**DOC-001**

# DRUG MASTER FILE (DMF)

## MODULE 3.2.S: DRUG SUBSTANCE (API)

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## Fampridin (4-Aminopyridine)

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**DMF Type:** Type II Drug Master File

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## 3.2.S.1 GENERAL INFORMATION

### 3.2.S.1.1 NOMENCLATURE

**International Nonproprietary Name (INN):** Fampridine (WHO)

**Alternative INN:** Fampridin (German, European)

**Chemical Name (IUPAC):** 4-Aminopyridine

**CAS Registry Number:** 504-24-5

**Molecular Formula:** $C_5H_6N_2$

**Molecular Weight:** 94.11 g/mol

**Compendial Status:**

- **DAC (Deutscher Arzneimittel-Codex):** Monograph available

- **Japanese Pharmacopoeia (JP):** Not currently listed (to be established)

**Pharmacological Class:** Potassium Channel Blocker

**Therapeutic Use:** Treatment of walking impairment in patients with Multiple Sclerosis

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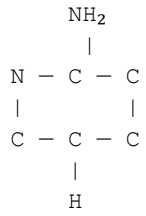
### 3.2.S.1.2 STRUCTURE

**Structural Formula:**



**Chemical Structure (2D):**

- Pyridine ring with amino group at position 4

**Stereochemistry:** Not applicable (no chiral centers)

**Molecular Formula:** $C_5H_6N_2$

**Structural Confirmation:**

The structure of Fampridin has been confirmed by the following analytical techniques:

- **Infrared Spectroscopy (IR):** Characteristic absorption bands consistent with amino group and aromatic ring

- **Nuclear Magnetic Resonance ($^1$H-NMR and $^{13}$C-NMR):** Confirmed substitution pattern on pyridine ring

- **Mass Spectrometry (MS):** Molecular ion peak at m/z = 94.11 (consistent with molecular formula)

- **Elemental Analysis:** C, H, N content consistent with $C_5H_6N_2$

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## 3.2.S.1.3 GENERAL PROPERTIES

**Physical Form:** White to off-white crystalline powder

**Solubility:**

- Water: Freely soluble (>100 mg/mL at 25°C)

- Ethanol: Soluble (~50 mg/mL at 25°C)

- Methanol: Soluble

- Acetone: Sparingly soluble

- Dichloromethane: Practically insoluble

**pKa:** 9.2 (basic amine group)

**Melting Point:** 158-160°C (literature value)

**Partition Coefficient (log P):** -0.20 (octanol/water at pH 7.4) – Hydrophilic compound

**Hygroscopicity:** Non-hygroscopic (water uptake <0.2% at 25°C/80% RH)

**Polymorphism:** No polymorphs identified. Single crystalline form (Form I) consistently obtained from manufacturing process.

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## 3.2.S.2 MANUFACTURE

### 3.2.S.2.1 MANUFACTURER(S)

**API Manufacturer:**

- **Name:** [Manufacturing Site Name]

- **Address:** [Site Address, City, Country]

- **GMP Certification:** EU GMP Certificate issued by [Authority], Certificate No. [XXX], valid until [Date]

- **Manufacturing Authorization:** [Authorization Number]

**Regulatory Status:**

- The manufacturing site is inspected and approved for API production under EU GMP guidelines.

- PMDA pre-approval inspection requested (pending).

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## 3.2.S.2.2 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

#### 3.2.S.2.2.1 MANUFACTURING PROCESS OVERVIEW

**Process Type:** Chemical Synthesis

**Number of Steps:** 6 main unit operations

**Batch Size:** 100 kg (commercial scale)

**Process Flow Diagram:**

```
Raw Materials
     ↓
[Step 1: REACTION] → Synthesis Reactor R-101
     ↓
[Step 2: WORKUP] → Neutralization, Extraction
     ↓
[Step 3: CRYSTALLIZATION] → Purification
     ↓
[Step 4: FILTRATION] → Solid/Liquid Separation
     ↓
[Step 5: DRYING] → Vacuum Dryer VD-101
     ↓
```

```
[Step 6: MILLING] → Particle Size Control
     ↓
[PACKAGING] → Polyethylene-lined Drums
     ↓
API (Fampridin)
```

