Penicillamine Capsules

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In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 1 Expert Committee intends to revise the Penicillamine Capsules monograph.

Based on supporting documents received from a manufacturer awaiting FDA approval, the Expert Committee proposes to delete the Loss on Drying test, which is formulation-specific.

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 Ramanujam Prasad, Senior Scientific Liaison (301-816-8211 or rsp@usp.org).

¹This 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 which 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 which are posted without prior publication for comment in Pharmacopeial Forum, must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF for Revision Bulletins.
Penicillamine Capsules

**DEFINITION**
Penicillamine Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of penicillamine (C₇H₁₁NO₅S).

**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 butyl alcohol, glacial acetic acid, and water (8:2:2)

**Adsorbent:** Layer Chromatography

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

• **D.**

  **Development solvent system:** Butyl alcohol, glacial acetic acid, and water (8:2:2)

  **Spray reagent:** 3-mg/mL solution of ninhydrin in butyl alcohol, glacial acetic acid, and water (8:2:2)

**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 Rₚ values, colors, and intensities of the principal spots from the Sample solution correspond to those from the Standard solution.

• **B. PROCEDURE**

  **Solution A:** 100 mg/mL of phosphotungstic acid in water

  **Sample solution:** Dissolve a portion of Capsule contents, containing nominally about 20 mg of penicillamine, in 4 mL of water.

  **Analysis:** To the Sample solution, add 2 mL of Solution A and heat nearly to boiling.

  **Acceptance criteria:** A deep blue color is produced immediately.

**ASSAY**

• **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 in Diluent

  **Sample solution:** Nominally equivalent to 1.25 mg/mL of penicillamine in Diluent prepared as follows. Transfer the contents of NLT 10 Capsules to a suitable volumetric flask. Add the empty Capsule shells to the flask, and add sufficient Diluent 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 to volume. Pass a portion of this solution through a suitable filter of 1-µm or finer porosity, and use the clear filtrate.

  **Chromatographic system**
  (See Chromatography 621, System Suitability.)

  **Mode:** LC

  **Detector:** UV 210 nm

  **Column:** 3.9-mm × 30-cm; packing L1

  **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 (C₇H₁₁NO₅S) in portion of Capsules taken:

  \[ \frac{ \text{Result} }{ \text{mg/mL} } = \left( \frac{r_v}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times 100 \]

  \[ r_v = \text{peak response of penicillamine from the Sample solution} \]

  \[ r_s = \text{peak response of penicillamine from the Standard solution} \]

  \[ C_s = \text{concentration of USP Penicillamine RS in the Standard solution (mg/mL)} \]

  \[ C_u = \text{nominal concentration of penicillamine in the Sample solution (mg/mL)} \]

  **Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

• **Dissolution (711)**

  **Medium:** 0.1 N hydrochloric acid; 900 mL

  **Apparatus 1:** 100 rpm

  **Time:** 30 min

  **Procedure for a pooled sample**

  **Dilute hydrochloric acid:** Dilute 37 mL of hydrochloric acid with water to 1 L.

  **Dilute sulfuric acid:** Dilute 1 mL of sulfuric acid with water to 50 mL.

  **Ammonium sulfamate reagent:** 2.5 mg/mL of ammonium sulfamate in Dilute hydrochloric acid

  **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

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2 Penicillamine

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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 Sodium acetate–ethylenediamine dihydrochloride 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 labeled amount of penicillamine (C\textsubscript{10}H\textsubscript{15}NO\textsubscript{5}) dissolved:

\[ \text{Result} = \left( \frac{A_s}{A_b} \right) \times \left( \frac{C_s}{C_b} \right) \times V \times (1/L) \times 100 \]

- \( A_s \) = absorbance of the Sample solution
- \( A_b \) = absorbance of the Standard solution
- \( C_s \) = concentration of USP Penicillamine RS in the Standard solution (µg/mL)
- \( C_b \) = nominal concentration of penicillamine in the Sample solution (µg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of penicillamine (C\textsubscript{10}H\textsubscript{15}NO\textsubscript{5}) is dissolved.

Procedure for a unit sample
Buffer solution: 50 mM solution of monobasic potassium phosphate buffer, pH 3.0
Mobile phase: Methanol and Buffer solution (3:97)
System suitability solution: 0.002 mg/mL of USP Penicillamine Disulfide RS in 0.1 N hydrochloric acid
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 0.45-µm polyvinylidene difluoride filter paper. Discard the first 2 mL of filtered solution, and chromatograph the remaining filtrate.
Standard solution: USP Penicillamine RS in 0.1 N hydrochloric acid at a concentration similar to 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: Standard solution and System suitability 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 penicillamine (C\textsubscript{10}H\textsubscript{15}NO\textsubscript{5}) released:

\[ \text{Result} = \left( \frac{r_o}{r_s} \right) \times \left( \frac{C_s}{C_b} \right) \times V \times (1/L) \times 100 \]

- \( r_o \) = peak area from the Sample solution
- \( r_s \) = peak area from the Standard solution
- \( C_s \) = concentration of USP Penicillamine RS in the Standard solution (mg/mL)
- \( C_b \) = nominal concentration of in the Sample solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of penicillamine (C\textsubscript{10}H\textsubscript{15}NO\textsubscript{5}) is dissolved.

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 (C\textsubscript{10}H\textsubscript{15}N\textsubscript{2}O\textsubscript{5}S\textsubscript{2}) in the portion of Capsules taken:

\[ \text{Result} = \left( \frac{r_o}{r_s} \right) \times \left( \frac{C_s}{C_b} \right) \times V \times (1/L) \times 100 \]

- \( r_o \) = peak area of penicillamine disulfide from the Sample solution
- \( r_s \) = peak area of penicillamine disulfide from the Standard solution
- \( C_s \) = concentration of USP Penicillamine Disulfide RS in the Standard solution (mg/mL)
- \( C_b \) = nominal concentration of penicillamine in the Sample solution (mg/mL)

Acceptance criteria: NMT 2.0%

SPECIFIC TESTS

Delete the following:

\* Loss on Drying (731):
Sample: 100 mg of Capsule contents.
Analysis: Dry Sample in a capillary-stoppered bottle in a vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 h.
Acceptance criteria: it loses NMT 1.0% of its weight. ▲ (TB)

ADDITIONAL REQUIREMENTS

Packaging and Storage: Preserve in tight containers.

USP Reference Standards (11)
USP Penicillamine RS
USP Penicillamine Disulfide RS C\textsubscript{10}H\textsubscript{15}N\textsubscript{2}O\textsubscript{5}S\textsubscript{2}

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