QM-001

QUALITY MANUAL

API-Herstellung nach GMP/ICH Q7

Version: 1.1
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API-Herstellung nach GMP/ICH Q7

Beispiel-Implementierung für Fampridin-Produktion

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1. INTRODUCTION AND SCOPE

1.1 PURPOSE

This Quality Manual describes the Quality Management System (QMS) for the manufacture of Active Pharmaceutical Ingredients (APIs) in accordance with:

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

- EU GMP Guidelines (EudraLex Volume 4)

- US FDA 21 CFR Part 211 (where applicable)

- Applicable national regulations (e.g., German AMG, AMWHV)

1.2 SCOPE

This Quality Manual applies to all activities related to:

- Development of API manufacturing processes

- Scale-up and technology transfer

- Commercial production of APIs

- Quality control and testing

- Storage and distribution of APIs

Example Product Scope:

This manual is demonstrated using Fampridin (4-Aminopyridine) as a representative API:

- CAS Number: 504-24-5

- Quality Standard: GMP, DAC

- Target Markets: EU, Japan (PMDA approval)

1.3 REGULATORY BASIS

The QMS is designed to ensure compliance with:

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

- **ICH Q10:** Pharmaceutical Quality System

- **EU GMP:** Parts I and II

- **PMDA Guidelines:** For export to Japan

- **ISO 9001:2015:** Quality Management Systems (adopted principles)

1.4 PRODUCT LIFE CYCLE

This QMS covers all stages of the API life cycle:

- **Development:** Process development, analytical method development

- **Technology Transfer:** Scale-up, process optimization

- **Commercial Manufacturing:** Routine production

- **Product Discontinuation:** Phase-out, documentation archiving

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2. QUALITY POLICY

2.1 QUALITY POLICY STATEMENT

Our Commitment:

"We are committed to manufacturing high-quality Active Pharmaceutical Ingredients that consistently meet or exceed customer requirements and applicable regulatory standards. We achieve this through:

- Strict adherence to GMP principles and ICH guidelines
- Continuous improvement of our processes and systems
- Investment in personnel training and development
- Implementation of robust quality control measures
- Maintenance of a culture of quality throughout the organization
- Open communication with regulatory authorities and customers

Quality is the responsibility of every employee, and we empower our teams to identify and resolve quality issues proactively."

Signed:

[Management Representative]

[Date: 03.12.2025]

2.2 QUALITY OBJECTIVES

Strategic Objectives (Annual):

1. Zero critical deviations in manufacturing
2. First-time approval rate >95% for regulatory submissions
3. Customer complaint rate <0.1% of batches
4. On-time delivery >98%

5. Employee GMP training completion rate 100%

Operational Objectives:

- All manufacturing batches meet specification (target: 100%)

- Deviation closure within 30 days (target: >90%)

- CAPA effectiveness verification rate >95%

- Annual product quality review completed on schedule

- Successful completion of all scheduled audits without major findings

2.3 MANAGEMENT RESPONSIBILITY

Senior Management commits to:

- Providing adequate resources (personnel, facilities, equipment)

- Ensuring quality objectives are established and monitored

- Conducting management reviews (minimum annually)

- Fostering a culture of continuous improvement

- Ensuring regulatory compliance at all times

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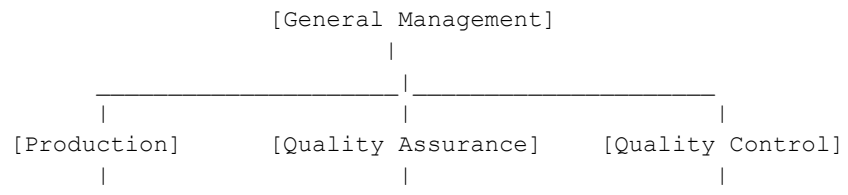
3. ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES

3.1 ORGANIZATIONAL CHART



```
[Process Dev]      [QA Manager]          [QC Manager]
[Manufacturing]    [Validation]          [Analytical Lab]
[Engineering]      [Regulatory]          [Micro Lab]
```

3.2 KEY POSITIONS AND RESPONSIBILITIES

3.2.1 General Management / Management Representative

Responsibilities:

- Ultimate responsibility for product quality

- Approval of Quality Manual and quality policy

- Ensuring adequate resources for QMS implementation

- Management review of QMS performance

- Approval of major quality decisions (e.g., batch release for sale, regulatory submissions)

Authority:

- Final decision on product release

- Approval of deviations requiring regulatory notification

- Authorization of major capital expenditures for quality improvements

Qualifications:

- Degree in relevant scientific discipline or equivalent

- Minimum 5 years senior management experience in pharmaceutical industry

- In-depth knowledge of GMP regulations

3.2.2 Quality Assurance (QA) Manager

Responsibilities:

- Oversight of the entire Quality Management System
- Ensuring GMP compliance in all operations
- Review and approval of:
  - Standard Operating Procedures (SOPs)
  - Validation protocols and reports
  - Deviations and CAPA
  - Change controls
  - Batch documentation review
- Coordination of internal and external audits
- Interface with regulatory authorities
- Trending and reporting of quality metrics
- Supervision of QA staff

Authority:

- Stop production if GMP compliance is at risk
- Reject non-conforming materials or products
- Independent from production (reporting line to General Management)

Qualifications:

- University degree in chemistry, pharmacy, or related science
- Minimum 5 years pharmaceutical quality assurance experience
- Thorough knowledge of ICH Q7, EU GMP, and applicable regulations
- Training in auditing and quality systems

3.2.3 Quality Control (QC) Manager

Responsibilities:

- Oversight of all testing activities (raw materials, intermediates, APIs, stability)
- Ensuring analytical methods are validated and qualified
- Review and approval of:
  - Analytical test results
  - Out-of-Specification (OOS) investigations
  - Certificates of Analysis (CoA)
  - Analytical method validations
- Maintenance and calibration of laboratory equipment
- Management of reference standards
- Supervision of QC laboratory staff
- Ensuring laboratory compliance with GMP

Authority:

- Reject materials or batches that do not meet specifications
- Independent testing authority
- Approval of CoA for release

Qualifications:

- University degree in analytical chemistry or related science
- Minimum 5 years pharmaceutical analytical experience
- Expertise in analytical techniques (HPLC, GC, spectroscopy, etc.)
- Knowledge of ICH Q2(R1) analytical validation guidelines