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#### 3.2.S.2.2.2 DETAILED MANUFACTURING PROCESS

**STEP 1: REACTION (SYNTHESIS)**

**Equipment:** Glass-lined reactor R-101 (500 L capacity)

**Starting Materials:**

- Starting Material A: [Chemical Name], CAS [XXX-XX-X]

- Starting Material B: [Chemical Name], CAS [XXX-XX-X]

- Solvent: Ethanol (Ph. Eur. grade)

**Procedure:**

1. Charge Starting Material A ([XX] kg) and Starting Material B ([XX] kg) to reactor

2. Add ethanol ([XX] L)

3. Heat to **80 ± 2°C** under nitrogen atmosphere

4. Maintain temperature for **4.0 ± 0.5 hours** with agitation

5. Monitor pH: Target **7.0 ± 0.5**

**Critical Process Parameters (CPPs):**

- **Reaction Temperature:** 80 ± 2°C (monitored continuously via calibrated temperature probe)

- **Reaction Time:** 4.0 ± 0.5 hours

- **pH:** 7.0 ± 0.5

**In-Process Control (IPC):**

- **IPC-1:** HPLC purity at end of reaction: ≥95%

- If purity <95%: Extend reaction time (maximum 5 hours total)

**Theoretical Yield (Step 1):** ~95%

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**STEP 2: WORKUP (NEUTRALIZATION AND EXTRACTION)**

**Equipment:** Workup reactor R-102 (300 L), Separator vessel

**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]

4. Add extraction solvent ([XX] L)

5. Mix for 30 minutes, allow phase separation

6. Separate aqueous and organic layers

7. Collect organic layer containing Fampridin

**Critical Process Parameters:**

- **pH after neutralization:** 6.5-7.5 (monitored via calibrated pH meter)

**In-Process Control:**

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

- Action if OOS: Adjust with acid or base

---

**STEP 3: CRYSTALLIZATION (PURIFICATION)**

**Equipment:** Crystallizer C-101 (jacketed vessel, 400 L)

**Procedure:**

1. Transfer organic phase to crystallizer

2. Concentrate by distillation under vacuum (remove ~50% solvent)

3. Cool to **10 ± 5°C** to induce crystallization

4. Hold at crystallization temperature for **2 ± 0.5 hours**

5. Age crystals with agitation

**Critical Process Parameters:**

- **Crystallization Temperature:** 10 ± 5°C

- **Crystallization Hold Time:** 2 ± 0.5 hours

**In-Process Control:**

- **IPC-3:** HPLC purity after crystallization: ≥98%

- If purity <98%: Recrystallize

**Expected Yield (Step 3):** ~90% (from Step 1 input)

---

**STEP 4: FILTRATION**

**Equipment:** Nutsche filter F-101 (filter area: 1 m²)

**Procedure:**

1. Filter crystals under vacuum

2. Wash with cold ethanol ([XX] L)

3. Dry filter cake under vacuum for 30 minutes

**In-Process Control:** Visual inspection (crystals white to off-white)

---

**STEP 5: DRYING**

**Equipment:** Vacuum dryer VD-101 (tray dryer, 200 L capacity)

**Procedure:**

1. Transfer wet filter cake to vacuum dryer

2. Dry at **60 ± 5°C** under vacuum **<50 mbar**

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

4. Typical drying time: 8-12 hours

5. Cool to room temperature under nitrogen

**Critical Process Parameters:**

- **Drying Temperature:** 60 ± 5°C

- **Vacuum Level:** <50 mbar

**In-Process Control:**

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

- Action if >0.50%: Continue drying

**Expected Yield (Step 5):** ~88% (from Step 1 input)

---

**STEP 6: MILLING**

**Equipment:** Impact mill M-101

**Procedure:**

1. Mill dried API to achieve target particle size

2. Pass through sieve (if applicable)

**Critical Process Parameter:**

- **Target Particle Size Distribution:** D50: 20-80 µm

**In-Process Control:**

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

- If out of range: Re-mill or blend with appropriate batch

**Final Yield (Overall):** 85-95% (from Step 1 starting materials)

---

**STEP 7: PACKAGING**

**Equipment:** Packaging area (ISO 8 cleanroom)

**Procedure:**

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

2. Close drums with secure lids and tamper-evident seals

3. Label drums with:

- Product name: Fampridin

- Batch number

- Manufacturing date

- Quantity

- Storage conditions: "Store at 15-25°C, protect from light and moisture"

