MVP-001

MASTER VALIDATION PLAN

API Production Facility

Version: 1.0
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API Production Facility

Beispiel-Implementierung für Fampridin-Produktion und Japan-Export

TABLE OF CONTENTS

1. INTRODUCTION AND SCOPE

1.1 PURPOSE

This Master Validation Plan (MVP) provides a comprehensive overview of the validation strategy and activities for the API manufacturing facility. The plan ensures that all critical systems, equipment, processes, and methods are validated in accordance with:

- ICH Q7: Good Manufacturing Practice for Active Pharmaceutical Ingredients
- EU GMP Annex 15: Qualification and Validation
- ICH Q11: Development and Manufacture of Drug Substances
- ICH Q9: Quality Risk Management
- ISPE Baseline Guides

1.2 SCOPE

This plan covers validation activities for:

Facility and Utilities:

- HVAC system (Heating, Ventilation, Air Conditioning)
- Water system (Purified Water)
- Compressed air system
- Clean steam system (if applicable)
- Cleanroom classification

Equipment:

- Production reactors and vessels
- Filtration equipment
- Drying equipment
- Milling equipment
- Packaging equipment

Analytical Instruments:

- HPLC systems
- GC systems
- Spectroscopy equipment (IR, UV, NMR, MS)
- Karl Fischer titrators
- Balances
- pH meters

Processes:

- Manufacturing process for API (example: Fampridin synthesis)
- Packaging process

Cleaning:

- Cleaning procedures for equipment

Analytical Methods:

- Identity, assay, impurity methods
- Dissolution, content uniformity (if applicable)
- Microbiological methods

Computer Systems:

- Laboratory Information Management System (LIMS)

- Manufacturing Execution System (MES) (if applicable)

- Electronic Batch Records (if applicable)

- Instrument control software

1.3 SITE INFORMATION

Facility: [Manufacturing Site Name]

Address: [Site Address]

GMP License: [License Number]

Scope of Operations: Manufacture of Active Pharmaceutical Ingredients (APIs) for pharmaceutical use

Example Product Scope:

This validation plan is demonstrated using **Fampridin (4-Aminopyridine)** as a representative API. The validation principles and approach are applicable to all APIs manufactured at this site.

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2. VALIDATION POLICY

2.1 POLICY STATEMENT

"All critical equipment, systems, processes, and analytical methods used in the manufacture, testing, and release of Active Pharmaceutical Ingredients will be validated to demonstrate that they consistently perform as intended and produce products meeting predetermined specifications and quality attributes."

Key Principles:

- Validation is a GMP requirement, not optional

- Validation is performed before routine production (prospective validation)

- All validation activities are documented and approved by QA

- Revalidation is performed when changes occur or periodically as defined

- Quality Risk Management (ICH Q9) guides validation efforts

Signed:

[Management Representative]

Date: 04.12.2025

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3. REGULATORY BASIS

This Master Validation Plan is aligned with the following regulatory guidelines:

International (ICH):

- ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

- ICH Q11: Development and Manufacture of Drug Substances

- ICH Q9: Quality Risk Management

- ICH Q2(R1): Validation of Analytical Procedures

Regional:

- EU GMP Annex 15: Qualification and Validation

- US FDA Guidance: Process Validation (2011)

- PMDA Guidelines (Japan)

Standards:

- ISPE Baseline Guide Volume 5: Commissioning and Qualification

- PDA Technical Reports (as applicable)

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4. ORGANIZATIONAL RESPONSIBILITIES

4.1 VALIDATION STEERING COMMITTEE

Composition:

- Validation Manager (Chair)

- QA Manager

- Production Manager

- QC Manager

- Engineering Manager

- Regulatory Affairs Manager (as needed)

Responsibilities:

- Approve Master Validation Plan

- Review validation strategies and priorities

- Approve validation protocols and reports

- Resolve validation-related issues

- Ensure resources are available

Meeting Frequency: Quarterly (or as needed)

4.2 VALIDATION MANAGER

Responsibilities:

- Develop and maintain Master Validation Plan

- Prepare validation protocols and reports

- Coordinate validation activities across departments

- Ensure compliance with GMP and validation guidelines

- Maintain validation documentation

- Train personnel on validation requirements

- Interface with vendors and contractors for qualification support

Authority:

- Recommend approval/rejection of validation results

- Stop production if validation status is compromised

4.3 QUALITY ASSURANCE (QA) MANAGER

Responsibilities:

- Review and approve Master Validation Plan

- Review and approve all validation protocols and reports

- Ensure validation activities comply with GMP

- Approve equipment/system for use after successful qualification

- Oversight of validation program

Authority:

- Final approval of validation documentation

- Authority to reject equipment/systems that are not adequately validated

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4.4 PRODUCTION MANAGER

Responsibilities:

- Participate in validation planning

- Provide personnel and resources for validation execution

- Execute validation protocols (as applicable)

- Ensure validated state is maintained during routine operations

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4.5 QC MANAGER

Responsibilities:

- Perform analytical method validation

- Support process validation (testing of samples)

- Review and approve analytical method validation protocols and reports

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4.6 ENGINEERING MANAGER

Responsibilities:

- Support equipment and utility qualification activities

- Provide technical expertise during IQ/OQ/PQ

- Ensure equipment design meets User Requirements Specifications (URS)

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5. VALIDATION STRATEGY AND APPROACH

5.1 VALIDATION PHILOSOPHY

Risk-Based Approach (ICH Q9):

Validation efforts are prioritized based on risk to product quality and patient safety. High-risk systems and processes receive more rigorous validation.

Risk Categories:

- **High Risk:** Direct contact with API, critical quality attributes affected

  - Examples: Reactors, filtration, drying, analytical methods for release testing

- **Medium Risk:** Indirect impact on product quality

  - Examples: HVAC system, water system, cleaning

- **Low Risk:** Minimal impact on product quality

  - Examples: Administrative systems, non-GMP areas

5.2 VALIDATION TYPES

1. Prospective Validation (Preferred)

- Validation performed before routine commercial production

- Minimum 3 consecutive batches at commercial scale

- All critical parameters monitored

2. Concurrent Validation (Exceptional)

- Validation performed during routine production

- Justified when:

  - Small number of batches produced (e.g., orphan drugs, limited market)

  - Risk assessment supports approach

- Requires thorough documentation and QA approval

3. Retrospective Validation (Not Preferred)

- Based on historical data

- Only acceptable for established products with:

  - Extensive production history

  - Consistent quality records

  - No significant changes

- Not used for new products

For this site: Prospective validation is the standard approach.

5.3 VALIDATION STAGES

Stage 1: Development and Risk Assessment

- Define user requirements (URS)

- Identify critical quality attributes (CQAs)

- Identify critical process parameters (CPPs)

- Risk assessment (FMEA, HAZOP, etc.)

Stage 2: Design Qualification (DQ)

- Verify that equipment/system design meets URS

- Review vendor documentation

Stage 3: Installation Qualification (IQ)

- Verify correct installation

- Document all components, utilities, instrumentation

Stage 4: Operational Qualification (OQ)

- Verify equipment operates within specified parameters

- Test all functions, alarms, interlocks

Stage 5: Performance Qualification (PQ)

- Verify equipment/system consistently performs under actual production conditions

- Process simulation with representative materials

Stage 6: Process Validation

- Demonstrate manufacturing process consistently produces API meeting specifications

- Minimum 3 consecutive batches at commercial scale

Stage 7: Ongoing Verification

- Continuous monitoring during routine production

- Periodic review of process performance

5.4 VALIDATION PROTOCOL STRUCTURE

All validation protocols follow a standardized format:

1. **Title and Identification**

   - Protocol number, version, product/equipment name

2. **Objective**

   - Purpose of validation

3. **Scope**

   - What is being validated

4. **Responsibilities**

   - Who executes, reviews, approves

5. **Equipment/System Description**

   - Technical specifications

6. **Acceptance Criteria**

   - Predetermined criteria for success

7. **Test Procedures**

   - Step-by-step test instructions

8. **Data Recording**

- Forms for recording results

9. **Deviations**

- Process for handling unexpected results

10. **Conclusion**

- Summary of results, recommendation for approval

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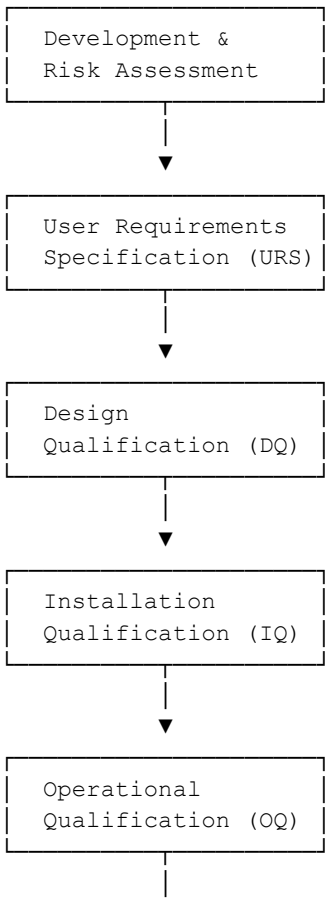
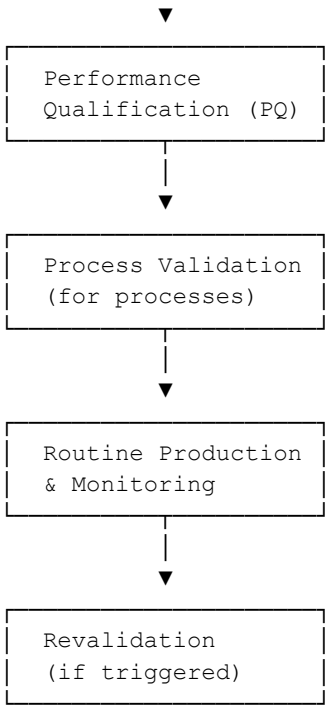
6. VALIDATION LIFE CYCLE





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7. EQUIPMENT AND UTILITIES QUALIFICATION

7.1 HVAC SYSTEM

Purpose: Control air quality, temperature, humidity, and prevent cross-contamination

Qualification Scope:

- Supply and exhaust air handling units

- HEPA filtration systems

- Pressure control systems

- Temperature and humidity control

- Monitoring and alarm systems

Key Parameters:

- Air changes per hour (ACH): Target (example: 20 ACH for production areas)

- Pressure differentials: (example: cleanest area at highest pressure)

- HEPA filter integrity: (example: H14 filters, 99.995% efficiency at 0.3 µm)

- Temperature: (example: 18-25°C)

- Humidity: (example: 30-60% RH)

Qualification Documents:

- URS-HVAC-001: User Requirement Specification

- DS-HVAC-001: Design Specification

- DQ-HVAC-001: Design Qualification

- IQ-HVAC-001: Installation Qualification

- OQ-HVAC-001: Operational Qualification

- PQ-HVAC-001: Performance Qualification

- VR-HVAC-001: Validation Report (Summary)

Timeline: Months 1-6 (see Section 15)

7.2 WATER SYSTEM

Purpose: Supply purified water for manufacturing, cleaning, and analytical use

Qualification Scope:

- Water generation system (RO, distillation, or other)

- Storage and distribution loop

- Sanitization system (hot water or chemical)

- Sampling points

- Monitoring systems

Key Parameters:

- Conductivity: ≤1.3 µS/cm at 25°C (Purified Water per Ph. Eur.)

- Total Organic Carbon (TOC): ≤500 ppb

- Microbial limits: ≤100 CFU/mL (Purified Water)

- Endotoxins: ≤0.25 EU/mL (if applicable)

Qualification Documents:

- URS-WATER-001

- DS-WATER-001

- DQ-WATER-001

- IQ-WATER-001

- OQ-WATER-001

- PQ-WATER-001 (including microbial monitoring over 4 weeks)

- VR-WATER-001

Timeline: Months 1-6

7.3 COMPRESSED AIR SYSTEM

Purpose: Supply compressed air for equipment operation, instrumentation

Qualification Scope:

- Air compressors

- Filtration (particulate, oil, water removal)

- Distribution piping

- Point-of-use testing

Key Parameters:

- Pressure: (example: 6-8 bar)

- Oil content: <0.1 mg/m³ (if used in product contact)

- Dew point: (example: -40°C for dry air)

- Particulate: <0.5 µm (for critical use)

- Microbial: (if product contact)

Qualification Documents:

- URS-CA-001

- IQ-CA-001

- OQ-CA-001

- PQ-CA-001

- VR-CA-001

Timeline: Months 2-4

7.4 PRODUCTION REACTORS

Purpose: Perform chemical synthesis for API production

Example Equipment:

- Reactor R-101 (Synthesis Reactor, 500 L)

- Reactor R-102 (Workup Reactor, 300 L)

