PVP-FAM-001

PROCESS VALIDATION PROTOCOL

Fampridin (4-Aminopyridine) Manufacturing Process

Version: 1.0
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Prospective Validation – Three Commercial-Scale Batches

Protocol Status: Draft for Approval

CAS Number: 504-24-5

Batch Size: 100 kg (per batch)

Number of Validation Batches: 3

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1. OBJECTIVE

The objective of this Process Validation Protocol is to demonstrate that the manufacturing process for **Fampridin (4-Aminopyridine)** consistently produces Active Pharmaceutical Ingredient (API) that meets predetermined specifications and quality attributes.

This validation will be performed prospectively using **three consecutive commercial-scale batches** manufactured according to the approved Master Batch Record.

Regulatory Basis:

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

- ICH Q11: Development and Manufacture of Drug Substances

- EU GMP Annex 15: Qualification and Validation

- ICH Q9: Quality Risk Management

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2. SCOPE

2.1 INCLUDED IN SCOPE

This protocol covers:

- Complete manufacturing process from raw materials to final packaged API

- All critical process parameters (CPPs)

- All in-process controls (IPCs)

- Final product testing per specification

- Statistical evaluation of process consistency

Manufacturing Steps:

1. Reaction (Synthesis)

2. Workup (Neutralization and Extraction)

3. Purification (Crystallization)

4. Drying

5. Milling

6. Packaging

2.2 EXCLUDED FROM SCOPE

- Equipment qualification (covered separately: IQ/OQ/PQ protocols)

- Analytical method validation (covered separately: AMV-HPLC-001, AMV-GC-001)

- Cleaning validation (covered separately: CVP-REACTOR-001)

- Raw material qualification

Prerequisite: All equipment used in this process must be successfully qualified (IQ/OQ/PQ completed) before process validation begins.

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3. RESPONSIBILITIES

3.1 VALIDATION MANAGER

- Prepare and finalize this protocol

- Coordinate validation activities

- Compile and analyze validation data

- Prepare Process Validation Report (PVR-FAM-001)

3.2 PRODUCTION MANAGER

- Ensure manufacturing personnel are trained on the Master Batch Record

- Execute validation batches according to protocol

- Document all process parameters and deviations

- Ensure equipment is available and qualified

3.3 QC MANAGER

- Perform all analytical testing per protocol

- Ensure analytical methods are validated

- Review and approve all test results

- Report Out-of-Specification (OOS) results immediately

3.4 QA MANAGER

- Review and approve this protocol before execution

- Review batch records and test results for each validation batch

- Approve/reject batches based on acceptance criteria

- Review and approve final Process Validation Report

3.5 MANAGEMENT REPRESENTATIVE

- Final approval of protocol and validation report

- Ensure resources are available

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4. PRODUCT DESCRIPTION

4.1 PRODUCT INFORMATION

Product Name: Fampridin (INN)

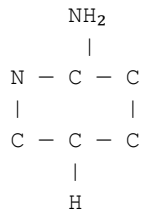
Chemical Name: 4-Aminopyridine

Molecular Formula: $C_5H_6N_2$

Molecular Weight: 94.11 g/mol

CAS Number: 504-24-5

Chemical Structure:



(Pyridine ring with amino group at position 4)

Appearance: White to off-white crystalline powder

Solubility: Freely soluble in water, soluble in ethanol

Therapeutic Use: Treatment of walking impairment in multiple sclerosis patients

4.2 QUALITY STANDARD

Compendial Status: DAC (Deutscher Arzneimittel-Codex)

GMP Classification: Active Pharmaceutical Ingredient (API)

Target Market: EU, Japan (PMDA approval planned)

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5. MANUFACTURING PROCESS DESCRIPTION

5.1 PROCESS OVERVIEW

Synthesis Route: (Simplified for validation purposes)

The manufacturing process consists of six main steps:

Step 1: Reaction (Synthesis)

- Pyridine derivative reacted with appropriate reagents

- Controlled temperature and pH

- Monitored by in-process HPLC

Step 2: Workup (Neutralization and Extraction)

- Reaction mixture neutralized to target pH

- Extraction with organic solvent

- Aqueous/organic phase separation

Step 3: Purification (Crystallization)