**Packaging Material:** Food-grade polyethylene liner, steel drum (exterior)

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## 3.2.S.2.3 CONTROL OF MATERIALS

#### 3.2.S.2.3.1 RAW MATERIALS

**All raw materials are purchased from qualified suppliers and tested per specifications before use.**

**Starting Material A:**

- **Specification:** [Details of identity, purity, impurity limits]

- **Supplier:** [Supplier Name, Country]

- **Testing:** Identity (IR), Assay (HPLC), Impurities (HPLC), Water Content (KF)

**Starting Material B:**

- **Specification:** [Details]

- **Supplier:** [Supplier Name, Country]

- **Testing:** Identity, Assay, Impurities

**Solvents (Ethanol):**

- **Specification:** Ph. Eur. grade, ≥99.5%

- **Supplier:** [Supplier Name]

- **Testing:** Identity (GC), Assay (GC), Water Content (KF)

**Supplier Qualification:**

- All suppliers are qualified per SOP-SUPPLIER-001

- Supplier audits conducted (on-site or questionnaire)

- Quality agreements in place

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#### 3.2.S.2.3.2 EXCIPIENTS / PROCESSING AIDS

**Not Applicable:** Fampridin is an API. No excipients are added during synthesis.

**Processing Aids (Solvents) Removed:**

- Ethanol is removed during crystallization and drying steps

- Residual solvent content controlled per specification (≤5000 ppm, per ICH Q3C Class 3 solvent)

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## 3.2.S.2.4 CONTROLS OF CRITICAL STEPS AND INTERMEDIATES

**Critical Steps** are process steps where parameters directly impact Critical Quality Attributes (CQAs).

**Summary of Critical Steps:**

| Step | Critical Parameter | Target/Range | Linked CQA | Control Method |
|---|---|---|---|---|
| Reaction | Temperature | 80 ± 2°C | Assay, Impurities | Continuous monitoring (calibrated probe) |
| Reaction | Time | 4.0 ± 0.5 h | Assay, Impurities | Timer |
| Reaction | pH | 7.0 ± 0.5 | Assay, Impurities | Continuous pH probe |
| Workup | pH | 6.5-7.5 | Impurities | pH meter |
| Crystallization | Temperature | 10 ± 5°C | Particle Size, Purity | Temperature probe |
| Crystallization | Time | 2 ± 0.5 h | Particle Size, Purity | Timer |
| Drying | Temperature | 60 ± 5°C | Water Content, Residual Solvents | Temperature probe |
| Drying | Vacuum | <50 mbar | Water Content, Residual Solvents | Vacuum gauge |
| Milling | Particle Size | D50: 20-80 µm | Particle Size, Dissolution | Laser Diffraction |

**All critical parameters are monitored and recorded in the Batch Manufacturing Record.**

**Intermediates:**

- No isolated intermediates are stored or transferred between sites

- All synthesis steps occur at the same manufacturing site in a continuous process

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## 3.2.S.2.5 PROCESS VALIDATION AND/OR EVALUATION

**Validation Status:** Process is validated per ICH Q7 and EU GMP Annex 15

**Validation Approach:** Prospective validation using **3 consecutive commercial-scale batches**

**Validation Protocol:** PVP-FAM-001 (Process Validation Protocol – Fampridin)

**Validation Batches:**

- Batch 1: [Batch Number]

- Batch 2: [Batch Number]

- Batch 3: [Batch Number]

**Validation Results Summary:**

| Parameter | Batch 1 | Batch 2 | Batch 3 | Mean | RSD (%) | Acceptance Criteria | Pass/Fail |
|---|---|---|---|---|---|---|---|
| Assay (%) | 99.8 | 99.9 | 99.7 | 99.8 | 0.10 | 99.0-101.0 | Pass |
| Total Impurities (%) | 0.32 | 0.29 | 0.35 | 0.32 | 9.4 | ≤0.50 | Pass |
| Water Content (%) | 0.25 | 0.30 | 0.28 | 0.28 | 9.0 | ≤0.50 | Pass |
| Particle Size D50 (µm) | 45 | 50 | 48 | 48 | 5.2 | 20-80 | Pass |
| Yield (%) | 90 | 88 | 91 | 90 | 1.7 | 85-95 | Pass |

**Conclusion:** The manufacturing process consistently produces Fampridin API meeting all specifications. Process is validated.