Qualification Scope:

- Vessel construction and materials

- Agitator and motor

- Heating/cooling system

- Temperature control and monitoring

- Pressure control (if applicable)

- Sampling ports

- Cleaning procedure validation

Key Parameters:

- Temperature control: ±2°C of setpoint

- Heating/cooling rate: (define acceptable range)

- Agitation speed: (define range)

Qualification Documents:

- URS-REACTOR-001

- IQ-REACTOR-001 (per reactor)

- OQ-REACTOR-001

- PQ-REACTOR-001 (process simulation or actual batches)

- VR-REACTOR-001

Timeline: Months 3-7

7.5 FILTRATION EQUIPMENT

Purpose: Remove solids from liquids during synthesis

Qualification Scope:

- Filter housing
- Filter integrity test
- Filtration performance

Qualification Documents:

- IQ-FILTER-001
- OQ-FILTER-001
- Included in Process Validation

Timeline: Months 4-6

7.6 DRYING EQUIPMENT

Purpose: Remove solvents/moisture from API

Example Equipment:

- Vacuum dryer VD-101

Qualification Scope:

- Temperature control

- Vacuum level control

- Drying time

- Solvent removal efficiency

Key Parameters:

- Temperature: ±5°C of setpoint (example: 60°C ±5°C)

- Vacuum: (example: <50 mbar)

Qualification Documents:

- URS-DRYER-001

- IQ-DRYER-001

- OQ-DRYER-001

- PQ-DRYER-001

- VR-DRYER-001

Timeline: Months 4-6

7.7 MILLING EQUIPMENT

Purpose: Control particle size of API

Qualification Scope:

- Mill operation

- Particle size distribution

- Reproducibility

Qualification Documents:

- IQ-MILL-001

- OQ-MILL-001

- Included in Process Validation

Timeline: Months 5-7

7.8 ANALYTICAL INSTRUMENTS

HPLC Systems:

- HPLC-01 (for assay, impurities)

- HPLC-02 (backup)

GC Systems:

- GC-01 (residual solvents)

Other:

- IR Spectrometer (identity)

- Karl Fischer Titrator (water content)

- Balances (weighing)

- pH meters

Qualification Scope:

- Installation Qualification (IQ)

- Operational Qualification (OQ)

- Performance Qualification (PQ) using system suitability tests

Analytical Method Validation:

- Separate from instrument qualification

- Validates the analytical method per ICH Q2(R1)

Qualification Documents (per instrument):

- IQ-[INSTRUMENT]-001

- OQ-[INSTRUMENT]-001

- PQ-[INSTRUMENT]-001

Timeline: Months 2-5

7.9 CLEANROOM CLASSIFICATION

Purpose: Verify cleanrooms meet ISO 14644-1 classification

Scope:

- Production areas (example: ISO 7 or ISO 8)

- Warehousing areas (as applicable)

Tests:

- Particle counting (at-rest and in-operation)

- Air velocity

- Pressure differentials

- Recovery time (for cleanrooms)

Qualification Documents:

- Cleanroom Classification Report (CCR-001)

Timeline: Month 3-4

Requalification: Annually or after significant changes

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8. PROCESS VALIDATION

8.1 OBJECTIVE

Demonstrate that the manufacturing process consistently produces API meeting predetermined specifications and quality attributes.

8.2 SCOPE

Example Product: Fampridin (4-Aminopyridine)

> **Note:** Fampridin is used as an illustrative example to demonstrate the validation approach. Actual products manufactured at this site will follow the same validation principles.

Manufacturing Process Steps:

1. Reaction (Synthesis)

2. Workup (Neutralization, Extraction)

3. Purification (Crystallization)

4. Drying

5. Milling

6. Packaging

8.3 CRITICAL QUALITY ATTRIBUTES (CQAs)

For API (Fampridin Example):

- Identity

- Assay (purity): 99.0-101.0%

- Impurities: Each ≤0.10%, Total ≤0.50%

- Residual solvents: Per ICH Q3C

- Water content: ≤0.50%

- Particle size distribution: D50 20-80 µm

8.4 CRITICAL PROCESS PARAMETERS (CPPs)

Example CPPs (Fampridin Synthesis):

- Reaction temperature: 80 ± 2°C

- Reaction time: 4 ± 0.5 hours

- pH during workup: 6.5-7.5

- Drying temperature: 60 ± 5°C

- Drying time: Until LOD ≤0.50%

8.5 PROCESS VALIDATION APPROACH

Prospective Validation:

- Minimum **3 consecutive commercial-scale batches**

- All CPPs controlled within validated ranges

- All CQAs tested and meet specifications

- Statistical evaluation of results

Validation Batches:

- Batch 1: [Batch Number to be assigned]

- Batch 2: [Batch Number to be assigned]

- Batch 3: [Batch Number to be assigned]

Batch Size: (example: 100 kg per batch)

8.6 IN-PROCESS CONTROLS (IPCs)

- pH after neutralization

- Purity by HPLC before drying (≥98%)

- Loss on drying (LOD) after drying (≤0.50%)

- Particle size after milling

8.7 SAMPLING PLAN

- Raw materials: Per specification

- In-process samples: At defined steps (post-reaction, post-crystallization, post-drying)

- Final API: Full specification testing

8.8 ACCEPTANCE CRITERIA

Per Batch:

- All CPPs within validated ranges

- All IPCs meet acceptance criteria

- Final API meets specification

Overall (3 Batches):

- All 3 batches meet specification

- No significant deviations

- Statistical analysis shows consistency (mean, standard deviation, range)

8.9 VALIDATION DOCUMENTS

- **PVP-FAM-001:** Process Validation Protocol – Fampridin Synthesis

- **Batch Records:** 3 complete batch records

- **PVR-FAM-001:** Process Validation Report – Fampridin Synthesis

Timeline: Months 7-9

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9. CLEANING VALIDATION

9.1 OBJECTIVE

Demonstrate that cleaning procedures effectively remove product residues, cleaning agents, and microorganisms from equipment surfaces.

9.2 SCOPE

Equipment to be Validated:

- Production reactors (R-101, R-102)
- Filters
- Dryers
- Mills

Worst-Case Approach:

- Hardest-to-clean product (if multiple products)
- Longest production campaign
- Most difficult-to-clean equipment surfaces

9.3 ACCEPTANCE CRITERIA

Product Residue:

- ≤10 ppm of previous product (or health-based limit, whichever is lower)
- Calculation based on surface area and subsequent batch size

Cleaning Agent Residue:

- ≤10 ppm (or specific limit for cleaning agent used)

Microbial Limits:

- ≤100 CFU per swab (for non-sterile products)

Visual Cleanliness:

- No visible residue

9.4 SAMPLING METHODS

Swab Sampling:

- Swab defined surface area (e.g., 25 cm²)

- Worst-case locations (hard-to-clean areas)

Rinse Sampling:

- Final rinse water collected

- Analyzed for residues

9.5 ANALYTICAL METHODS

- HPLC for product and cleaning agent residues

- Total Organic Carbon (TOC) as alternative

- Bioburden testing for microbial limits

Methods must be validated to detect residues at acceptance criteria levels.

9.6 VALIDATION BATCHES

- Minimum **3 consecutive successful cleaning cycles**

- After worst-case production scenario

9.7 VALIDATION DOCUMENTS

- **CVP-REACTOR-001:** Cleaning Validation Protocol – Reactors

- **CVP-DRYER-001:** Cleaning Validation Protocol – Dryer

- **CVR-001:** Cleaning Validation Report (Summary)

Timeline: Months 8-10

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10. ANALYTICAL METHOD VALIDATION

10.1 OBJECTIVE

Demonstrate that analytical methods are suitable for their intended purpose and provide reliable, accurate, and reproducible results.

10.2 REGULATORY BASIS

ICH Q2(R1): Validation of Analytical Procedures

10.3 METHODS TO BE VALIDATED

For API (Example: Fampridin):

Identity Methods:

- Infrared Spectroscopy (IR)

- HPLC (Retention Time)

Quantitative Methods:

- Assay by HPLC

- Impurities by HPLC

- Water content by Karl Fischer

- Residual solvents by GC

Physical Tests:

- Particle size by laser diffraction

Microbiological Methods:

- Total aerobic microbial count

- Yeast and mold count

10.4 VALIDATION PARAMETERS (ICH Q2(R1))

For Identity Tests:

- Specificity

For Quantitative Tests (Assay, Impurities):

- **Specificity:** Method detects analyte in presence of impurities, excipients

- **Linearity:** Response proportional to concentration (5-6 levels, $R^2 \geq 0.999$)