- Solvent evaporation/concentration

- Crystallization from appropriate solvent system

- Filtration and washing

Step 4: Drying

- Vacuum drying at controlled temperature

- Endpoint determined by Loss on Drying (LOD)

Step 5: Milling

- Particle size reduction to target distribution

- Sieving (if applicable)

Step 6: Packaging

- Transfer to polyethylene-lined drums

- Labeling with batch number, manufacturing date, specifications

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5.2 DETAILED PROCESS DESCRIPTION

STEP 1: REACTION (SYNTHESIS)

Equipment: Reactor R-101 (500 L capacity)

Procedure:

1. Charge starting materials to reactor:

   - Starting Material A: [XX] kg

   - Starting Material B: [XX] kg

   - Solvent: [XX] L

2. Heat to reaction temperature: **80 ± 2°C** (CPP-1)

3. Maintain reaction for: **4.0 ± 0.5 hours** (CPP-2)

4. Monitor pH: Target pH **7.0 ± 0.5** during reaction (CPP-3)

5. In-Process Control: HPLC purity ≥95% (IPC-1)

Critical Process Parameters (CPPs):

- **CPP-1:** Reaction temperature: 80 ± 2°C

- **CPP-2:** Reaction time: 4.0 ± 0.5 hours

- **CPP-3:** pH during reaction: 7.0 ± 0.5

In-Process Controls:

- **IPC-1:** Purity by HPLC ≥95%

STEP 2: WORKUP (NEUTRALIZATION AND EXTRACTION)

Equipment: Reactor R-102 (300 L capacity), Separator

Procedure:

1. Transfer reaction mixture to workup reactor R-102

2. Cool to **25 ± 5°C**

3. Adjust pH to **6.5-7.5** using [Acid/Base] (CPP-4)

4. Add extraction solvent: [XX] L

5. Mix for 30 minutes, allow phase separation

6. Separate aqueous and organic layers

7. In-Process Control: pH verification (IPC-2)

Critical Process Parameters:

- **CPP-4:** pH after neutralization: 6.5-7.5

In-Process Controls:

- **IPC-2:** pH verification: 6.5-7.5

STEP 3: PURIFICATION (CRYSTALLIZATION)

Equipment: Crystallizer C-101, Filter F-101

Procedure:

1. Concentrate organic phase by distillation under vacuum

2. Cool to **10 ± 5°C** to induce crystallization (CPP-5)

3. Hold at crystallization temperature for **2 ± 0.5 hours** (CPP-6)

4. Filter crystals on Nutsche filter F-101

5. Wash crystals with cold solvent: [XX] L

6. In-Process Control: Purity by HPLC ≥98% (IPC-3)

Critical Process Parameters:

- **CPP-5:** Crystallization temperature: 10 ± 5°C

- **CPP-6:** Crystallization hold time: 2 ± 0.5 hours

In-Process Controls:

- **IPC-3:** Purity by HPLC ≥98%

STEP 4: DRYING

Equipment: Vacuum Dryer VD-101

Procedure:

1. Transfer wet cake to vacuum dryer

2. Dry at **60 ± 5°C** under vacuum **<50 mbar** (CPP-7, CPP-8)

3. Dry until Loss on Drying (LOD) **≤0.50%** (IPC-4)

4. Typical drying time: 8-12 hours

5. Cool to room temperature under nitrogen

Critical Process Parameters:

- **CPP-7:** Drying temperature: 60 ± 5°C

- **CPP-8:** Vacuum level: <50 mbar

In-Process Controls:

- **IPC-4:** Loss on Drying (LOD) ≤0.50%

STEP 5: MILLING

Equipment: Mill M-101

Procedure:

1. Mill dried API to achieve target particle size

2. Target particle size distribution: **D50: 20-80 µm** (CPP-9)

3. In-Process Control: Particle size distribution (IPC-5)

Critical Process Parameters:

- **CPP-9:** Target D50: 20-80 µm

In-Process Controls:

- **IPC-5:** Particle size distribution D50: 20-80 µm

STEP 6: PACKAGING

Equipment: Packaging area

Procedure:

1. Transfer milled API to polyethylene-lined drums (25 kg per drum)

2. Close drums with secure lids

3. Label drums with:

  - Product name: Fampridin

- Batch number
- Manufacturing date
- Quantity
- Storage conditions: "Store at 15-25°C, protect from light"