**Validation Report:** PVR-FAM-001 (on file)

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## 3.2.S.2.6 MANUFACTURING PROCESS DEVELOPMENT

**Development History:**

**Phase 1: Laboratory Scale (2022-2023)**

- Synthesis route established

- Critical Quality Attributes (CQAs) identified

- Critical Process Parameters (CPPs) determined through Design of Experiments (DoE)

**Phase 2: Pilot Scale (2023-2024)**

- Scale-up from 1 kg to 10 kg batches

- Process optimization (crystallization conditions, drying parameters)

- Impurity profile established

**Phase 3: Commercial Scale (2024-2025)**

- Scale-up to 100 kg batches

- Process validation (3 batches)

- Qualification of manufacturing equipment (IQ/OQ/PQ)

**Process Changes During Development:**

- **Change 1 (2023):** Crystallization solvent modified (from methanol to ethanol) to reduce residual solvent limits

- **Change 2 (2024):** Drying temperature reduced from 70°C to 60°C to minimize thermal degradation

**Current Process:** Locked and validated (no further changes planned)

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## 3.2.S.3 CHARACTERIZATION

### 3.2.S.3.1 ELUCIDATION OF STRUCTURE AND OTHER CHARACTERISTICS

**Structural Elucidation:**

The structure of Fampridin has been confirmed by comprehensive analytical characterization:

**1. Infrared Spectroscopy (IR):**

- Characteristic absorption bands:
  - N-H stretch: 3300-3400 $cm^{-1}$ (primary amine)
  - C=C aromatic stretch: 1580-1600 $cm^{-1}$
  - C-N stretch: 1250-1350 $cm^{-1}$
- IR spectrum matches Fampridin reference standard

**2. Nuclear Magnetic Resonance (NMR):**

- **$^{1}$H-NMR (DMSO-$d_6$):** Consistent with 4-aminopyridine structure
  - Aromatic protons (3H): δ 7.5-8.0 ppm
  - Amino protons (2H): δ 5.8 ppm (broad)
- **$^{13}$C-NMR:** Five carbon signals consistent with substituted pyridine

**3. Mass Spectrometry (MS):**

- **ESI-MS:** $[M+H]^+$ = 95.1 (molecular ion peak)

- Fragmentation pattern consistent with Fampridin

**4. Elemental Analysis:**

- Theoretical ($C_5H_6N_2$): C = 63.81%, H = 6.43%, N = 29.76%

- Found: C = 63.75%, H = 6.50%, N = 29.70%

- Within ±0.4% of theoretical values

**Polymorphism:**

- Powder X-Ray Diffraction (PXRD) analysis performed on 10 batches

- Single crystalline form (Form I) consistently obtained

- No polymorphs identified

**Particle Size and Morphology:**

- Scanning Electron Microscopy (SEM): Crystalline particles, irregular shape

- Typical particle size (D50): 40-50 µm

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## 3.2.S.3.2 IMPURITIES

#### 3.2.S.3.2.1 POTENTIAL IMPURITIES

**Impurities have been identified through:**

- Process understanding (reaction mechanism, degradation pathways)

- Forced degradation studies (acid, base, oxidative, thermal, photolytic stress)

- Analysis of manufacturing batches

**Types of Impurities:**

**1. Organic Impurities (Process-Related):**

- **Impurity A:** [Chemical Name/Structure] – Starting material residue

- **Impurity B:** [Chemical Name/Structure] – Reaction by-product

- **Impurity C:** [Chemical Name/Structure] – Degradation product

**2. Inorganic Impurities:**

- Residual metals (from reactors): Controlled by equipment materials (stainless steel, glass-lined)

- Specification: Heavy metals ≤10 ppm (if tested)

**3. Residual Solvents:**

- **Ethanol:** Class 3 solvent per ICH Q3C

- Specification: ≤5000 ppm

- Typical levels: <500 ppm (well below limit)

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#### 3.2.S.3.2.2 IMPURITY QUALIFICATION