- **Accuracy:** Recovery 98-102% (3 levels, triplicate)

- **Precision:**

  - Repeatability: RSD ≤2.0% (6 replicates)

  - Intermediate precision: Different days, analysts, equipment

- **Range:** 80-120% of specification (or wider if justified)

- **Detection Limit (LOD):** Lowest detectable concentration

- **Quantitation Limit (LOQ):** Lowest quantifiable concentration

- **Robustness:** Method stability to small variations (pH, temperature, flow rate)

For Limit Tests (Impurities):

- Specificity, LOD, LOQ

10.5 VALIDATION DOCUMENTS

Per Method:

- **AMV-HPLC-001:** Analytical Method Validation – Fampridin Assay and Impurities by HPLC

- **AMV-GC-001:** Analytical Method Validation – Residual Solvents by GC

- **AMV-KF-001:** Analytical Method Validation – Water Content by Karl Fischer

Timeline: Months 4-6

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11. COMPUTER SYSTEM VALIDATION

11.1 SCOPE

Systems to be Validated:

Laboratory Systems:

- Laboratory Information Management System (LIMS) – if implemented

- Chromatography Data Systems (CDS) on HPLC, GC

Manufacturing Systems:

- Manufacturing Execution System (MES) – if implemented

- Batch record system (if electronic)

Utilities:

- HVAC control system (BMS – Building Management System)

- Water system monitoring

11.2 VALIDATION APPROACH

Based on GAMP 5 (Good Automated Manufacturing Practice):

Category 3 (Non-configured products):

- Standard software (e.g., Microsoft Excel, standard CDS)

- Validation: Installation check, operational testing

Category 4 (Configured products):

- Configurable systems (e.g., LIMS)

- Validation: IQ, OQ, PQ equivalent for software

Category 5 (Custom applications):

- Bespoke software

- Validation: Full life cycle (URS, FS, design, coding, testing)

11.3 VALIDATION ACTIVITIES

User Requirements Specification (URS):

- What should the system do?

Functional Specification (FS):

- How will the system meet requirements?

Installation Qualification (IQ):

- Software installed correctly

- Hardware verified

- Network connections

Operational Qualification (OQ):

- Functions tested (login, data entry, calculations, reports)

- Security tested (user access levels)

Performance Qualification (PQ):

- End-to-end testing with actual workflows

Data Integrity:

- Audit trails enabled and tested

- Electronic signatures (21 CFR Part 11 compliance, if applicable)

11.4 VALIDATION DOCUMENTS

Per System:

- **CSV-LIMS-001:** Computer System Validation – LIMS (if applicable)

- **CSV-CDS-001:** Computer System Validation – Chromatography Data System

Timeline: Months 3-6

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12. VALIDATION DOCUMENTATION

12.1 DOCUMENT HIERARCHY

Level 1: Master Validation Plan (this document)

- Overview, strategy, responsibilities

Level 2: Validation Protocols

- Detailed test procedures, acceptance criteria

- Examples: IQ-HVAC-001, PVP-FAM-001, AMV-HPLC-001

Level 3: Executed Documents

- Completed protocols with results, signatures

Level 4: Validation Reports

- Summary of results, conclusion, approval

- Examples: VR-HVAC-001, PVR-FAM-001

Level 5: Supporting Documents

- Calibration certificates, test records, vendor documentation

12.2 DOCUMENT CONTROL

All validation documents must:

- Be approved before execution (protocols)

- Be executed with original signatures and dates

- Include deviations (if any) with justification

- Be reviewed and approved by QA

- Be archived per GMP requirements (life of product + 1 year minimum)

12.3 VALIDATION REPORT CONTENT

Each validation activity must be summarized in a Validation Report:

1. **Introduction:** Objective, scope

2. **Summary of Results:** Key tests performed, results

3. **Deviations:** Any deviations from protocol, with impact assessment

4. **Conclusion:** System/process/method is validated (or not)

5. **Recommendation:** Approve for use / Retest / Reject

6. **Approval Signatures:** Validation Manager, QA Manager

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13. REVALIDATION AND CHANGE CONTROL

13.1 REVALIDATION TRIGGERS

Revalidation is required when:

Equipment/Systems:

- Major repair or replacement of critical components
- Relocation of equipment
- Significant change to operating parameters
- Preventive maintenance identifies recurring issues