3.2.4 Production Manager

Responsibilities:

- Planning and execution of manufacturing operations
- Ensuring manufacturing is performed according to:
  - Approved manufacturing procedures
  - Batch manufacturing records
  - GMP requirements
- Ensuring equipment is qualified and maintained
- Management of production staff and training
- Investigation of production-related deviations
- Coordination with QA on manufacturing changes

Authority:

- Scheduling of production batches
- Allocation of production resources
- Initiation of deviation reports

Qualifications:

- Degree in chemistry, chemical engineering, or related field
- Minimum 3 years pharmaceutical manufacturing experience
- Knowledge of GMP requirements for API production

3.2.5 Validation Manager

Responsibilities:

- Development and execution of validation strategies
- Creation of validation master plan
- Preparation and execution of:
  - Equipment qualification (IQ/OQ/PQ)
  - Process validation
  - Cleaning validation
  - Analytical method validation
  - Computer system validation
- Coordination with equipment suppliers and contractors
- Maintenance of validation documentation
- Revalidation and ongoing verification programs

Authority:

- Approval of validation protocols
- Recommendation for equipment/process qualification status

Qualifications:

- University degree in engineering, chemistry, or related science
- Minimum 3 years validation experience in pharmaceutical industry
- Knowledge of ICH Q11, EU GMP Annex 15, and validation principles

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3.2.6 Regulatory Affairs Manager

Responsibilities:

- Preparation and submission of regulatory documentation:
  - Drug Master Files (DMF)
  - Certificate of Suitability (CEP) applications
  - Regulatory change notifications
- Communication with regulatory authorities (e.g., PMDA, FDA, EMA)
- Maintenance of regulatory dossiers
- Tracking of regulatory requirements and guideline updates
- Coordination of regulatory inspections

Authority:

- Approval of regulatory submissions
- Communication with health authorities

Qualifications:

- Degree in pharmacy, chemistry, or related science
- Minimum 3 years regulatory affairs experience
- Knowledge of ICH guidelines, CTD format, and regional requirements

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3.3 INDEPENDENCE OF QUALITY UNIT

Key Principle:

The Quality Assurance and Quality Control functions are **independent from production** to ensure objective quality decisions.

Organizational Independence:

- QA and QC report directly to General Management (not to Production)

- QA/QC have authority to reject materials, batches, or stop production

- No production pressure can override quality decisions

This independence is fundamental to GMP compliance (ICH Q7, Section 2).

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4. QUALITY MANAGEMENT SYSTEM OVERVIEW

4.1 QMS STRUCTURE

The Quality Management System consists of:

1. Quality Manual (this document)

- High-level description of QMS

- Quality policy and objectives

- Organizational structure

2. Standard Operating Procedures (SOPs)

- Detailed instructions for specific activities

- Approximately 50-100 SOPs covering all GMP-relevant operations

3. Work Instructions / Batch Records

- Step-by-step instructions for specific tasks

- Manufacturing batch records

- Analytical test methods

4. Records and Documentation

- Evidence of compliance

- Batch records, test results, deviations, CAPA, validation reports

5. Specifications and Standards

- Raw material specifications

- Intermediate specifications

- API specifications

- Equipment specifications

4.2 QUALITY SYSTEM PROCESSES

The QMS covers the following key processes:

Core Processes:

1. **Production Planning and Execution**

   - Material procurement

   - Manufacturing operations

   - Packaging and labeling

2. **Quality Control**

   - Raw material testing

   - In-process testing

   - Final product testing

- Stability testing

3. **Product Release**

- Batch record review
- QC data review
- QA approval
- Certificate of Analysis issuance

Support Processes:

4. **Document Management**

- SOP creation, review, approval
- Document control and archiving
- Record retention

5. **Training**

- GMP training
- Job-specific training
- Competency assessment

6. **Equipment Management**

- Qualification (IQ/OQ/PQ)
- Preventive maintenance
- Calibration

7. **Facilities and Utilities**

- HVAC system management
- Water system management

- Environmental monitoring

8. **Validation**

- Process validation
- Cleaning validation
- Analytical method validation

9. **Deviation Management**

- Deviation reporting and investigation
- Root cause analysis
- CAPA implementation

10. **Change Control**

- Assessment of proposed changes
- Implementation and verification

11. **Supplier Management**

- Supplier qualification and approval
- Supplier audits
- Material specifications

12. **Audits and Inspections**

- Self-inspections
- Internal audits
- External audits (customer, regulatory)

13. **Management Review**

- Annual review of QMS performance

- Quality metrics trending

- Continuous improvement initiatives

4.3 PROCESS INTERACTIONS

Example: Manufacturing Process Flow

```
[Material Receipt] → [Material Testing (QC)] → [Material Release (QA)]
        ↓
[Production Planning] → [Batch Manufacturing] → [In-Process Testing]
        ↓
[Packaging] → [Final Testing (QC)] → [Batch Review (QA)]
        ↓
[Batch Release] → [Storage] → [Distribution]
```

Quality Oversight at Each Step:

- Material receipt: QC testing, QA release

- Manufacturing: GMP compliance, deviation management

- Final product: QC testing, batch record review, QA approval

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5. DOCUMENTATION SYSTEM

5.1 DOCUMENTATION HIERARCHY

Level 1: Quality Manual (this document)

- Strategic overview of QMS

Level 2: Standard Operating Procedures (SOPs)

- Detailed procedures for all GMP activities

- Examples:

  - SOP-001: Document Control

  - SOP-002: Manufacturing Process for Fampridin

  - SOP-010: HPLC Operation and Maintenance

  - SOP-020: Deviation Management

  - SOP-025: CAPA Process

Level 3: Work Instructions / Batch Records

- Specific instructions for tasks

- Manufacturing Batch Records (executed documents)

- Analytical test methods

Level 4: Records

- Evidence of execution

- Batch records, test results, training records, calibration certificates

5.2 DOCUMENT CONTROL PRINCIPLES

All GMP documents must be:

- **Controlled:** Version control, unique document number

- **Approved:** Appropriate signatures before use

- **Current:** Obsolete versions removed from use areas

- **Legible:** Clear, readable (handwritten entries in indelible ink)

- **Attributable:** Dated signatures identifying who did what and when

- **Original:** Retained as official records

Key Requirements (ICH Q7, Section 6):

- Documents reviewed and approved by appropriate personnel

- Distribution controlled (only current versions in use)

