list of selected vendors, historical review of test results of previous suppliers, and formal inspection on site and decision making.

1. Selection of Vendors to be Certified

The selection of vendors to be certified should be jointly made by the heads of purchasing and production and the quality assurance manager.

2. Review of Historical Data and Test Results

Summarize the quality data of batches delivered during the last 3 years and prepare trend analysis. Report deviations with regard to normal failure levels, out-of-specification situations, and corrective actions. The quality control and quality assurance managers shall review the trend.

3. Site Audit

The quality assurance manager or the system in charge may perform an on-site audit. The audit should specifically:

- Determine the accuracy, precision, and reliability of test and inspection data of the vendor.
- Review the process reproducibility and the batch records for process variations.
- Perform general GMP compliance inspection. Review the potential for contamination and mix-ups thoroughly.
- Ensure that vendors' in-process controls include the use of statistical process control critical product parameters that are significant and may affect the final product quality
- Ensure the absence of significant online problems.

4. Recommendations

It is not essential to perform on-site inspections. As an alternative, evaluation questionnaires can be used. Vendors can also be certified based on an extensive review of historical analytical inspection data and their performance over the last 3 years. Alternatively, third-party audits may be conducted for a predefined period.

5. Decision on Certification

The data obtained as a result of these reviews and audits shall be reviewed by the QA manager and sent for approval to quality control, production, and purchasing. Final release must be authorized by quality control.

6. Steps after Certification

- After vendor approval, quality control or quality assurance will reduce the number of tests and inspections of incoming goods as agreed in the certification report, e.g., one out of ten batches.
- For packaging materials certification, it is sufficient to review the results of three suppliers.
- If during this process of verification no discrepancies appear, the verification may be discontinued.

- For incomplete certification, a provisional classification report shall be published by the QA manager for components.
- Materials to be used in production without complete testing must be supported with acceptable certificates of analysis by manufacturers.
- Active ingredients should be checked for their identity.
- All deviations regarding purchased materials encountered by production must be reported to the quality assurance manager for referral to the manufacturer or supplier.

7. Recertification

Recertification of an active and excepient manufacturer may be performed on request. Recertification can be requested by quality control and production. The certification is valid for a period determined by the QA manager. Certification of packaging materials is valid for 5 years.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

SECTION

VAL 1300.00

YOUR COMPANY
VALIDATION STANDARD OPERATING PROCEDURE

SOP No. Val. 1300.10 **Effective date: mm/dd/yyyy**
Approved by:

TITLE: **Facility Qualification**

AUTHOR: _____
Name/Title/Department

_____
Signature/Date

CHECKED BY: _____
Name/Title/Department

_____
Signature/Date

APPROVED BY: _____
Name/Title/Department

_____
Signature/Date

REVISIONS:

No.	Section	Pages	Initials/Date

SOP No. Val. 1300.10 **Effective date: mm/dd/yyyy**

Approved by:

SUBJECT: Facility Qualification

PURPOSE

To provide guidelines for checking facility construction and finishing to ensure that they meet the facility design qualification requirement

RESPONSIBILITY

It is the responsibility of all concerned managers and contractors to follow the procedure. The quality assurance manager is responsible for SOP compliance.

PROCEDURE

The conceptual design of the facility (approved civil layout) should be available and be compared with the actual construction. Details should be summarized in a tabular form describing:

- Room number
- Activity
- Room classification (e.g., class 100, 10,000, etc.)
- Utilities required and their quality (e.g., WFI, distilled water, compressed air, etc.)
- Room finishes (floor, walls, ceilings, partitions)
- Illumination
- Safety features
- Pass-throughs
- Communicators
- Prefabricated partitions

1. Materials

The quality of materials used shall be confirmed from the purchasing specification and the materials receiving reports. Generally, the use of wooden materials is not recommended.

1.1 Materials for floor construction

Epoxy resin-welded PVC sheets and epoxy terrazzo are generally recommended.

1.2 Materials for walls

Generally acceptable materials are as follows:

- Epoxy coating
- Polyester coating
- Seamless PVC coating
- Welded sheets of PVC
- Prefabricated wall panels

1.3 Materials for ceilings

Commonly used materials are gypsum board with epoxy, polyester coating, and seamless PVC coating.