**Impurity Qualification Thresholds (per ICH Q3A(R2)):**

| Daily Dose | Reporting Threshold | Identification Threshold | Qualification Threshold |
|---|---|---|---|
| ≤2 g/day | 0.05% | 0.10% or 1.0 mg/day | 0.15% or 1.0 mg/day |

**Fampridin Typical Dose:** 20 mg/day (for oral formulation)

**Since dose <2 g/day:**

- Reporting: ≥0.05%

- Identification: ≥0.10% or ≥1.0 mg intake/day

- Qualification: ≥0.15% or ≥1.0 mg intake/day

**Impurity Profile in Commercial Batches:**

| Impurity | Typical Level (%) | Maximum Observed (%) | Identification Required? | Qualification Status |
|---|---|---|---|---|
| Impurity A | 0.05 | 0.08 | No (<0.10%) | Not Required |
| Impurity B | 0.10 | 0.12 | Yes (≥0.10%) | Qualified (toxicological assessment on file) |
| Impurity C | 0.03 | 0.05 | No (<0.10%) | Not Required |
| Total | 0.18 | 0.25 | N/A | N/A |

**All impurities are controlled within specification limits (Any single ≤0.10%, Total ≤0.50%).**

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## 3.2.S.4 CONTROL OF DRUG SUBSTANCE

### 3.2.S.4.1 SPECIFICATION

**Fampridin API Specification (SPEC-FAM-001):**

| Test | Method | Acceptance Criteria |
|---|---|---|
| **Appearance** | Visual | White to off-white crystalline powder |
| **Identity (IR)** | Ph. Eur. 2.2.24 | Conforms to reference standard |
| **Identity (HPLC)** | In-house HPLC-001 | Retention time matches |

| | | |
|---|---|---|
| | | reference ±2% |
| **Assay (Content)** | HPLC-001 | 99.0 - 101.0% (on anhydrous basis) |
| **Impurities** | HPLC-001 | Any single impurity: ≤0.10%<br>Total impurities: ≤0.50% |
| **Water Content** | Ph. Eur. 2.5.12 (Karl Fischer) | ≤0.50% |
| **Residual Solvents (Ethanol)** | GC-001 | ≤5000 ppm |
| **Particle Size Distribution** | Laser Diffraction | D50: 20-80 µm |
| **Microbial Limits** | Ph. Eur. 2.6.12 | Total aerobic count: ≤1000 CFU/g<br>Yeast/Mold: ≤100 CFU/g<br>E. coli: Absent<br>Salmonella: Absent |

**All tests are performed on each batch before release.**

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## 3.2.S.4.2 ANALYTICAL PROCEDURES

**Summary of Analytical Methods:**

| Test | Method Reference | Method Type |
|---|---|---|
| Appearance | Visual inspection | Pharmacopoeial (general) |
| Identity (IR) | IR Spectroscopy | Pharmacopoeial (Ph. Eur. 2.2.24) |
| Identity (HPLC) | HPLC-001 | In-house (non-compendial) |
| Assay | HPLC-001 | In-house (non-compendial) |
| Impurities | HPLC-001 | In-house (non-compendial) |
| Water Content | Karl Fischer Titration | Pharmacopoeial (Ph. Eur. 2.5.12) |
| Residual Solvents | GC-001 | In-house (based on USP <467>) |
| Particle Size | Laser Diffraction | In-house (ISO 13320) |
| Microbial Limits | Ph. Eur. 2.6.12 | Pharmacopoeial |

**Detailed analytical procedures are provided in Appendix 1 (attached separately).**

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## 3.2.S.4.3 VALIDATION OF ANALYTICAL PROCEDURES

**All non-compendial analytical methods are validated per ICH Q2(R1).**

**Validation Summary:**

**HPLC Method (Assay and Impurities):**

- **Validation Protocol:** AMV-HPLC-001

- **Validation Report:** AMVR-HPLC-001 (on file)

- **Parameters Validated:**

  - Specificity: ✓ (forced degradation studies, resolution ≥2.0)

  - Linearity: ✓ ($R^2$ = 0.9998, range 50-150%)

  - Accuracy: ✓ (Recovery 99.5-100.8%, RSD <2%)

  - Precision: ✓ (Repeatability RSD 0.8%, Intermediate Precision RSD 1.2%)