- Changes documented and justified

- Periodic review (e.g., every 2-3 years)

5.3 TYPES OF DOCUMENTS

5.3.1 Standard Operating Procedures (SOPs)

Purpose: Provide detailed instructions for routine operations

Structure:

1. Purpose

2. Scope

3. Responsibilities

4. Procedure (step-by-step)

5. Documentation

6. References

7. Revision history

Review Cycle: Every 2 years (or when process changes)

5.3.2 Manufacturing Batch Records

Purpose: Document each step of production for traceability

Content:

- Batch number, product name, date
- List of raw materials (including batch numbers and quantities)
- Manufacturing steps (with actual values recorded)
- In-process controls and results
- Operator signatures and dates
- Deviations (if any)
- Batch yield
- Review and approval signatures

Retention: According to regulatory requirements (minimum 1 year after expiry date)

5.3.3 Specifications

Types:

- **Raw Material Specifications:** Identity, purity, acceptable limits
- **Intermediate Specifications:** Critical quality attributes during process
- **API Specifications:** Final product quality standards (identity, assay, impurities, etc.)

Approval: QA and QC (and Regulatory for customer-facing specifications)

5.3.4 Protocols and Reports

Validation Protocols:

- Objective, scope, acceptance criteria

- Executed before validation activities

Validation Reports:

- Summary of results

- Conclusion (qualified/validated or not)

- Approved by QA and relevant technical personnel

5.4 DATA INTEGRITY

Principles (ALCOA+):

- **Attributable:** Who created the data? (signature, user ID)

- **Legible:** Readable throughout data lifecycle

- **Contemporaneous:** Recorded at time of activity (not retrospectively)

- **Original:** First recording (or certified true copy)

- **Accurate:** Error-free, verified

Additional (+):

- **Complete:** All data, including repeat tests or failed runs

- **Consistent:** Data is traceable and audit trail exists

- **Enduring:** Data retained for required period

- **Available:** Accessible for review and audit

Electronic Records:

- Compliance with 21 CFR Part 11 (if applicable)

- Audit trails enabled

- Password-protected access

- Regular backups

5.5 RECORD RETENTION

Retention Periods:

- **Batch Records:** Minimum 1 year after API expiry date

- **Stability Data:** Minimum 1 year after expiry

- **Validation Records:** Life of product + 1 year

- **Training Records:** Duration of employment + 2 years

- **Deviation/CAPA:** Minimum 5 years

- **Regulatory Submissions:** Indefinitely (or as required by regulation)

Archive Conditions:

- Secure, controlled access

- Protected from damage (fire, water, etc.)

- Retrievable within reasonable time

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6. PERSONNEL AND TRAINING

6.1 PERSONNEL QUALIFICATIONS

All personnel involved in API manufacturing must:

- Have appropriate education and experience

- Receive initial and ongoing GMP training

- Demonstrate competency in assigned tasks

Minimum Qualifications by Role:

- **QA/QC Staff:** University degree in relevant science + GMP training

- **Production Operators:** Technical education/apprenticeship + on-the-job training

- **Management:** University degree + relevant industry experience

6.2 TRAINING PROGRAM

Types of Training:

1. GMP Induction Training (all new employees)

- Introduction to GMP principles

- Hygiene and contamination control

- Documentation requirements

- Data integrity

2. Job-Specific Training

- SOPs relevant to role

- Equipment operation

- Safety procedures

3. Ongoing Training

- Annual GMP refresher

- Training on new/revised SOPs

- Regulatory updates

4. Competency Assessment

- Practical demonstration of skills

- Written tests (where appropriate)

- Re-training if deficiencies identified

6.3 TRAINING RECORDS

Documentation:

- Training curriculum

- Attendance records (who, what, when)

- Competency assessment results

- Trainer qualifications

Retention: Duration of employment + 2 years

6.4 HYGIENE AND HEALTH

Requirements:

- Personnel with infectious diseases excluded from manufacturing areas

- Regular health monitoring (where relevant)

- Personal hygiene practices (handwashing, gowning)

- No eating, drinking, smoking in production areas

- Jewelry and personal items restricted

Gowning Requirements:

- Clean, dedicated clothing in production areas

- Hairnets, beard covers

- Gloves (where appropriate)

- Shoe covers or dedicated footwear

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7. PREMISES AND EQUIPMENT

7.1 FACILITY DESIGN

Principles:

- Designed to facilitate cleaning and maintenance

- Minimize risk of contamination or cross-contamination

- Adequate space for operations

- Separation of different operations (if needed)

- Controlled environmental conditions

Cleanroom Classification (where applicable):

- Cleanrooms classified according to ISO 14644-1

- Example: ISO 7 (Class 10,000) for certain API manufacturing steps

- Regular monitoring and re-classification

7.2 HVAC SYSTEM

Purpose:

- Control temperature, humidity
- Provide adequate air changes
- Prevent cross-contamination (e.g., via pressure cascades)
- Filter air to required cleanliness level

Key Parameters:

- Air changes per hour (ACH): e.g., 20 ACH for production areas
- Pressure differentials: e.g., +20 Pa in cleanest areas
- HEPA filtration: e.g., H14 filters (99.995% efficiency at 0.3 µm)

Monitoring:

- Continuous monitoring of pressure differentials
- Regular airflow velocity measurements
- Particle counting (for cleanrooms)
- Temperature and humidity recording

Qualification:

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

Maintenance:

- Preventive maintenance schedule

- Filter replacement based on differential pressure

- Annual recertification

7.3 WATER SYSTEM

Purpose:

- Supply of purified water for:

  - Equipment cleaning

  - Product synthesis (as solvent/reagent)

  - Preparation of analytical solutions

Quality Standards:

- Purified Water: Ph. Eur. / USP standards

- Water for Injection (WFI): if required (typically not for APIs unless sterile)

Key Parameters:

- Conductivity (≤1.3 µS/cm at 25°C for purified water)

- Total Organic Carbon (TOC) (≤500 ppb)

- Microbial limits (≤100 CFU/mL for purified water)

System Design:

- Continuous circulation to prevent microbial growth

- Hot water sanitization (e.g., 80°C) or chemical sanitization

- Use of materials resistant to corrosion (e.g., 316L stainless steel)

Monitoring:

- Daily conductivity checks

- Weekly TOC and microbial testing

- Monthly endotoxin testing (if applicable)

Qualification:

- IQ, OQ, PQ (similar to HVAC)