Processes:

- Change to manufacturing process (e.g., scale, equipment, critical parameters)
- Change to raw material supplier (if impacts quality)
- Transfer to new facility
- Trend of declining process performance

Analytical Methods:

- Change to method (e.g., column, reagents, conditions)
- Transfer to different laboratory

Computer Systems:

- Software upgrades or patches
- Hardware changes
- Configuration changes

13.2 PERIODIC REVALIDATION

Even without changes, periodic revalidation may be needed:

Equipment/Utilities:

- HVAC: Recertification annually (particle count, airflow)

- Water system: Periodic sanitization validation (annually)

- Analytical instruments: Annual PQ (system suitability)

Processes:

- Not routinely revalidated unless triggered by changes or poor performance

- Ongoing verification through process monitoring

Cleaning:

- Periodic recleaning validation (e.g., every 3 years or after significant change)

13.3 CHANGE CONTROL INTEGRATION

All changes impacting validated state must go through Change Control (per Quality Manual Section 13).

Change Control will assess:

- Does the change impact validation status?

- What level of requalification/revalidation is needed? (partial vs. full)

- Risk to product quality (ICH Q9)

After change implementation:

- Requalification/revalidation performed per approved plan

- Validation documentation updated

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14. TRAINING

14.1 TRAINING REQUIREMENTS

All personnel involved in validation activities must be trained on:

- GMP and validation principles

- This Master Validation Plan

- Specific validation protocols they will execute

- Documentation requirements (data integrity, signatures)

14.2 TRAINING RECORDS

- Training documented in personnel training files

- Competency assessed (e.g., practical demonstration, written test)

- Retraining when procedures change

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15. VALIDATION SCHEDULE

Overall Timeline: 12 Months from Facility Commissioning

15.1 PHASE 1: UTILITIES AND EQUIPMENT (Months 1-6)

Activity	Month	Responsible	Status
HVAC IQ/OQ/PQ	1-4	Validation, Engineering	Planned
Water System IQ/OQ/PQ	1-4	Validation, Engineering	Planned

Compressed Air IQ/OQ	2-4	Validation, Engineering	Planned
Cleanroom Classification	3-4	Validation	Planned
Analytical Instruments IQ/OQ/PQ	2-5	Validation, QC	Planned
Production Reactors IQ/OQ	3-5	Validation, Production	Planned
Dryer IQ/OQ/PQ	4-6	Validation, Production	Planned
Mill IQ/OQ	5-6	Validation, Production	Planned

15.2 PHASE 2: ANALYTICAL METHODS (Months 4-6)

Activity	Month	Responsible	Status
HPLC Method Validation (Assay/Impurities)	4-6	QC	Planned
GC Method Validation (Residual Solvents)	5-6	QC	Planned
Karl Fischer Method Validation	5-6	QC	Planned
Microbiological Methods	5-6	QC	Planned

15.3 PHASE 3: PROCESS VALIDATION (Months 7-9)

Activity	Month	Responsible	Status
Process Validation Protocol Approval	6	Validation, QA	Planned
Validation Batch 1	7	Production, QC	Planned
Validation Batch 2	8	Production, QC	Planned
Validation Batch 3	9	Production, QC	Planned
Process Validation Report	9	Validation, QA	Planned

15.4 PHASE 4: CLEANING VALIDATION (Months 8-10)

Activity	Month	Responsible	Status
Cleaning Validation Protocol Approval	7	Validation, QA	Planned
Cleaning Validation Execution (3 cycles)	8-10	Production, QC	Planned
Cleaning Validation	10	Validation, QA	Planned

Report			

15.5 PHASE 5: COMPUTER SYSTEMS (Months 3-6)

Activity	Month	Responsible	Status
LIMS Validation (if applicable)	3-6	Validation, IT, QC	Planned
CDS Validation (HPLC/GC)	4-5	Validation, QC	Planned
BMS Validation (HVAC control)	3-4	Validation, Engineering	Planned

15.6 FINAL REVIEW (Month 12)

Activity	Month	Responsible	Status
Review all validation documentation	12	Validation, QA	Planned
Master Validation Plan update (if needed)	12	Validation	Planned
Validation Steering Committee Review	12	Committee	Planned

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16. APPENDICES

APPENDIX A: LIST OF VALIDATION DOCUMENTS

Utilities:

- URS-HVAC-001, DQ/IQ/OQ/PQ/VR-HVAC-001

- URS-WATER-001, DQ/IQ/OQ/PQ/VR-WATER-001

- URS-CA-001, IQ/OQ/PQ/VR-CA-001

Equipment:

- URS-REACTOR-001, IQ/OQ/PQ/VR-REACTOR-001

- URS-DRYER-001, IQ/OQ/PQ/VR-DRYER-001

- IQ/OQ-MILL-001

- IQ/OQ/PQ per analytical instrument

Process:

- PVP-FAM-001: Process Validation Protocol – Fampridin

- PVR-FAM-001: Process Validation Report – Fampridin

Cleaning:

- CVP-REACTOR-001, CVP-DRYER-001

- CVR-001: Cleaning Validation Report

Analytical Methods:

- AMV-HPLC-001, AMV-GC-001, AMV-KF-001

Computer Systems:

- CSV-LIMS-001 (if applicable)

- CSV-CDS-001

Cleanroom:

- CCR-001: Cleanroom Classification Report

APPENDIX B: RISK ASSESSMENT MATRIX (ICH Q9)

Risk = Severity × Probability

Severity	Probability	Risk Level	Action
High	High	**Critical**	Full validation required
High	Medium	**High**	Extensive validation
High	Low	**Medium**	Standard validation
Medium	High	**High**	Extensive validation
Medium	Medium	**Medium**	Standard validation
Medium	Low	**Low**	Reduced validation acceptable
Low	High	**Medium**	Standard validation
Low	Medium	**Low**	Reduced validation acceptable
Low	Low	**Minimal**	Verification acceptable

APPENDIX C: ABBREVIATIONS

- ACH: Air Changes per Hour

- API: Active Pharmaceutical Ingredient

- BMS: Building Management System

- CAPA: Corrective and Preventive Action

- CDS: Chromatography Data System

- CEP: Certificate of Suitability

- CFU: Colony Forming Units

- CQA: Critical Quality Attribute

- CPP: Critical Process Parameter

- CSV: Computer System Validation

- DQ: Design Qualification

- EU: Endotoxin Units

- FMEA: Failure Mode and Effects Analysis

- FS: Functional Specification

- GAMP: Good Automated Manufacturing Practice

- GC: Gas Chromatography

- GDP: Good Distribution Practice

- GMP: Good Manufacturing Practice

- HAZOP: Hazard and Operability Study

- HEPA: High-Efficiency Particulate Air (filter)

- HPLC: High-Performance Liquid Chromatography

- ICH: International Council for Harmonisation

- IPC: In-Process Control

- IQ: Installation Qualification

- IR: Infrared Spectroscopy

- ISPE: International Society for Pharmaceutical Engineering

- LIMS: Laboratory Information Management System

- LOD: Loss on Drying / Limit of Detection

- LOQ: Limit of Quantitation

- MES: Manufacturing Execution System

- MS: Mass Spectrometry

- MVP: Master Validation Plan

- NMR: Nuclear Magnetic Resonance

- OOS: Out-of-Specification

- OQ: Operational Qualification

- PQ: Performance Qualification

- QA: Quality Assurance

- QC: Quality Control

- RH: Relative Humidity

- RO: Reverse Osmosis

- RSD: Relative Standard Deviation

- SOP: Standard Operating Procedure

- TOC: Total Organic Carbon

- URS: User Requirement Specification

- UV: Ultraviolet Spectroscopy

REVISION HISTORY

Version	Date	Author	Description of Changes	Approved By
1.0	04.12.2025	Validation Department	Initial release	Management Representative

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APPROVAL SIGNATURES

Prepared by:

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Date: 04.12.2025

Reviewed by:

[Name, Title: QA Manager]

Signature: _____

Date: 04.12.2025

Reviewed by:

[Name, Title: Production Manager]

Signature: _____

Date: 04.12.2025

Reviewed by:

[Name, Title: QC Manager]

Signature: _____

Date: 04.12.2025

Approved by:

[Name, Title: Management Representative / General Manager]

Signature: _____

Date: 04.12.2025

END OF MASTER VALIDATION PLAN

Distribution:

- Management Representative (Controlled Copy #1)
- Validation Manager (Controlled Copy #2)
- QA Manager (Controlled Copy #3)
- Production Manager (Controlled Copy #4)
- QC Manager (Controlled Copy #5)
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