4. Quarantine until QC release

5.3 PROCESS FLOW DIAGRAM

```
Raw Materials
      ↓
[REACTION] ← Reactor R-101 (80°C, 4h, pH 7.0)
      ↓
[WORKUP] ← Reactor R-102 (pH 6.5-7.5, Extraction)
      ↓
[CRYSTALLIZATION] ← Crystallizer C-101 (10°C, 2h)
      ↓
[FILTRATION] ← Filter F-101
      ↓
[DRYING] ← Vacuum Dryer VD-101 (60°C, <50 mbar)
      ↓
[MILLING] ← Mill M-101 (D50: 20-80 µm)
      ↓
[PACKAGING] ← Drums (25 kg)
      ↓
Quarantine → QC Testing → QA Release → Approved Stock
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6. CRITICAL QUALITY ATTRIBUTES (CQAs)

Critical Quality Attributes (CQAs) are physical, chemical, biological, or microbiological properties that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

6.1 IDENTIFIED CQAs FOR FAMPRIDIN

CQA	Specification	Criticality	Control Method
Identity	IR spectrum conforms to reference	High	IR Spectroscopy
Assay (Purity)	99.0 - 101.0%	High	HPLC
Impurities	Any single impurity ≤0.10% Total impurities ≤0.50%	High	HPLC
Residual Solvents	Ethanol ≤5000 ppm Others per ICH Q3C	High	GC
Water Content	≤0.50%	Medium	Karl Fischer
Particle Size	D50: 20-80 µm	Medium	Laser Diffraction
Appearance	White to off-white crystalline powder	Low	Visual
Microbial Limits	Total aerobic count ≤1000 CFU/g Yeast/Mold ≤100 CFU/g E. coli, Salmonella: Absent	Medium	Ph. Eur. 2.6.12

Justification:

- **Identity, Assay, Impurities:** Directly impact efficacy and safety (High criticality)

- **Residual Solvents:** Toxicological concern (High criticality)

- **Water Content, Particle Size, Microbial Limits:** Impact stability, bioavailability, and quality (Medium criticality)

- **Appearance:** Quality indicator, low impact on safety/efficacy (Low criticality)

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7. CRITICAL PROCESS PARAMETERS (CPPs)

Critical Process Parameters (CPPs) are process parameters whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality.

7.1 IDENTIFIED CPPs

CPP ID	Process Step	Parameter	Target/Range	Linked CQA	Monitoring Method
CPP-1	Reaction	Temperature	80 ± 2°C	Assay, Impurities	Temperature probe (continuous)
CPP-2	Reaction	Time	4.0 ± 0.5 hours	Assay, Impurities	Timer
CPP-3	Reaction	pH	7.0 ± 0.5	Assay, Impurities	pH probe (continuous)
CPP-4	Workup	pH	6.5 - 7.5	Impurities	pH meter
CPP-5	Crystallization	Temperature	10 ± 5°C	Particle Size, Purity	Temperature probe
CPP-6	Crystallization	Hold Time	2 ± 0.5 hours	Particle Size, Purity	Timer
CPP-7	Drying	Temperature	60 ± 5°C	Water Content, Residual Solvents	Temperature probe
CPP-8	Drying	Vacuum Level	<50 mbar	Water Content, Residual Solvents	Vacuum gauge
CPP-9	Milling	Particle Size (D50)	20-80 µm	Particle Size, Dissolution	Laser Diffraction

Risk Assessment (ICH Q9):

All CPPs identified through FMEA (Failure Mode and Effects Analysis) during process development. Each CPP has potential HIGH impact on product quality if out of specification.

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8. IN-PROCESS CONTROLS (IPCs)

In-Process Controls (IPCs) are checks performed during production to monitor and, if necessary, adjust the process to ensure the final product meets specifications.

8.1 IDENTIFIED IPCs

IPC ID	Process Step	Test	Acceptance Criteria	Frequency	Action if OOS
IPC-1	Reaction	Purity by HPLC	≥95%	End of reaction (each batch)	Extend reaction time, investigate
IPC-2	Workup	pH	6.5 - 7.5	After neutralization	Adjust with acid/base
IPC-3	Crystallization	Purity by HPLC	≥98%	After crystallization	Recrystallize if <98%
IPC-4	Drying	Loss on Drying (LOD)	≤0.50%	After drying	Continue drying if >0.50%
IPC-5	Milling	Particle Size (D50)	20-80 µm	After milling	Re-mill if out of range