7.4 EQUIPMENT

Equipment Requirements:

- Designed for intended purpose

- Easy to clean and maintain

- Constructed of non-reactive materials (e.g., stainless steel, glass-lined)

- Identified with unique equipment number

Equipment Qualification:

- **Design Qualification (DQ):** Equipment design meets user requirements

- **Installation Qualification (IQ):** Equipment installed correctly

- **Operational Qualification (OQ):** Equipment operates within specified limits

- **Performance Qualification (PQ):** Equipment consistently performs as intended

Maintenance:

- Preventive Maintenance (PM) program

- Maintenance logs (who, what, when)

- Spare parts inventory

Calibration:

- Critical instruments calibrated against traceable standards

- Calibration frequency based on risk and manufacturer recommendations

- Calibration records maintained

7.5 DISTRIBUTION AND STORAGE CONTROL

Purpose:

- Ensure API quality is maintained throughout storage and distribution

- Compliance with Good Distribution Practice (GDP) principles

Warehouse Qualification:

- Temperature and humidity mapping performed

- Monitoring systems validated

- Alarms for out-of-specification conditions

- Regular re-mapping (e.g., annually or after facility changes)

Storage Conditions:

- APIs stored according to labeled conditions (e.g., "Store at 15-25°C", "Protect from light")

- Segregation by status:

  - Quarantined (pending QC release)

  - Approved (released for distribution)

- Rejected (segregated, clearly labeled)

- FIFO (First In, First Out) or FEFO (First Expiry, First Out) system

Environmental Monitoring:

- Continuous temperature and humidity monitoring (where required)

- Data logging with periodic review

- Investigation of excursions

Distribution Controls:

- Qualified transporters / logistics providers

- Temperature-controlled transport (if required)

- Documentation:

  - Shipping documentation (bill of lading, CoA)

  - Temperature records during transport (if applicable)

- Packaging validated to protect product during transport

GDP Compliance:

- Distribution activities comply with EU GDP Guidelines (where applicable)

- Transportation providers qualified

- Agreements with distributors/agents define quality responsibilities

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8. MATERIALS MANAGEMENT

8.1 RAW MATERIALS

Supplier Qualification:

- Assessment of supplier quality system
- Audits (on-site or questionnaire)
- Review of Certificates of Analysis
- Approval by QA before use

Incoming Inspection:

- Identity testing (all containers)
- Full testing per specification (or skip-lot testing if justified)
- Quarantine until released by QA

Specifications:

- Identity tests (e.g., IR, NMR)
- Purity / Assay
- Impurities
- Physical properties
- Microbiological limits (if relevant)

Storage:

- Controlled conditions (temperature, humidity)
- Segregated by status (quarantine, approved, rejected)
- FIFO (First In, First Out) or FEFO (First Expiry, First Out)

Labeling:

- Material name, batch number, supplier
- Receipt date, retest date
- Status (quarantined, approved, rejected)

8.2 INTERMEDIATES

Definition: Materials produced during API synthesis, intended for further processing

Control:

- Specifications for critical intermediates
- In-process testing (if appropriate)
- Storage conditions defined
- Expiry/retest dates

8.3 SOLVENTS AND REAGENTS

Control:

- Specifications (purity, grade)
- Storage in original containers or dedicated vessels
- Segregation of flammable/hazardous materials
- Proper labeling and Material Safety Data Sheets (MSDS) available

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8.4 PACKAGING MATERIALS

Examples:

- Containers (drums, bottles)

- Labels

- Seals

Control:

- Specifications for packaging materials

- Incoming inspection

- Storage to prevent contamination or damage

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9. PRODUCTION AND PROCESS CONTROLS

9.1 MANUFACTURING PROCESS

EXAMPLE: Fampridin Synthesis Process

> **Note:** The following process description is provided as an illustrative example to demonstrate the level of detail required in process documentation. This is not an operational manufacturing process for this site.

Process Description (Example: Fampridin Synthesis)

Note: This is a simplified example. Actual synthesis route may vary.

Step 1: Reaction

- Charge pyridine derivative and reagents to reactor

- Heat to 80°C, maintain for 4 hours

- Monitor temperature, pH

Step 2: Workup

- Cool to 25°C

- Neutralize with acid

- Extract with solvent

Step 3: Purification

- Crystallization from solvent

- Filter, wash crystals

- Dry under vacuum at 60°C

Step 4: Milling and Packaging

- Mill to target particle size

- Package in polyethylene-lined drums

Critical Process Parameters (CPPs):

- Reaction temperature (80 ± 2°C)

- Reaction time (4 ± 0.5 hours)

- pH (controlled range)

- Drying temperature (60 ± 5°C)

In-Process Controls (IPCs):

- pH measurement after neutralization

- Purity check by HPLC (before drying)

- Particle size distribution (after milling)

9.2 BATCH NUMBERING

Format: YYYY-MM-NNN

- YYYY: Year

- MM: Month

- NNN: Sequential number

Example: 2025-12-001 (first batch in December 2025)

Traceability:

- Each batch assigned unique number

- All materials used in batch recorded (with their batch numbers)

- Complete genealogy from raw materials to final API

9.3 YIELDS

Expected Yield:

- Defined in Master Batch Record

- Example: 85-95% for Fampridin synthesis

Actual Yield:

- Calculated after each batch

- Significant deviations investigated

9.4 PROCESS VALIDATION

Objective: Demonstrate that the manufacturing process consistently produces API meeting specifications

Approach:

- **Prospective Validation:** Validation before routine production (required for new products)

- **Concurrent Validation:** Validation during routine production (exceptional, justified)

- **Retrospective Validation:** Based on historical data (not preferred)

Validation Batches:

- Minimum 3 consecutive batches at commercial scale

- All batches must meet specifications

- Process parameters within validated ranges

- Statistical analysis of critical quality attributes

Documentation:

- Validation Protocol (before execution)

- Validation Report (summary of results, conclusion)

Revalidation:

- After significant process changes

- Periodically (e.g., every 5 years)

- If process performance degrades

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10. QUALITY CONTROL AND TESTING

10.1 ANALYTICAL LABORATORY

Function:

- Testing of raw materials, intermediates, APIs
- Method development and validation
- Stability studies
- Reference standard management

Organization:

- Independent from production (reports to QC Manager)
- Adequate space, equipment, and personnel
- Controlled environmental conditions (temperature, humidity)

10.2 TEST METHODS

Compendial Methods:

- Methods from pharmacopoeias (Ph. Eur., USP, JP)
- Used as written, or validated if modified

Non-Compendial Methods:

- Developed in-house or from literature

- Must be validated per ICH Q2(R1)

Analytical Method Validation:

- **Specificity:** Method detects target analyte

- **Linearity:** Response proportional to concentration

- **Accuracy:** Closeness to true value

- **Precision:** Repeatability and reproducibility

- **Range:** Concentration range validated

- **Detection Limit (LOD) / Quantitation Limit (LOQ):** Sensitivity

- **Robustness:** Method stable to small variations

10.3 SPECIFICATIONS

EXAMPLE: API Specification (Fampridin)

> **Note:** The following specification is provided as an illustrative example. Product specifications are maintained in separate, controlled specification documents.

