Penicillamine Capsules

**Type of Posting**
Notice of Intent to Revise

**Posting Date**
30-Jul-2021

**Targeted Official Date**
To Be Determined, Revision Bulletin

**Expert Committee**
Small Molecules 1

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 1 Expert Committee intends to revise the Penicillamine Capsules monograph.

The purpose of this revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

- *Dissolution Test 2* was validated using the Atlantis dC18 brand of column with L1 packing (4.6-mm × 15-cm; 5 µm). The typical retention time for penicillamine is about 4.1 min.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Robyn Fales, Scientist IV (240-221-2047 or rnp@usp.org).

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¹ This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product’s final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
Penicillamine Capsules

DEFINITION
Penicillamine Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of penicillamine \((\text{C}_5\text{H}_{11}\text{NO}_2\text{S})\).

IDENTIFICATION

A. Thin-Layer Chromatography

**Standard solution:** 100 mg of USP Penicillamine RS in 10 mL of methanol. Add 2 drops of 3 N hydrochloric acid and mix.

**Sample solution:** Transfer a portion of Capsule contents, containing nominally about 100 mg of penicillamine, to a 10-mL volumetric flask, and dilute with methanol to volume. Add 2 drops of 3 N hydrochloric acid, mix, and filter. Use the filtrate.

Chromatographic system

(See Chromatography (621), General Procedures, Thin-Layer Chromatography.)

- **Mode:** TLC
- **Adsorbent:** 0.25-mm layer of chromatographic silica gel mixture, heated at 105° for 30 min, and allowed to cool before use
- **Application volume:** 10 µL
- **Developing solvent system:** Butyl alcohol, glacial acetic acid, and water (8:2:2)
- **Spray reagent:** 3-mg/mL solution of ninhydrin in dehydrated alcohol

Analysis

**Samples:** Standard solution and Sample solution

Separately apply the Sample solution and the Standard solution to the plate. Develop the chromatogram in the Developing solvent system until the solvent front has moved three-fourths the length of the plate. Remove the plate, mark the solvent front, allow the solvent to evaporate, and place the plate in an atmosphere of iodine vapors. After a few minutes, spray the plate with Spray reagent, heat it at 105° for 10 min, allow it to cool, and examine it.

**Acceptance criteria:** The \(R_f\) values, colors, and intensities of the principal spots from the Sample solution correspond to those from the Standard solution.

**Change to read:**

B. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

**Change to read:**

**PROCEDURE**

- **Mobile phase:** 6.9 g/L of monobasic sodium phosphate and 0.2 g/L of sodium 1-hexanesulfonate in water. Adjust with phosphoric acid to a pH of 3.0 ± 0.1.
- **Diluent:** 1.0 g/L of edetate disodium in water
- **System suitability solution:** 1 mg/mL of USP Penicillamine RS and 0.1 mg/mL of USP Penicillamine Disulfide RS in Diluent
**Standard solution:** 1.25 mg/mL of [USP Penicillamine RS](https://www.usp.org) in [Diluent](https://www.usp.org)

**Sample solution:** Nominally equivalent to 1.25 mg/mL of penicillamine in [Diluent](https://www.usp.org) prepared as follows. Transfer the contents of Capsules (NLT 10) to a suitable volumetric flask. Add the empty Capsule shells to the flask, and add sufficient [Diluent](https://www.usp.org) to the flask to fill it to three-fourths of its capacity. Shake for 1 min, and allow the mixture to stand for 90 min. Dilute with [Diluent](https://www.usp.org) to volume. Pass a portion of this solution through a suitable filter of 1-µm or finer pore size, and use the clear filtrate.

**Chromatographic system**
(See [Chromatography](https://www.usp.org) (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 210 nm
- **Column:** 3.9-mm × 30-cm; 10-µm packing (USP 1-Dec-2021)
- **Flow rate:** 1.6 mL/min
- **Injection volume:** 20 µL

**System suitability**

- **Samples:** System suitability solution and Standard solution
  - **Note**—The relative retention times for penicillamine and penicillamine disulfide are 0.7 and 1.0, respectively.

**Suitability requirements**

- **Resolution:** NLT 3.0 between penicillamine and penicillamine disulfide, System suitability solution
- **Relative standard deviation:** NMT 1.0%, Standard solution

**Analysis**

- **Samples:** Standard solution and Sample solution
  
  Calculate the percentage of penicillamine (C₅H₁₁NO₂S) in the portion of Capsules taken:

  \[
  \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
  \]

  \[r_U\] = peak response of penicillamine from the Sample solution
  \[r_S\] = peak response of penicillamine from the Standard solution
  \[C_S\] = concentration of USP Penicillamine RS in the Standard solution (mg/mL)
  \[C_U\] = nominal concentration of penicillamine in the Sample solution (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution** (711)