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9. EQUIPMENT AND UTILITIES

9.1 EQUIPMENT USED

All equipment must be qualified (IQ/OQ/PQ completed) before use in validation batches.

Equipment ID	Description	Qualification Status	Protocol Reference
R-101	Reactor (500 L)	Qualified	IQ/OQ/PQ-REACTOR-001
R-102	Workup Reactor (300 L)	Qualified	IQ/OQ/PQ-REACTOR-002
C-101	Crystallizer	Qualified	IQ/OQ-CRYST-001
F-101	Nutsche Filter	Qualified	IQ/OQ-FILTER-001
VD-101	Vacuum Dryer	Qualified	IQ/OQ/PQ-DRYER-001
M-101	Mill	Qualified	IQ/OQ-MILL-001

9.2 UTILITIES

Utility	Specification	Qualification Status

Purified Water	Ph. Eur., Conductivity ≤1.3 µS/cm	Qualified (IQ/OQ/PQ-WATER-001)
HVAC	Production area ISO 8, Pressure +15 Pa	Qualified (IQ/OQ/PQ-HVAC-001)
Compressed Air	Oil-free, dry	Qualified (IQ/OQ-CA-001)
Nitrogen	Inert gas for drying	Qualified

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10. SAMPLING PLAN

10.1 RAW MATERIAL SAMPLING

All raw materials must be released by QA before use.

- Identity testing: 100% of containers

- Full testing per specification: Per approved sampling plan (e.g., skip-lot testing if justified)

10.2 IN-PROCESS SAMPLING

Sample ID	Process Step	Sample Point	Test	Frequency
IPS-1	Reaction	End of reaction	HPLC purity	Each batch
IPS-2	Workup	After neutralization	pH	Each batch
IPS-3	Crystallization	After crystallization	HPLC purity	Each batch
IPS-4	Drying	After drying	LOD	Each batch
IPS-5	Milling	After milling	Particle size	Each batch

Sample Size: Minimum 10 g per sample (or as required by analytical method)

Sample Handling:

- Label immediately with batch number, sample ID, date, sampler initials

- Store under appropriate conditions (room temperature, protected from light)

- Submit to QC within 2 hours of sampling

10.3 FINAL PRODUCT SAMPLING

Sampling per approved SOP:

- Sample from multiple drums (minimum 3 drums or 10% of drums, whichever is greater)

- Composite sample for homogeneity

- Minimum sample size: 100 g

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11. ANALYTICAL TESTING PLAN

11.1 IN-PROCESS TESTING

Test	Method	Specification	Validated?
HPLC Purity (IPC-1, IPC-3)	HPLC-IPC-001	IPC-1: ≥95% IPC-3: ≥98%	Yes (AMV-HPLC-001)
pH (IPC-2)	pH Meter	6.5 - 7.5	Yes (SOP-pH-001)
Loss on Drying (IPC-4)	Ph. Eur. 2.2.32	≤0.50%	Yes
Particle Size (IPC-5)	Laser Diffraction	D50: 20-80 µm	Yes (AMV-PSD-001)

11.2 FINAL PRODUCT TESTING

Full specification testing per API Specification (SPEC-FAM-001):

Test	Method	Acceptance Criteria	Validated?
Appearance	Visual	White to off-white crystalline powder	N/A
Identity (IR)	IR Spectroscopy	Conforms to reference	Yes
Identity (HPLC RT)	HPLC	Matches reference ±2%	Yes (AMV-HPLC-001)

Assay	HPLC	99.0 - 101.0%	Yes (AMV-HPLC-001)
Impurities	HPLC	Any single ≤0.10% Total ≤0.50%	Yes (AMV-HPLC-001)
Water Content	Karl Fischer	≤0.50%	Yes (AMV-KF-001)
Residual Solvents	GC	Ethanol ≤5000 ppm Others per ICH Q3C	Yes (AMV-GC-001)
Particle Size	Laser Diffraction	D50: 20-80 µm	Yes (AMV-PSD-001)
Microbial Limits	Ph. Eur. 2.6.12	Total aerobic ≤1000 CFU/g Yeast/Mold ≤100 CFU/g E. coli, Salmonella: Absent	Yes

All analytical methods must be validated per ICH Q2(R1) before use.

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12. ACCEPTANCE CRITERIA

12.1 BATCH ACCEPTANCE CRITERIA

Each validation batch is acceptable if:

1. Process Compliance:

- All CPPs maintained within validated ranges (see Section 7)

- All IPCs meet acceptance criteria (see Section 8)

- No critical deviations (or deviations are investigated and justified)

2. Final Product Compliance:

- All final product tests meet specification (see Section 11.2)

3. Yield:

- Yield within expected range: **85-95%** (theoretical yield calculated from starting materials)