Test	Method	Acceptance Criteria
Appearance	Visual	White to off-white crystalline powder
Identity	IR	Conforms to reference standard
Identity	HPLC (Retention Time)	Matches reference standard ±2%
Assay	HPLC	99.0 - 101.0%
Impurities	HPLC	Any single impurity: ≤0.10%
		Total impurities: ≤0.50%

Water Content	Karl Fischer	≤0.50%
Residual Solvents	GC	Ethanol: ≤5000 ppm
		Other solvents: Per ICH Q3C
Particle Size	Laser Diffraction	D50: 20-80 µm
Microbial Limits	Ph. Eur. 2.6.12	Total aerobic count: ≤1000 CFU/g
		Yeast/Mold: ≤100 CFU/g
		E. coli, Salmonella: Absent

10.4 OUT-OF-SPECIFICATION (OOS) RESULTS

Definition: Test result outside specification limits

Investigation:

- **Phase 1:** Laboratory investigation
  - Check for calculation errors, instrument malfunction, analyst error
  - If laboratory error identified and confirmed → Invalidate result, retest
  - If no laboratory error → Proceed to Phase 2

- **Phase 2:** Extended investigation
  - Review manufacturing process
  - Identify potential root cause (e.g., process deviation, raw material issue)
  - Decide on batch disposition (release, reprocess, reject)

Documentation:

- OOS report with investigation details
- Root cause analysis
- CAPA (if systemic issue identified)

- QA approval of conclusion

10.5 CERTIFICATES OF ANALYSIS (CoA)

Content:

- Product name, batch number
- Manufacturing date
- Test results (all specification tests)
- Conclusion: "Meets specification" or "Does not meet specification"
- Signatures (QC Manager, QA Manager)
- Date of issue

Issuance:

- Only after batch released by QA

10.6 REFERENCE STANDARDS

Types:

- **Primary Standards:** Highest purity, used to prepare secondary standards
- **Secondary Standards:** Working standards for routine testing

Management:

- Purchased from reputable suppliers (e.g., pharmacopoeia, certified suppliers)

- Certificate of Analysis retained

- Storage under appropriate conditions

- Expiry dates observed

- Periodic re-qualification (if used beyond expiry)

10.7 STABILITY STUDIES

Purpose: Establish retest date or expiry date for API

Study Design (per ICH Q1A):

- **Long-Term:** 25°C / 60% RH, minimum 12 months (ideally 24-36 months)

- **Accelerated:** 40°C / 75% RH, 6 months

- **Intermediate:** 30°C / 65% RH (if significant change at accelerated)

Testing Frequency:

- Long-term: 0, 3, 6, 9, 12, 18, 24, 36 months

- Accelerated: 0, 3, 6 months

Stability Protocol:

- Number of batches (minimum 3 pilot/commercial scale)

- Storage conditions

- Test parameters (assay, impurities, physical properties)

- Acceptance criteria

Stability Report:

- Summary of results

- Statistical analysis (degradation kinetics)

- Proposed retest date / expiry date

Ongoing Stability Program:

- At least 1 batch per year placed on long-term stability

- Results reviewed as part of Annual Product Quality Review

---

11. VALIDATION

11.1 MASTER VALIDATION PLAN (MVP)

Purpose: Provide overview of all validation activities

Content:

- Scope (products, processes, equipment)

- Validation strategy

- List of items to be validated (equipment, processes, methods, cleaning, computer systems)

- Responsibilities

- Timeline

See separate document: Master Validation Plan (MVP-001)

11.2 TYPES OF VALIDATION

11.2.1 Equipment Qualification

Design Qualification (DQ):

- Verify equipment design meets user requirements (URS)

- Review drawings, specifications, vendor documentation

Installation Qualification (IQ):

- Verify equipment installed per manufacturer specifications

- Check utilities (power, water, compressed air)

- Verify instrumentation and calibration

Operational Qualification (OQ):

- Verify equipment operates within specified parameters

- Test all functions (normal and abnormal conditions)

- Alarm testing

Performance Qualification (PQ):

- Verify equipment consistently performs under actual production conditions

- Process simulation using representative materials

- Acceptance criteria met

11.2.2 Process Validation

Objective: Demonstrate manufacturing process consistently produces API meeting specifications

Protocol:

- Minimum 3 consecutive batches at commercial scale
- All critical process parameters monitored
- All in-process controls and final tests performed
- Statistical evaluation of results

Report:

- Summary of results (yield, impurity profile, physical properties)
- Conclusion: Process validated or not
- Recommendations (if any)

11.2.3 Cleaning Validation

Objective: Demonstrate cleaning procedures effectively remove residues (product, cleaning agents, microorganisms)

Acceptance Criteria:

- Product residue: e.g., ≤10 ppm (or health-based limit)
- Cleaning agent residue: e.g., ≤10 ppm
- Microbial limits: e.g., ≤100 CFU per surface area

Approach:

- Worst-case scenario (hardest-to-clean product, longest campaign, most difficult-to-clean equipment)

- Swab sampling and/or rinse sampling

- Analytical method validated for detection of residues

Frequency:

- Initial validation: 3 consecutive successful cleaning cycles

- Re-validation: After process changes, periodically (e.g., every 3 years)

11.2.4 Analytical Method Validation

Per ICH Q2(R1):

- Specificity, Linearity, Accuracy, Precision, Range, LOD/LOQ, Robustness

Documentation:

- Validation Protocol

- Validation Report (data tables, statistical analysis, conclusion)

11.2.5 Computer System Validation

Applicable to:

- Laboratory Information Management Systems (LIMS)