1.4 Materials for doors

The following materials are generally used:

- Standard painted timber
- Timber with plastic lamination
- Stainless steel
- Glass

2. Measurement Checks of Construction and Finishes

The area of each room shall be checked to ensure that it meets specifications (length, width, and height).

- Rooms should be designed and constructed so that air leakage through openings or penetration is kept to a minimum.
- All surfaces must be completely cleanable and resistant to germicidal solutions.

- Horizontal or other surfaces on which dust can accumulate shall be kept to an absolute minimum, and they shall be completely avoided above areas where the product or washed product containers are exposed.

3. Quality Checks of Floors

The material used for the construction of floor shall be free from seams, cracks, or holes, and shall be durable, washable, and cleanable.

- Floor–wall joints, building columns, equipment pads, and other obstructions should be completely sealed.
- Floor drains should be provided only where large volumes of liquids are anticipated.
- The floor should be pitched toward the drain (if available) to prevent accumulation of liquids.
- The floor drain should not be located in the aseptic clean room because of concerns about microbiological growth in the trap.
- Trapped floor drains should be provided.

4. Quality Checks of Walls

- Construction materials shall be free from seams, cracks, or holes, and also washable, cleanable, and free from rust or corrosion.
- Walls should be smooth, rigid, and resistant to impact and abrasion.
- Walls should be protected by physical barriers such as stainless steel subrails (if necessary).
- Wall surfaces should be easy to clean and resistant to repeated exposure to disinfectants.
- Floor–wall, wall–wall, and ceiling–wall intersections should be properly sealed to prevent dirt accumulation and pest entry.
- Floor–wall and wall–wall joints should be coved.
- Ledges should be sloped to reduce dust accumulation.

5. Quality Checks of Ceiling

- Construction materials shall be durable, cleanable, and washable.
- Ceilings should be smooth, nonperforated, and properly sealed to the framing.

- All penetration through ceilings must be designed to establish and maintain the integrity of a 100% sealed system.
- The suspension system should be heavy-duty aluminum with anodized or leaked-on, even-finish stainless steel.

6. Quality Checks of Entryway, Doors, and Air Locks

- Construction materials, door openings and door gaskets should be satisfactory.
- Glass fixing should be satisfactory (if used).
- Entry of all personnel, materials, and equipment should be through a suitable air lock.
- The design and arrangement should minimize migration of particulate and other contaminants into the controlled process area.
- Door should have automatic closing systems.
- Locks and latches should be avoided.

7. Quality Checks of Windows

- Materials shall be durable, washable, and cleanable.
- Windows between class 100 areas and other areas should have sloping sills on both sides of glass to facilitate cleanliness.

8. Quality Checks of Curtains and Partitions

- To maintain the cleanliness classification and protect the critical areas of equipment from air turbulence, the following equipment should be surrounded by a curtain:
  - Equipment
  - Curtain Material
  - Curtain Height

9. Quality Checks of Conveyor Passages and Partition Holes

The passage of conveyors through partition is adjusted using polycarbonate sheets cut as needed.

10. Equipment Maintenance Provision

Access to the critical parts of the equipment for maintenance and cleaning should be available.

11. Critical Checks of Illumination

Check the units of lux and compare with the standard for each room.

12. Utility Lines Check

Check and ensure that utilities are installed per the room requirement list:

- Industrial steam
- Pure steam
- Chilled water
- Tap water (warm)
- Tap water (cold)
- Distilled water
- Water for injection
- Compressed air
- Nitrogen gas
- Exposed piping and conduit should be avoided as much as possible.
- Exposed piping should be completely cleanable by being set out approximately 1 to 1.5 in. from the wall or other surfaces.
- Check that all piping is properly labeled with flow directions.

13. Safety Features Checks

Check and ensure that safety equipment is installed per room requirement list:

- Location, condition, and number of water showers available
- Location and number of fire extinguishers available
- Location, condition, and number of smoke detectors available
- Location and number of emergency doors available

14. Drainage System Checks

- Drainage should be designed and constructed per approved layout.
- Verify the drainage locations using building specification.
- The floor should be pitched toward drain holes to prevent accumulation of liquids.
- All surfaces must be cleanable.
- All drains should have deep seal traps to avoid back-flow (nonreturn valves).
- Open drains should be avoided in manufacturing and packaging areas.
- Process and sanitary drains should be separate to avoid the possibility of introducing sanitary waste into process systems.
- Drains must be covered with secured lids.
- Check that drain flushing procedure is established and identified.
- Check that drainage lines are sanitized according to procedure and that records are available.
- Check that drain pipe slope is toward outside.