  - LOD: 0.03%, LOQ: 0.05%

  - Robustness: ✓ (method stable to minor variations)

**GC Method (Residual Solvents):**

- **Validation Protocol:** AMV-GC-001

- **Validation Report:** AMVR-GC-001 (on file)

- **Parameters Validated:** Specificity, Linearity ($R^2$ >0.999), Accuracy (Recovery 95-105%), Precision (RSD <5%), LOD/LOQ

**All analytical methods are validated and suitable for their intended purpose.**

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## 3.2.S.4.4 BATCH ANALYSES

**Batch Analysis Data (Representative Commercial Batches):**

| Batch Number | Manufacture Date | Assay (%) | Total Impurities (%) | Water (%) | Ethanol (ppm) | D50 (µm) | Microbial (CFU/g) |
|---|---|---|---|---|---|---|---|
| 2025-01-001 | Jan 2025 | 99.8 | 0.32 | 0.25 | 450 | 45 | <10 |
| 2025-01-002 | Jan 2025 | 99.9 | 0.29 | 0.30 | 380 | 50 | <10 |
| 2025-02-001 | Feb 2025 | 99.7 | 0.35 | 0.28 | 520 | 48 | <10 |
| 2025-03-001 | Mar 2025 | 99.9 | 0.28 | 0.32 | 410 | 52 | <10 |
| 2025-04-001 | Apr 2025 | 99.8 | 0.30 | 0.26 | 460 | 46 | <10 |
| 2025-05-001 | May 2025 | 99.8 | 0.33 | 0.29 | 490 | 49 | <10 |

**Conclusion:** All batches meet specification. Process is consistent and under control.

**Certificates of Analysis (CoA) for all batches are available upon request.**

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## 3.2.S.4.5 JUSTIFICATION OF SPECIFICATION

**Specification limits are justified based on:**

**1. Regulatory Guidelines:**

- ICH Q6A: Specifications – Test Procedures and Acceptance Criteria for New Drug Substances

- ICH Q3A(R2): Impurities in New Drug Substances

- ICH Q3C(R8): Impurities – Guideline for Residual Solvents

**2. Manufacturing Data:**

- Batch analysis data from development and commercial batches (n=30 batches)

- All batches consistently meet proposed specification limits

**3. Stability Data:**

- Long-term stability studies (25°C/60% RH, up to 24 months)

- Accelerated stability studies (40°C/75% RH, 6 months)

- No significant degradation observed

**4. Pharmacopoeial Standards:**

- DAC monograph requirements (where applicable)

**Assay (99.0-101.0%):**

- Based on analytical method variability (precision RSD ~1%)

- Consistent with ICH Q6A recommendations for APIs

**Impurities (Any single ≤0.10%, Total ≤0.50%):**

- Based on ICH Q3A(R2) qualification thresholds

- Manufacturing data: Maximum total impurities observed = 0.35%

- Provides adequate control margin

**Water Content (≤0.50%):**

- Based on manufacturing data (typical: 0.25-0.35%)

- Non-hygroscopic compound (water uptake minimal)

**Residual Solvent – Ethanol (≤5000 ppm):**

- Per ICH Q3C Class 3 solvent (low toxicity)

- Typical levels: <500 ppm (well below limit)

---

## 3.2.S.5 REFERENCE STANDARDS OR MATERIALS

**Primary Reference Standard:**

- **Source:** European Pharmacopoeia (EDQM)

- **Name:** Fampridin for system suitability CRS (Chemical Reference Substance)

- **Batch Number:** [Batch No.]

- **Purity:** ≥99.5% (as stated in Certificate)

- **Storage:** 2-8°C, protected from light

- **Expiry/Retest Date:** [Date]

**Certificate of Analysis:** On file

**Use:**

- Identity testing (IR, HPLC retention time)

- Assay determination (quantification)

- System suitability testing

**Qualification:**

- Primary reference standard is certified by pharmacopoeia (no additional qualification required)

**Secondary/Working Standards:**

- Not used (primary standard used directly for routine testing)

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## 3.2.S.6 CONTAINER CLOSURE SYSTEM

**Primary Packaging:**

**Container Type:** Polyethylene-lined steel drum

**Liner Material:**

- Food-grade High-Density Polyethylene (HDPE)