- Manufacturing Execution Systems (MES)

- Electronic Batch Records

- Instrument software

Approach (GAMP 5):

- Risk-based approach

- Validation based on system complexity (Category 3, 4, 5)

- User Requirements Specification (URS)

- Functional Specification (FS)

- Testing (IQ, OQ, PQ equivalent for software)

- Ongoing periodic review

11.3 REVALIDATION / ONGOING VERIFICATION

Revalidation Triggers:

- Significant process changes

- Equipment changes or major maintenance

- Transfer to new facility

- Trend of declining process performance

Ongoing Verification:

- Periodic review of process performance (e.g., annual)

- Continued monitoring of critical parameters

- Trending of quality attributes

---

12. DEVIATION MANAGEMENT AND CAPA

12.1 DEVIATIONS

Definition: Departure from approved procedures, specifications, or standards

Classification:

Critical Deviation:

- Impacts product quality or patient safety

- Requires immediate action and regulatory notification (if applicable)

Major Deviation:

- Significant departure, but product quality likely unaffected

- Requires thorough investigation

Minor Deviation:

- Small departure, no impact on product quality

- Documented, but limited investigation

12.2 DEVIATION PROCESS

Step 1: Identification and Reporting

- Any employee can report a deviation

- Deviation form initiated immediately

- Production may be stopped if product quality at risk

Step 2: Immediate Action

- Quarantine affected materials/batches

- Implement containment measures

Step 3: Investigation

- Root Cause Analysis (5-Why, Fishbone, Fault Tree)

- Assess impact on product quality

- Determine if other batches affected

Step 4: Corrective Action (CA)

- Action to fix the specific problem

Step 5: Preventive Action (PA)

- Action to prevent recurrence

Step 6: CAPA Implementation

- Assign responsibilities and deadlines

- Implement actions

- Verify effectiveness

Step 7: Closure

- QA approval after effectiveness check

- Typical timeline: 30-60 days

12.3 CAPA (CORRECTIVE AND PREVENTIVE ACTION)

Purpose: Systematic approach to prevent recurrence of problems

Triggers:

- Deviations
- Out-of-Specification results
- Audit findings
- Customer complaints
- Trends indicating systemic issues

CAPA Process:

1. **Problem Definition:** What happened?
2. **Root Cause Analysis:** Why did it happen?
3. **Corrective Action:** Fix this instance
4. **Preventive Action:** Prevent future occurrences (e.g., SOP revision, training, equipment modification)
5. **Implementation:** Execute actions
6. **Effectiveness Check:** After 3-6 months, verify actions were effective (problem has not recurred)

Documentation:

- CAPA form with all details
- Root cause analysis documentation (e.g., 5-Why chart)
- Evidence of action completion (e.g., revised SOP, training records)
- Effectiveness check results

Metrics:

- Number of open CAPAs

- Average time to closure

- Recurrence rate

---

13. CHANGE CONTROL

13.1 PURPOSE

Ensure changes to processes, equipment, facilities, or materials are:

- Evaluated for impact on product quality

- Approved before implementation

- Documented

- Communicated to relevant personnel

13.2 TYPES OF CHANGES

Major Changes:

- Impact product quality, safety, or efficacy

- Require validation/qualification

- May require regulatory notification

- Examples: New equipment, process parameter changes outside validated range

Minor Changes:

- Limited or no impact on product quality

- May require verification but not full validation

- Examples: Administrative changes, equipment relocation (if qualified)

13.3 CHANGE CONTROL PROCESS

Step 1: Change Request

- Initiator proposes change (with justification)

Step 2: Impact Assessment

- Evaluate impact on:
  - Product quality
  - Validation status
  - Documentation (SOPs, batch records)
  - Regulatory requirements
- **Risk assessment (ICH Q9):**
  - Risk to product quality (severity × probability)
  - Risk-based approach determines level of testing/validation required
  - FMEA or similar risk assessment tools may be used for complex changes

Step 3: Approval

- QA must approve all changes impacting product quality
- Management approval for significant changes

Step 4: Implementation

- Execute change
- Update documentation (SOPs, batch records, etc.)

- Train personnel (if applicable)

Step 5: Verification

- Confirm change implemented correctly

- Re-qualification/re-validation if needed

Step 6: Effectiveness Check

- Monitor process performance after change

- Ensure no adverse impact

Step 7: Closure

- QA approval after verification

13.4 EMERGENCY CHANGES

Definition: Urgent changes needed for safety or regulatory compliance

Process:

- Verbal approval from QA (documented immediately after)

- Full change control documentation completed retrospectively (within 24-48 hours)

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14. AUDITS AND INSPECTIONS

14.1 SELF-INSPECTIONS

Purpose: Proactive assessment of GMP compliance

Frequency: Annually (minimum), or more frequently if issues identified

Scope:

- All GMP-relevant areas (production, QC, QA, warehousing)

- Review of documentation, processes, facilities, equipment

Checklist:

- Based on GMP requirements (ICH Q7, EU GMP)

Report:

- Findings categorized (critical, major, minor, observation)

- CAPA for findings

- Follow-up to verify correction

14.2 INTERNAL AUDITS

Purpose: Independent assessment by trained auditors (may be external consultants)

Frequency: Every 1-2 years

Similar to self-inspection, but more formal and independent.

14.3 SUPPLIER AUDITS

Purpose: Verify supplier quality system and GMP compliance

Frequency:

- Before approval of new supplier
- Periodically for approved suppliers (e.g., every 3 years)
- Risk-based (critical materials audited more frequently)

Report:

- Assessment of supplier facilities, QMS, testing capabilities
- Findings and CAPA required from supplier
- Approval decision

14.4 REGULATORY INSPECTIONS

Types:

- **Pre-Approval Inspection:** Before regulatory approval of DMF/CEP
- **GMP Inspection:** Routine surveillance or for-cause
- **For-Cause Inspection:** Triggered by quality issues, complaints

Preparation:

- Mock inspection (internal rehearsal)

- Ensure all documents up-to-date

- Designated company representative (e.g., QA Manager, Regulatory Manager)

During Inspection:

- Escort inspectors

- Answer questions honestly

- Provide requested documents promptly

- Take notes (inspector comments, observations)

After Inspection:

- Review inspection report

- Respond to findings with CAPA plan (typically within 15-30 days)