REASONS FOR REVISION

Effective date: mm/dd/yyyy

- First time issued for your company, affiliates, and contract manufacturers

RECOMMENDED READING

Baker, G.S. and Rhodes, C.T., *Modern Pharmaceutics*, Marcel Dekker, Inc., New York, 1996.

Berry, I.R. and Harpaz, D., *Validation of Bulk Pharmaceutical Chemicals*, Interpharm Press, Inc., Buffalo Grove, IL, 1997.

Berry, I.R. and Nash, R.A., *Pharmaceutical Process Validation*, Marcel Dekker, Inc., New York, 1993.

British Pharmacopoeia, 1993.

Bulk Pharmaceutical Chemicals, ISPE, 1996.

Carleton, F.J. and Agalloco, J.P., *Validation of Aseptic Pharmaceutical Processes*, Marcel Dekker, Inc., New York, 1986.

Carleton, F.J. and Agalloes, J.P., *Validation of Pharmaceutical Process*, Marcel Dekker, Inc., New York, 1986.

Cloud, P., *How to Develop and Manage Qualification Protocols for FDA Compliance*, Interpharm Press, Buffalo Grove, IL, 1999.

Cloud P., *Pharmaceutical Equipment Validation Qualification*, Interpharm Press, 1998.

Commission of the European Communities, The rules governing medicinal products in the European Community, Guide to II/2244/87-EN, Rev. 3, 1989.

DeSain, C., *Documentation Basics That Support Good Manufacturing Practices*, Advanstar Communications, Cleveland, 1993.

Development Pharmaceutics and Process Validation, CPMP, 1988.

Gibson, W. and Evans, K.P., *Validation Fundamentals How to, What to, When to Validate*, Interpharm Press, Buffalo Grove, IL, 1998.

Good Manufacturing Practice for Medical Products, European Community, 1992.

Guide to Inspection of High Purity Water System, Interpharm Press, Buffalo Grove, IL, 1993.

Guide to Inspection of Microbiological Pharmaceutical Quality Control Laboratories, Interpharm Press, Buffalo Grove, IL, 1993.

Guidelines for Good Validation Practice, FIP, 1988.

Guideline of the Commission for Principles of Good Manufacturing Practice for Medical Products, Directive 91/356/EEC, 1991.

Guidelines on the Validation of Manufacturing Process, WHO, 1996.

Huber, L., *Validation and Qualification in Analytical Laboratories*, Interpharm Press, Buffalo Grove, IL, 1998.

Huber, L., *Validation of Computerized Analytical System*, Interpharm Press, Buffalo Grove, IL, 2000.

Isaacs, A., Validating machinery with electronic control systems, *Manuf. Chemist*, 19, 1992.

Knapp, J.Z. and Kushner, H.K., Generalized methodology for evaluation of parenteral inspection, *J. Parenteral Drug Assoc.*, 34(I), 1980.

Loftus, B.T. and Nash, R.A., *Pharmaceutical Process Validation*, Marcel Dekker, Inc., New York, 1984.
Oral Solid Dosage Forms, ISPE, 1997.
Parenteral Drug Association, Technical Report No. 3, Validation of dry heat process used for sterilization and depyrogeneration, 1981.
PMA's Computer Systems Validation Committee, Validation concepts for computer systems used in the manufacture of drug products, *Pharm. Technol.*, 10(5), 24, 1986.
PMA's Computer Systems Validation Committee, Computer system validation — staying current: introduction, *Pharm. Technol.*, 13(5), 60, 1989.
Principles of Qualification and Validation in Pharmaceutical Manufacture, PIC, 1996.
Stokes, T. et al., *Good Computer Validation Practices: Common Sense Implementation*, Interpharm Press, Inc., Buffalo Grove, IL, 1994.
United States Pharmacopia, USP-23, 1995.
United States Pharmacopia 24, 2000.
Validation Documentation Inspection Guide, Interpharm Press, Buffalo Grove, IL, 1993.
Wingate, G., *Validating Automated Manufacturing and Laboratory Applications: Putting Principles into Practice*, Interpharm Press, Inc., Buffalo Grove, IL, 1997.