  **Test 1** (TBD)

  - **Medium:** 0.1 N [hydrochloric acid](https://www.usp.org); 900 mL
  - **Apparatus 1:** 100 rpm
  - **Time:** 30 min

  **Procedure for a pooled sample**

  - **Dilute hydrochloric acid:** Dilute 37 mL of [hydrochloric acid](https://www.usp.org) with [water](https://www.usp.org) to 1 L.
  - **Dilute sulfuric acid:** Dilute 1 mL of [sulfuric acid](https://www.usp.org) with [water](https://www.usp.org) to 50 mL.
  - **Ammonium sulfamate reagent:** 2.5 mg/mL of [ammonium sulfamate](https://www.usp.org) in [Dilute hydrochloric acid](https://www.usp.org)
**N-(1-Naphthyl)ethylenediamine dihydrochloride reagent:** 1 mg/mL of *N-(1-naphthyl)ethylenediamine dihydrochloride* in *Dilute hydrochloric acid*

**Sulfanilamide–mercuric chloride reagent:** 1 mg/mL of *sulfanilamide* and 1 mg/mL of *mercuric chloride* in *Dilute hydrochloric acid*

**Sodium nitrite reagent:** 2 mg/mL of *sodium nitrite* in *Dilute sulfuric acid*. Prepare fresh.

**Standard solution:** 250 µg/mL of *USP Penicillamine RS* in 0.1 N *hydrochloric acid*

**Sample solution:** Withdraw a portion of the solution under test, containing nominally about 278 µg of penicillamine, and pass through a suitable filter.

**Blank:** Volume of 0.1 N hydrochloric acid equivalent to a volume of the *Sample solution*

**Instrumental conditions**
- **Mode:** UV-Vis
- **Analytical wavelength:** 540 nm
- **Cell:** 1 cm

**Analysis:** Pipet the *Sample solution* into a 100-mL volumetric flask. Into a similar flask, transfer the reagent *Blank*, and into a third 100-mL volumetric flask, pipet 1 mL of *Standard solution*. Treat each flask as follows. Add by pipet 3 mL of *Sodium nitrite reagent*, and mix by swirling occasionally. After 5 min, add 10 mL of *Ammonium sulfamate reagent*, swirl, and allow to stand for an additional 5 min. Add 5 mL of *Sulfanilamide–mercuric chloride reagent*, swirl, and immediately add 10 mL of *N-(1-Naphthyl)ethylenediamine dihydrochloride reagent*. Dilute with water to volume and mix. Determine the absorbances of both solutions against the *Blank*.

Calculate the percentage of the labeled amount of penicillamine (C₅H₁₁NO₂S) dissolved:

\[
\text{Result} = \left( \frac{A_U}{A_S} \right) \times C_S \times V \times \left( \frac{1}{L} \right) \times 100
\]

- \( A_U \) = absorbance of the *Sample solution*
- \( A_S \) = absorbance of the *Standard solution*
- \( C_S \) = concentration of *USP Penicillamine RS* in the *Standard solution* (mg/mL)
- \( V \) = volume of the Medium, 900 mL
- \( L \) = label claim (mg/Capsule)

**Tolerances:** NLT 80% (*Q*) of the labeled amount of penicillamine (C₅H₁₁NO₂S) is dissolved.

**Procedure for a unit sample**
- **Buffer solution:** 50 mM solution of *monobasic potassium phosphate* buffer at a pH of 3.0
- **Mobile phase:** *Methanol* and *Buffer solution* (3:97)

**Sample solution:** Proceed as directed in *Dissolution* (711), *Procedure*. After 30 min, withdraw 10 mL of solution from each vessel, and immediately pass each aliquot through a polyvinylidene difluoride filter of 0.45-µm pore size. Discard the first 2 mL of filtered solution, and chromatograph the remaining filtrate.

**System suitability solution:** ▲*USP Penicillamine RS* at a concentration similar to the *Sample solution* and ▲(USP 1-Dec-2021) 0.002 mg/mL of *USP Penicillamine Disulfide RS* in 0.1 N *hydrochloric acid*

**Standard solution:** *USP Penicillamine RS* in 0.1 N *hydrochloric acid* at a concentration similar to the *Sample solution*

**Chromatographic system**
(See *Chromatography* (621), *System Suitability*.)
Mode: LC  
Detector: UV 210 nm  
Column: 4.6-mm × 15-cm; 5-µm packing L1  
Flow rate: 1.0 mL/min  
Injection volume: 30 µL  

System suitability  
Samples: System suitability solution and Standard solution  
Suitability requirements  
Resolution: NLT 2.0 between penicillamine and penicillamine disulfide, System suitability solution  
Tailing factor: NMT 2.0, Standard solution  
Relative standard deviation: NMT 2.0%, Standard solution  

Analysis  
Samples: Sample solution and Standard solution  
Calculate the percentage of penicillamine (C₅H₁₁NO₂S) dissolved:

\[
\text{Result} = \left(\frac{r_U}{r_S}\right) \times C_S \times V \times \left(\frac{1}{L}\right) \times 100
\]

\(r_U\) = peak response from the Sample solution  
\(r_S\) = peak response from the Standard solution  
\(C_S\) = concentration of USP Penicillamine RS in the Standard solution (mg/mL)  
\(V\) = volume of Medium, 900 mL  
\(L\) = label claim (mg/Capsule)  

Tolerances: NLT 80% (Q) of the labeled amount of penicillamine (C₅H₁₁NO₂S) is dissolved.  