- Implement corrective actions

- Verification and effectiveness check

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15. PRODUCT QUALITY REVIEW

15.1 ANNUAL PRODUCT QUALITY REVIEW (APQR)

Purpose: Systematic review of all batches to identify trends and areas for improvement

Frequency: Annually (for each API)

Content:

- **Review of Batches:**

  - Number of batches manufactured

  - Yield (average, range, trends)

  - Batch failures and investigations

- **Quality Control:**

  - Review of all test results (assay, impurities, physical properties)

  - OOS results and investigations

  - Trends in impurity profiles

- **Deviations and CAPA:**

  - Summary of deviations

  - CAPA effectiveness

- **Changes:**

  - Summary of changes made during year

  - Impact on product quality

- **Stability:**

  - Ongoing stability results

  - Any out-of-trend or out-of-specification results

- **Customer Complaints:**

  - Number and nature of complaints

  - Investigations and resolutions

- **Returned Products:**

- Reasons for return

- **Process Performance:**

- Process capability (Cpk) if applicable

- Opportunities for improvement

Report:

- Summary of findings

- Conclusions (is product quality consistent? Are there adverse trends?)

- Recommendations for improvements

- CAPA if issues identified

Approval: QA Manager, Production Manager, Management

---

16. COMPLAINTS, RECALLS, AND RETURNS

16.1 CUSTOMER COMPLAINTS

Definition: Any written, electronic, or oral communication that alleges deficiencies related to identity, quality, durability, reliability, safety, or performance of an API.

Complaint Handling Process:

Step 1: Receipt and Documentation

- All complaints recorded in complaint log

- Unique complaint number assigned
- Details captured:
  - Customer information
  - Product name, batch number
  - Nature of complaint
  - Date received

Step 2: Initial Assessment

- QA reviews complaint
- Classify severity:
  - **Critical:** Product defect impacting patient safety
  - **Major:** Significant quality issue
  - **Minor:** Administrative or minor quality concern

Step 3: Investigation

- Review batch records, test results, stability data
- Inspect retained samples (if available)
- Determine root cause
- Assess if other batches affected

Step 4: Response to Customer

- Acknowledge complaint (within 2 business days)
- Provide investigation summary and conclusion (within 30 days)
- Propose corrective action (if applicable)

Step 5: CAPA

- If systemic issue identified → Initiate CAPA

- Implement preventive actions

Step 6: Trending

- Regular review of complaints for trends

- Include in Annual Product Quality Review

Records:

- Complaint form with all details

- Investigation report

- Customer correspondence

- CAPA (if initiated)

Retention: Minimum 5 years

16.2 PRODUCT RECALLS

Definition: Action to remove API from the market due to quality defect that could pose risk to patient safety or non-compliance with specifications.

Recall Classification:

- **Class I:** Life-threatening or serious health hazard (immediate action)

- **Class II:** May cause temporary or medically reversible adverse health consequences

- **Class III:** Not likely to cause adverse health consequences (minor defect)

Recall Procedure:

Step 1: Recall Decision

- QA Manager, in consultation with Management, decides on recall

- Regulatory authorities notified (as required by regulation)

Step 2: Recall Team Activation

- Recall team: QA Manager, Regulatory Manager, Sales/Distribution

- Define scope: Which batches? Which customers?

Step 3: Customer Notification

- Urgent notification to all customers who received affected batches

- Communication method: Email, phone, fax (documented)

- Recall notice includes:

  - Product name, batch numbers

  - Reason for recall

  - Instructions (return, quarantine, dispose)

Step 4: Product Retrieval

- Track returned product

- Quarantine and clearly label recalled material

- Destruction or reprocessing (if justified)

Step 5: Effectiveness Check

- Verify all distributed product accounted for

- Reconcile: Quantity distributed vs. quantity returned

Step 6: Recall Report

- Summary of recall (scope, effectiveness, root cause)

- Submitted to regulatory authorities (if required)

- CAPA to prevent recurrence

Step 7: Closure

- QA approval after effectiveness verification and CAPA implementation

Mock Recall:

- Annual mock recall exercise to test system effectiveness

- Verify traceability and speed of retrieval

16.3 RETURNED PRODUCTS

Definition: API returned by customer for any reason (complaint, overstocking, expiry, etc.)

Returned Product Handling:

Step 1: Receipt

- Returned product received in designated area

- Immediately quarantined and labeled "RETURNED"

- Unique return number assigned

Step 2: Documentation

- Return form completed:

  - Product name, batch number, quantity

- Reason for return
- Condition of product (packaging intact? Temperature excursions?)
- Customer information

Step 3: Evaluation

- QA evaluates:
  - Is product suitable for return to stock? (intact packaging, within expiry, proper storage)
  - Is reprocessing possible?
  - Must it be destroyed?

Step 4: Decision

- **Release for resale:** If product meets all requirements, QA releases back to approved stock
- **Reprocess/Rework:** If justifiable (see Section 17)
- **Reject and destroy:** If quality compromised

Step 5: Documentation

- Decision documented with justification
- QA approval required

Records:

- Return form
- Evaluation report
- CoA (if retested)
- Destruction certificate (if destroyed)

---

17. REJECTED MATERIALS AND REPROCESSING

17.1 REJECTED MATERIALS

Definition: Materials (raw materials, intermediates, APIs) that do not meet specifications.

Handling:

- Immediately quarantined
- Clearly labeled "REJECTED" (red label)
- Segregated from approved materials
- Documented in deviation report

Disposition Options:

Option 1: Return to Supplier

- For raw materials that do not meet specification
- Supplier notified, CAPA requested

Option 2: Destruction

- If no alternative use possible
- Destruction documented (certificate)
- Witnessed by QA

Option 3: Downgrade / Alternative Use

- If material suitable for non-pharmaceutical use (rare for APIs)
- Requires QA approval
- Clearly labeled with new use

Option 4: Reprocessing (see Section 17.2)

17.2 REPROCESSING

Definition: Introducing an intermediate or API that does not meet specification back into the manufacturing process and repeating a specific step(s) to achieve acceptable quality.

Policy:

- Reprocessing permitted only if:
  - Scientifically justified
  - Does not adversely affect product quality
  - Does not introduce new impurities or risks

Procedure:

Step 1: Reprocessing Request

- Production/QC identifies need for reprocessing
- Reprocessing form completed with justification

Step 2: Evaluation

- QA reviews:
  - Root cause of failure
  - Proposed reprocessing method
  - Impact on impurity profile

- Risk assessment (ICH Q9)

Step 3: Approval

- QA approves reprocessing plan

- Specific instructions documented (which step to repeat, how)

Step 4: Reprocessing Execution

- Reprocessed material labeled with original batch number + "-R1" (R2, R3, etc.)