- Significant yield deviations (e.g., <80%) require investigation

12.2 OVERALL VALIDATION ACCEPTANCE CRITERIA

Process Validation is successful if:

1. All Three Batches Pass:

- All 3 validation batches meet individual batch acceptance criteria

2. Statistical Consistency:

- Mean, standard deviation, and range for CQAs are acceptable (see Section 15)

- No significant trends indicating process drift

3. No Critical Deviations:

- No unresolved critical deviations

- All deviations investigated with CAPA (if needed)

4. Documentation Complete:

- All batch records complete and signed

- All test results documented and approved by QC/QA

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13. VALIDATION BATCH EXECUTION

13.1 VALIDATION BATCHES

Three consecutive commercial-scale batches will be manufactured:

Batch Number	Planned Manufacturing Date	Batch Size	Status
[To be assigned]	[Month 7, 2026]	100 kg	Planned
[To be assigned]	[Month 8, 2026]	100 kg	Planned
[To be assigned]	[Month 9, 2026]	100 kg	Planned

Batch Size Justification:

- 100 kg represents the intended commercial batch size

- Equipment operated at normal capacity (R-101: 500 L, 20% fill)

13.2 PERSONNEL

All personnel involved in validation batches must be:

- Trained on Master Batch Record (MBR-FAM-001)

- Trained on GMP and validation requirements

- Competency assessed and documented

13.3 MANUFACTURING SEQUENCE

Batches will be manufactured consecutively with minimal time between batches:

- No process or equipment changes between batches

- Same raw material lots used (where possible)

- Same personnel (where possible)

13.4 BATCH RECORD EXECUTION

Each batch will be manufactured according to:

- Master Batch Record (MBR-FAM-001)

- This Process Validation Protocol (PVP-FAM-001)

All process parameters, IPCs, and deviations must be documented in the batch record.

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14. DATA RECORDING AND DOCUMENTATION

14.1 BATCH MANUFACTURING RECORD

For each validation batch, the following data will be recorded:

Raw Materials:

- Name, batch number, quantity used, supplier

Process Parameters:

- All CPPs (temperature, time, pH, vacuum, etc.)

- Recorded continuously or at defined intervals

In-Process Controls:

- All IPC results (HPLC purity, pH, LOD, particle size)

Yield:

- Theoretical yield

- Actual yield

- % Yield

Deviations:

- Description, impact assessment, corrective action

Signatures:

- Operator, Production Supervisor, QA Reviewer

14.2 DATA RECORDING TABLES

The following data tables are included in Appendix A (to be completed during execution):

- **Table A1:** Raw Material Usage (per batch)
- **Table A2:** Critical Process Parameters (CPP) – Batch 1
- **Table A3:** Critical Process Parameters (CPP) – Batch 2
- **Table A4:** Critical Process Parameters (CPP) – Batch 3
- **Table A5:** In-Process Controls (IPC) – All Batches
- **Table A6:** Final Product Test Results – All Batches
- **Table A7:** Yield Summary – All Batches

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15. STATISTICAL EVALUATION

15.1 OBJECTIVE

Statistical evaluation will be performed to demonstrate:

- Process consistency across 3 batches

- CQAs are within acceptable limits

- No adverse trends

15.2 PARAMETERS TO BE EVALUATED

For each CQA, calculate:

- **Mean (Average)**

- **Standard Deviation (SD)**

- **Relative Standard Deviation (RSD%)**

- **Range (Min - Max)**

Evaluated CQAs:

- Assay (%)

- Total Impurities (%)

- Water Content (%)

- Particle Size D50 (µm)

- Yield (%)

15.3 STATISTICAL ACCEPTANCE CRITERIA

General Criteria:

- **RSD ≤5%** for Assay, Impurities, Water Content