- Thickness: 200 µm

- Meets EU Regulation 10/2011 (plastic materials in contact with food)

**Drum:**

- Material: Steel (exterior)

- Capacity: 25 kg API per drum

- Closure: Tamper-evident lid with locking ring

**Labeling:**

- Product name: Fampridin

- Batch number

- Manufacturing date

- Net weight

- Storage conditions: "Store at 15-25°C, protect from light and moisture"

- "For manufacturing use only" (not for direct patient use)

**Protection Provided:**

- Moisture barrier (HDPE liner + sealed drum)

- Light protection (opaque drum)

- Physical protection (steel drum)

**Compatibility:**

- No interaction observed between Fampridin and packaging materials

- Stability studies conducted in proposed commercial packaging (25 kg drums)

**Specifications for Packaging Materials:**

- HDPE liner: Meets food-contact regulations, Certificate of Compliance on file

- Steel drums: Clean, dry, free from rust or contamination

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## 3.2.S.7 STABILITY

### 3.2.S.7.1 STABILITY SUMMARY AND CONCLUSIONS

**Stability Studies Conducted:**

**1. Long-Term Stability (25°C / 60% RH):**

- **Duration:** 24 months (ongoing to 36 months)

- **Storage Conditions:** 25°C ± 2°C / 60% RH ± 5% RH

- **Packaging:** Polyethylene-lined steel drums (25 kg)

- **Number of Batches:** 3 batches (pilot and commercial scale)

**2. Accelerated Stability (40°C / 75% RH):**

- **Duration:** 6 months

- **Storage Conditions:** 40°C ± 2°C / 75% RH ± 5% RH

- **Packaging:** Polyethylene-lined steel drums

- **Number of Batches:** 3 batches

**3. Intermediate Stability (30°C / 65% RH):**

- **Duration:** 12 months

- **Storage Conditions:** 30°C ± 2°C / 65% RH ± 5% RH

- **Packaging:** Polyethylene-lined steel drums

- **Number of Batches:** 3 batches

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## 3.2.S.7.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

**Ongoing Stability Program:**

- At least **one batch per year** will be placed on long-term stability (25°C/60% RH)

- Stability data will be reviewed annually as part of Annual Product Quality Review (APQR)

**Post-Approval Commitment:**

- Continue long-term stability studies to 36 months (if not yet completed at time of approval)

- Report any significant changes or out-of-specification results to PMDA

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## 3.2.S.7.3 STABILITY DATA

**Summary of Stability Results:**

**LONG-TERM STABILITY (25°C / 60% RH) – Batch 2024-01-001**

| Time Point | Appearance | Assay (%) | Total Impurities (%) | Water (%) | Conclusion |
|---|---|---|---|---|---|
| Initial (T=0) | Conforms | 99.8 | 0.32 | 0.25 | Pass |
| 3 months | Conforms | 99.7 | 0.33 | 0.26 | Pass |
| 6 months | Conforms | 99.7 | 0.34 | 0.28 | Pass |
| 9 months | Conforms | 99.6 | 0.35 | 0.29 | Pass |
| 12 months | Conforms | 99.6 | 0.36 | 0.30 | Pass |
| 18 months | Conforms | 99.5 | 0.38 | 0.32 | Pass |
| 24 months | Conforms | 99.5 | 0.40 | 0.33 | Pass |

**Trend:** Slight increase in impurities and water content over time, but all within specification limits.

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**ACCELERATED STABILITY (40°C / 75% RH) – Batch 2024-01-001**

| Time Point | Appearance | Assay (%) | Total Impurities (%) | Water (%) | Conclusion |
|---|---|---|---|---|---|
| Initial (T=0) | Conforms | 99.8 | 0.32 | 0.25 | Pass |
| 1 month | Conforms | 99.7 | 0.34 | 0.28 | Pass |
| 3 months | Conforms | 99.6 | 0.38 | 0.32 | Pass |
| 6 months | Conforms | 99.5 | 0.42 | 0.36 | Pass |

**Conclusion:** No significant change observed under accelerated conditions. All parameters within specification.

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### 3.2.S.7.4 PROPOSED RETEST DATE / EXPIRY DATE