- Full batch record maintained

Step 5: Testing

- Reprocessed material retested per specification

- Additional testing if needed (e.g., impurity profile)

Step 6: Release Decision

- If reprocessed material meets specification → QA releases

- If fails again → Reject

Documentation:

- Reprocessing request and approval

- Batch record of reprocessing

- Test results

- QA release decision

Limits:

- Maximum number of reprocessing attempts defined (e.g., 2 times)

- Repeated reprocessing requires additional justification

17.3 REWORK

Definition: Subjecting an intermediate or API that meets specification to additional processing to improve quality (e.g., particle size reduction, additional drying).

Difference from Reprocessing:

- Rework: Material already meets specification, but further processing improves properties

- Reprocessing: Material does NOT meet specification

Policy:

- Rework permitted if:

  - Does not adversely affect quality

  - Scientifically justified

  - Within validated process

Procedure:

- Similar to reprocessing (evaluation, approval, documentation)

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18. OUTSOURCED ACTIVITIES AND CONTRACT MANUFACTURERS

18.1 SCOPE

Definition: Activities performed by external parties on behalf of the API manufacturer, including:

- Contract manufacturing (full or partial synthesis)

- Contract testing (analytical services)

- Contract packaging/labeling

- Warehouse/distribution services

- Validation services

Responsibility:

- The API manufacturer (sponsor) retains ultimate responsibility for quality, even when activities are outsourced.

18.2 CONTRACTOR QUALIFICATION

Qualification Process:

Step 1: Initial Assessment

- Review contractor's quality system

- Request quality questionnaire

- Review of contractor's GMP certificates/licenses

Step 2: On-Site Audit

- Audit of contractor facilities

- Review of QMS, equipment, personnel competency

- Review of batch records, deviations, CAPA

- Audit report with findings

Step 3: Approval

- QA approves contractor based on audit results

- Approved Contractor List maintained

Re-Qualification:

- Periodic audits (e.g., every 2-3 years)

- Risk-based frequency (critical activities audited more frequently)

18.3 QUALITY AGREEMENTS

Purpose: Define quality responsibilities between sponsor and contractor

Content:

- Scope of work

- Quality standards to be met (specifications, GMP compliance)

- Responsibilities:

  - Who performs testing?

  - Who releases batches?

  - Who handles deviations?

- Change control process

- Audit rights

- Documentation and record retention

- Confidentiality

Approval: QA from both parties

18.4 OVERSIGHT

Ongoing Monitoring:

- Regular review of contractor performance (quality metrics)

- Review of CoAs, test results

- Trending of deviations or OOS results

- Periodic audits

Communication:

- Regular meetings (e.g., quarterly)

- Immediate notification of critical issues (recalls, major deviations)

18.5 CONTRACT TESTING

Applicability: When testing is outsourced to contract labs

Controls:

- Contract lab must be qualified

- Test methods transferred and validated at contract lab

- Quality agreement defines responsibilities

- Review of test results before batch release

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19. DISTRIBUTION AND STORAGE CONTROL

[NOTE: This section was previously integrated into Section 7.5. It is cross-referenced here for clarity.]

See **Section 7.5: Distribution and Storage Control** for full details on:

- Warehouse qualification

- Storage conditions and segregation

- Environmental monitoring

- Distribution controls and GDP compliance

- Transportation provider qualification

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20. REFERENCE DOCUMENTS

16.1 REGULATORY GUIDELINES

International:

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

- ICH Q10: Pharmaceutical Quality System

- ICH Q2(R1): Validation of Analytical Procedures

- ICH Q1A: Stability Testing of New Drug Substances and Products

- ICH Q3A/Q3B: Impurities in New Drug Substances and Products

- ICH Q11: Development and Manufacture of Drug Substances

Regional:

- EU GMP (EudraLex Volume 4)

- US FDA 21 CFR Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals (applicable portions)

- PMDA Guidelines (Japan)

- German Medicinal Products Act (AMG) and AMWHV

Standards:

- ISO 9001:2015: Quality Management Systems

- ISO 14644: Cleanrooms and Associated Controlled Environments

- Ph. Eur. (European Pharmacopoeia)

- USP (United States Pharmacopeia)

- JP (Japanese Pharmacopoeia)

16.2 INTERNAL DOCUMENTS

Key SOPs (Examples):

- SOP-001: Document Control

- SOP-005: Training

- SOP-010: Manufacturing Process (Product-Specific)

- SOP-015: Equipment Cleaning

- SOP-020: Deviation Management

- SOP-025: CAPA Process

- SOP-030: Change Control

- SOP-035: Batch Record Review and Product Release

- SOP-040: Stability Testing

- SOP-050: Internal Audits

- SOP-060: Supplier Qualification

Plans:

- Master Validation Plan (MVP-001)

- Annual Product Quality Review Plan

Specifications:

- Raw Material Specifications

- Intermediate Specifications

- API Specifications (e.g., Fampridin Specification)

REVISION HISTORY

Version	Date	Author	Description of Changes	Approved By
1.0	03.12.2025	QA Department	Initial release	Management Representative
1.1	04.12.2025	QA Department	Added Sections 16-19: Complaints/Recalls/Returns, Rejected Materials/Reprocessing, Outsourced Activities, Distribution Control (7.5). Enhanced ICH Q9 integration in Change Control. Visual separation of Fampridin examples.	Management Representative

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APPROVAL SIGNATURES

Prepared by:

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Date: 04.12.2025

Reviewed by:

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Date: 04.12.2025

Reviewed by:

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Signature: _____

Date: 04.12.2025

Approved by:

[Name, Title: Management Representative / General Manager]

Signature: _____

Date: 04.12.2025

END OF QUALITY MANUAL

Distribution:

- Management Representative (Controlled Copy #1)

- QA Manager (Controlled Copy #2)

- QC Manager (Controlled Copy #3)

- Production Manager (Controlled Copy #4)

- Regulatory Affairs (Controlled Copy #5)

- Validation Manager (Controlled Copy #6)

Document Control:

- Total Controlled Copies: 6

- Uncontrolled copies are for reference only

- Obsolete versions must be removed from all work areas

Next Scheduled Review Date: 04. Dezember 2026