- **RSD ≤15%** for Particle Size (acceptable variability)

- No significant trend (e.g., increasing impurities, decreasing yield)

Example Statistical Table (to be completed in validation report):

CQA	Batch 1	Batch 2	Batch 3	Mean	SD	RSD (%)	Acceptance
Assay (%)	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	RSD ≤5%
Total Impurities (%)	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	RSD ≤5%
Water Content (%)	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	RSD ≤5%
Particle Size D50 (µm)	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	RSD ≤15%
Yield (%)	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	[TBD]	Range 85-95%

TBD = To Be Determined (filled in after batch execution)

15.4 TREND ANALYSIS

Visual inspection of data:

- Plot Assay, Impurities, Yield across 3 batches

- Check for increasing or decreasing trends

- Trends may indicate process drift (requires investigation)

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16. DEVIATIONS

16.1 DEVIATION MANAGEMENT

Any deviation from this protocol or the Master Batch Record must be:

- Documented immediately in the batch record

- Reported to QA within 24 hours

- Investigated for root cause

- Impact on product quality assessed

16.2 DEVIATION CLASSIFICATION

Critical Deviation:

- Direct impact on product quality or patient safety

- Examples: CPP out of range, equipment failure, OOS result

- Requires immediate action and CAPA

Major Deviation:

- Potential impact on quality, but batch may still be acceptable

- Requires investigation and justification

Minor Deviation:

- No impact on quality (e.g., documentation error, late sampling)

- Documented, but limited investigation

16.3 IMPACT ON VALIDATION

Critical Deviations:

- Batch may be rejected

- Validation may need to be repeated (if multiple batches affected)

Major Deviations:

- Acceptable if investigation shows no impact on quality

- May require additional testing

Minor Deviations:

- Generally do not impact validation outcome

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17. CONCLUSION AND APPROVAL

17.1 COMPLETION OF VALIDATION

After all 3 validation batches are manufactured and tested:

1. Validation Manager compiles all data
2. Statistical evaluation performed (Section 15)
3. All deviations reviewed and resolved
4. Process Validation Report (PVR-FAM-001) prepared

17.2 VALIDATION REPORT

The Process Validation Report will include:

- Summary of results (all batches)
- Statistical analysis
- Deviations and investigations
- Conclusion: **Process is validated** or **Additional batches required**
- Recommendations (if any)

17.3 APPROVAL

The validation is successful when:

- All acceptance criteria met (Sections 12.1 and 12.2)

- Process Validation Report approved by:

  - Validation Manager

  - QA Manager

  - Production Manager

  - Management Representative

After approval:

- Routine commercial production may begin

- Process must be maintained in validated state (per Change Control SOP)

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18. APPENDICES

APPENDIX A: DATA RECORDING TABLES

(To be completed during validation batch execution)

TABLE A1: RAW MATERIAL USAGE

Raw Material	Specification	Batch 1 Lot No. / Qty	Batch 2 Lot No. / Qty	Batch 3 Lot No. / Qty
Starting Material A	[Spec]			
Starting Material	[Spec]			

B				
Solvent (Ethanol)	[Spec]			
[Other materials]				

TABLE A2: CRITICAL PROCESS PARAMETERS – BATCH 1

CPP ID	Parameter	Target/Range	Actual Value	Within Spec? (Y/N)	Comments
CPP-1	Reaction Temp (°C)	80 ± 2			
CPP-2	Reaction Time (h)	4.0 ± 0.5			
CPP-3	Reaction pH	7.0 ± 0.5			
CPP-4	Workup pH	6.5 - 7.5			
CPP-5	Crystallization Temp (°C)	10 ± 5			