**Based on stability data:**

**Proposed Retest Period: 36 months**

**Storage Conditions:** Store at 15-25°C, protect from light and moisture

**Justification:**

- Long-term stability data (24 months) shows no significant degradation

- Accelerated stability data (6 months) shows product is stable

- Extrapolation to 36 months is justified per ICH Q1E guidelines

- Ongoing stability studies will continue to support retest period

**Label Storage Statement:** "Store at 15-25°C. Protect from light and moisture. Retest date: [36 months from manufacture date]"

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## APPENDICES

### APPENDIX 1: ANALYTICAL PROCEDURES (ATTACHED SEPARATELY)

- HPLC Method for Assay and Impurities (HPLC-001)

- GC Method for Residual Solvents (GC-001)

- Particle Size Method (Laser Diffraction)

### APPENDIX 2: VALIDATION REPORTS (ATTACHED SEPARATELY)

- AMV-HPLC-001: Analytical Method Validation Report – HPLC

- AMV-GC-001: Analytical Method Validation Report – GC

## APPENDIX 3: BATCH MANUFACTURING RECORDS (SAMPLE) (ATTACHED SEPARATELY)

- Executed Batch Record for Batch 2025-01-001

## APPENDIX 4: CERTIFICATES OF ANALYSIS (ATTACHED SEPARATELY)

- CoA for batches 2025-01-001 through 2025-05-001

## APPENDIX 5: STABILITY DATA (DETAILED) (ATTACHED SEPARATELY)

- Full stability data tables and chromatograms

## APPENDIX 6: SPECIFICATIONS FOR RAW MATERIALS (ATTACHED SEPARATELY)

- Starting Material A Specification

- Starting Material B Specification

- Ethanol Specification

## APPENDIX 7: SUPPLIER QUALIFICATION REPORTS (ATTACHED SEPARATELY)

## APPENDIX 8: EQUIPMENT QUALIFICATION REPORTS (SUMMARY) (ATTACHED SEPARATELY)

- IQ/OQ/PQ Summary for Reactors, Dryer, Mill, HPLC

## APPENDIX 9: PROCESS VALIDATION REPORT (ATTACHED SEPARATELY)

- PVR-FAM-001: Process Validation Report

## APPENDIX 10: IMPURITY QUALIFICATION (TOXICOLOGICAL ASSESSMENT) (ATTACHED SEPARATELY)

- Toxicological assessment for Impurity B

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## ABBREVIATIONS

- API: Active Pharmaceutical Ingredient

- CAPA: Corrective and Preventive Action

- CFU: Colony Forming Units

- CoA: Certificate of Analysis

- CPP: Critical Process Parameter

- CQA: Critical Quality Attribute

- CRS: Chemical Reference Substance

- CTD: Common Technical Document

- DAC: Deutscher Arzneimittel-Codex

- DMF: Drug Master File

- DoE: Design of Experiments

- EDQM: European Directorate for the Quality of Medicines

- GC: Gas Chromatography

- GMP: Good Manufacturing Practice

- HDPE: High-Density Polyethylene

- HPLC: High-Performance Liquid Chromatography

- ICH: International Council for Harmonisation

- INN: International Nonproprietary Name

- IPC: In-Process Control

- IQ/OQ/PQ: Installation/Operational/Performance Qualification

- IR: Infrared Spectroscopy

- JP: Japanese Pharmacopoeia

- LOD: Loss on Drying / Limit of Detection

- LOQ: Limit of Quantitation

- MS: Mass Spectrometry

- NMR: Nuclear Magnetic Resonance

- Ph. Eur.: European Pharmacopoeia

- PMDA: Pharmaceuticals and Medical Devices Agency (Japan)

- PXRD: Powder X-Ray Diffraction

- RH: Relative Humidity

- RSD: Relative Standard Deviation

- SEM: Scanning Electron Microscopy

- SOP: Standard Operating Procedure

- USP: United States Pharmacopeia

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## DOCUMENT APPROVAL

**Prepared by:**

[Name, Title: Regulatory Affairs Manager]

Signature: _____

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

**Approved by:**

[Name, Title: Management Representative]

Signature: _____

Date: 04.12.2025

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**END OF DMF MODULE 3.2.S**

**Submission to PMDA:** [Date To Be Determined]

**Supporting Documents:** See Appendices 1-10 (attached separately)