▲ Test 2: If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 2.

Medium: 0.1 N hydrochloric acid; 500 mL  
Apparatus 1: 100 rpm  
Time: 30 min  
Buffer: pH 3.0 phosphate buffer (Dissolve 6.8 g of potassium phosphate monobasic in 1 L of water. Sonicate to dissolve. Adjust with 10% phosphoric acid TS to a pH of 3.0.)  
Mobile phase: Methanol and Buffer (3:97)  
System suitability solution: 0.5 mg/mL of USP Penicillamine RS and 0.002 mg/mL of USP Penicillamine Disulfide RS prepared as follows. Transfer suitable amounts of USP Penicillamine RS and USP Penicillamine Disulfide RS to an appropriate volumetric flask. Add about 70% of the flask volume of Medium and sonicate to dissolve. Dilute with Medium to volume.  
Standard solution: 0.5 mg/mL of USP Penicillamine RS in Medium. Sonicate to dissolve, if necessary.  
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding NLT 5 mL of the filtrate.  

Chromatographic system  
(See Chromatography (621), System Suitability.)  
Mode: LC  
Detector: UV 210 nm  
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 15 μL
Run time: NLT 1.5 times the retention time of penicillamine

System suitability
[Note—The relative retention times for penicillamine and penicillamine disulfide are about 1.0 and 1.1, respectively.]

Samples: System suitability solution and Standard solution

Suitability requirements
Resolution: NLT 2.0 between penicillamine and penicillamine disulfide, System suitability solution
Tailing factor: NMT 2.0, Standard solution
Relative standard deviation: NMT 2.0%, Standard solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of penicillamine (C₉H₁₁NO₂S) dissolved:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{1}{L} \right) \times 100 \]

\[ r_U = \text{peak response of penicillamine from the Sample solution} \]
\[ r_S = \text{peak response of penicillamine from the Standard solution} \]
\[ C_S = \text{concentration of USP Penicillamine RS in the Standard solution (mg/mL)} \]
\[ V = \text{volume of Medium, 500 mL} \]
\[ L = \text{label claim (mg/Capsule)} \]

Tolerances: NLT 80% (Q) of the labeled amount of penicillamine (C₉H₁₁NO₂S) is dissolved.▲ (TBD)

- **Uniformity of Dosage Units** (905): Meet the requirements

**IMPURITIES**

- **Limit of Penicillamine Disulfide**

Mobile phase, Diluent, System suitability solution, Sample solution, and Chromatographic system: Proceed as directed in the Assay.

Standard solution: 0.025 mg/mL of USP Penicillamine Disulfide RS in Diluent

System suitability
Samples: System suitability solution and Standard solution
[Note—The relative retention times for penicillamine and penicillamine disulfide are 0.7 and 1.0, respectively.]

Suitability requirements
Resolution: NLT 3.0 between penicillamine and penicillamine disulfide, System suitability solution
Relative standard deviation: NMT 2.0% for penicillamine disulfide, Standard solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of penicillamine disulfide (C₁₀H₂₀N₂O₄S₂) in the portion of Capsules taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 \]

\[ r_U = \text{peak area of penicillamine disulfide from the Sample solution} \]
\[ r_S = \text{peak area of penicillamine disulfide from the Standard solution} \]
\[ C_S = \text{concentration of USP Penicillamine Disulfide RS in the Standard solution (mg/mL)} \]
\[ C_U = \text{nominal concentration of penicillamine in the Sample solution (mg/mL)} \]

**Acceptance criteria:** NMT 2.0%

**ADDITIONAL REQUIREMENTS**

**Change to read:**

- **Packaging and Storage:** Preserve in tight containers. ▲Store at controlled room temperature. ▲(USP 1-Dec-2021)

**Add the following:**

▲LABELING: When more than one dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used. ▲(TBD)

**Change to read:**

- **USP Reference Standards (11):**
  - USP Penicillamine RS
  - USP Penicillamine Disulfide RS
  ▲3,3′-Dithiodi-D-valine. ▲(USP 1-Dec-2021)

\[ C_{10}H_{20}N_2O_4S_2 \] ▲296.40 ▲(USP 1-Dec-2021)

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**Page Information:**

Not Applicable

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