CPP-6	Crystallization Time (h)	2 ± 0.5			
CPP-7	Drying Temp (°C)	60 ± 5			
CPP-8	Vacuum (mbar)	<50			
CPP-9	Particle Size D50 (µm)	20-80			

(Repeat Table A2 structure for Batch 2 and Batch 3)

TABLE A5: IN-PROCESS CONTROLS – ALL BATCHES

IPC ID	Test	Acceptance Criteria	Batch 1	Batch 2	Batch 3	Pass/Fail
IPC-1	HPLC Purity (Reaction)	≥95%				
IPC-2	pH (Workup)	6.5-7.5				
IPC-3	HPLC Purity	≥98%				

	(Crystallization)					
IPC-4	LOD (Drying)	≤0.50%				
IPC-5	Particle Size D50 (Milling)	20-80 µm				

TABLE A6: FINAL PRODUCT TEST RESULTS – ALL BATCHES

Test	Specification	Batch 1	Batch 2	Batch 3	Pass/Fail
Appearance	White to off-white powder				
Identity (IR)	Conforms				
Identity (HPLC RT)	Matches reference				
Assay (%)	99.0-101.0				
Total Impurities (%)	≤0.50				
Largest Impurity (%)	≤0.10				
Water Content (%)	≤0.50				
Residual Ethanol (ppm)	≤5000				
Particle Size D50 (µm)	20-80				
Microbial Count (CFU/g)	≤1000				
Yeast/Mold (CFU/g)	≤100				
E. coli	Absent				
Salmonella	Absent				

TABLE A7: YIELD SUMMARY

Batch	Theoretical Yield (kg)	Actual Yield (kg)	% Yield	Within Range (85-95%)?	Comments
Batch 1	[TBD]				
Batch 2	[TBD]				

Batch 3	[TBD]				
Average					

APPENDIX B: ABBREVIATIONS

- API: Active Pharmaceutical Ingredient

- CAPA: Corrective and Preventive Action

- CFU: Colony Forming Units

- CPP: Critical Process Parameter

- CQA: Critical Quality Attribute

- DAC: Deutscher Arzneimittel-Codex

- FMEA: Failure Mode and Effects Analysis

- GC: Gas Chromatography

- GMP: Good Manufacturing Practice

- HPLC: High-Performance Liquid Chromatography

- ICH: International Council for Harmonisation

- IPC: In-Process Control

- IQ: Installation Qualification

- IR: Infrared Spectroscopy

- LOD: Loss on Drying

- OOS: Out-of-Specification

- OQ: Operational Qualification

- Ph. Eur.: European Pharmacopoeia

- PMDA: Pharmaceuticals and Medical Devices Agency (Japan)

- PQ: Performance Qualification

- PVP: Process Validation Protocol

- PVR: Process Validation Report

- QA: Quality Assurance

- QC: Quality Control

- RSD: Relative Standard Deviation

- RT: Retention Time

- SD: Standard Deviation

- SOP: Standard Operating Procedure

- URS: User Requirement Specification

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19. REFERENCES

Regulatory Guidelines:

- 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

- ICH Q3C: Impurities: Guideline for Residual Solvents

- EU GMP Annex 15: Qualification and Validation

- Ph. Eur. (European Pharmacopoeia)

Internal Documents:

- QM-001: Quality Manual

- MVP-001: Master Validation Plan

- MBR-FAM-001: Master Batch Record – Fampridin

- SPEC-FAM-001: Specification – Fampridin API

- AMV-HPLC-001: Analytical Method Validation – HPLC (Assay, Impurities)

- AMV-GC-001: Analytical Method Validation – GC (Residual Solvents)

- AMV-KF-001: Analytical Method Validation – Karl Fischer (Water Content)

- IQ/OQ/PQ Protocols for all equipment (Reactors, Dryer, Mill, etc.)

REVISION HISTORY

Version	Date	Author	Description of Changes	Approved By
1.0	04.12.2025	Validation Department	Initial Protocol	[Pending Approval]

APPROVAL SIGNATURES

Prepared by:

[Name, Title: Validation Manager]

Signature: _____

Date: _____

Reviewed by:

[Name, Title: QA Manager]

Signature: _____

Date: _____

Reviewed by:

[Name, Title: Production Manager]

Signature: _____

Date: _____

Reviewed by:

[Name, Title: QC Manager]

Signature: _____

Date: _____

Approved by:

[Name, Title: Management Representative]

Signature: _____

Date: _____

END OF PROCESS VALIDATION PROTOCOL

Protocol Status: Draft – Pending Approval

Effective Date: Upon approval and signature

Supersedes: N/A (New document)