Thalidomide Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	26–April–2019
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 3

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 3 Expert Committee intends to revise the Thalidomide Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to the monograph.

- *Dissolution Test 2* was validated using a Kinetex C18 brand of L1 column. The typical retention time for thalidomide is about 14 min.

Labeling information has been incorporated to support the inclusion of *Dissolution Test 2*.

Additionally, minor editorial changes have been made to update the monograph to current *USP* style.

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 Feiwen Mao, Senior Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-816-8320 or fm@usp.org).

[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*.

Thalidomide Capsules

DEFINITION

Thalidomide Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of thalidomide ($C_{13}H_{10}N_2O_4$).

IDENTIFICATION

• **A. Thin-Layer Chromatographic Identification Test** ⟨201⟩
Sample solution: 3 mg/mL of thalidomide in acetonitrile
Chromatographic system
Mode: TLC
Application volume: 5 µL
Developing solvent system: *n*-Butyl acetate, glacial acetic acid, and butyl alcohol (50:25:5)
Acceptance criteria: Meets the requirements
• **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

• **Procedure**
Solution A: Transfer 1 mL of phosphoric acid to a 100-mL volumetric flask and dilute with water to volume.
Mobile phase: Acetonitrile, water, and phosphoric acid (15: 85: 0.1)
Internal standard solution: 1.5 mg/mL of phenacetin in acetonitrile
Standard stock solution: 1 mg/mL of USP Thalidomide RS in acetonitrile. Sonicate to dissolve if necessary.
Standard solution: 0.1 mg/mL of USP Thalidomide RS and 0.075 mg/mL of phenacetin prepared as follows. Transfer 10.0 mL of *Standard stock solution* and 5.0 mL of *Internal standard solution* to a 100-mL volumetric flask, add 10.0 mL of *Solution A*, and dilute with water to volume.
Sample stock solution: Nominally equivalent to 0.5 mg/mL of thalidomide prepared as follows. Remove, as completely as possible, the contents of NLT 20 Capsules. Mix the combined contents, and transfer a weighed portion of the powder, equivalent to 50 mg of thalidomide, to a 100-mL volumetric flask. Add 80 mL of acetonitrile to dissolve, and sonicate for 20 min. Dilute with acetonitrile to volume.
Sample solution: Nominally equivalent to 0.1 mg/mL of thalidomide and 0.075 mg/mL of phenacetin prepared as follows. Transfer 20.0 mL of *Sample stock solution* and 5.0 mL of *Internal standard solution* to a 100-mL volumetric flask, add 10.0 mL of *Solution A*, and dilute with water to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 237 nm
Column: 3.9-mm × 15-cm; 4-µm packing L1
Flow rate: 1 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 3.0 between the thalidomide and phenacetin peaks
Column efficiency: NLT 7000 theoretical plates for thalidomide; NLT 9000 theoretical plates for phenacetin
Tailing factor: NMT 2.0
Relative standard deviation: NMT 1.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of thalidomide ($C_{13}H_{10}N_2O_4$) in the Capsules taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of thalidomide to phenacetin from the *Sample solution*
R_S = peak response ratio of thalidomide to phenacetin from the *Standard solution*
C_S = concentration of USP Thalidomide RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of thalidomide in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩
▲Test 1▲ (TBD)
Solution A: 0.5 g/mL of polyoxyethylene (23) lauryl ether in water
Solution B: 1% (v/v) phosphoric acid in water
Medium: Add 1.0 mL of *Solution A* to 0.225 M hydrochloric acid to make a total volume of 4000 mL; 4000 mL
Apparatus 2: 75 rpm
Time: 60 min
Mobile phase: Acetonitrile, water, and phosphoric acid (15: 85: 0.1)
Internal standard stock solution: 375 µg/mL of phenacetin in acetonitrile
Internal standard solution: 75 µg/mL of phenacetin prepared as follows. Transfer 20.0 mL of *Internal standard stock solution* to a 100-mL volumetric flask, add 10.0 mL of *Solution B*, and dilute with water to volume.
Standard stock solution: 0.25 mg/mL of USP Thalidomide RS in acetonitrile
Standard solution: 0.02 mg/mL of USP Thalidomide RS and 15 µg/mL of phenacetin prepared as follows. Transfer 10.0 mL of *Standard stock solution* to a 100-mL volumetric flask, add 10.0 mL of *Solution B*, and dilute with water to volume. Add 5.0 mL of *Internal standard solution* to 20.0 mL of this solution, and mix.
Sample solution: Add 5.0 mL of *Internal standard solution* to 20.0 mL of filtered solution under test, and mix.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 237 nm
Column: 3.9-mm × 15-cm; 4-µm packing L1
Flow rate: 1 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 3.0 between the thalidomide and phenacetin peaks
Column efficiency: NLT 7000 theoretical plates for thalidomide; NLT 9000 theoretical plates for phenacetin
Tailing factor: NMT 2.0
Relative standard deviation: NMT 1.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of thalidomide ($C_{13}H_{10}N_2O_4$) dissolved:

$$\text{Result} = (R_U/R_S) \times C_S \times V \times (1/L) \times 100$$

R_U = peak response ratio of thalidomide to phenacetin from the *Sample solution*
R_S = peak response ratio of thalidomide to phenacetin from the *Standard solution*
C_S = concentration of USP Thalidomide RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 4000 mL
L = label claim (mg/Capsule)

Tolerances: NLT 70% (Q) of the labeled amount of thalidomide ($C_{13}H_{10}N_2O_4$) is dissolved.

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

Tier 1

Medium: 15 g/L of sodium lauryl sulfate in water, adjusted with hydrochloric acid or sodium hydroxide to a pH of 3.0; 900 mL

Apparatus 2: 100 rpm, with sinkers. [NOTE—A suitable sinker is available from QLA Quality Lab, www.qla-llc.com, catalog number CAPWHT-02.]

Times

For 50 and 100 mg/Capsule: 30 min

For 150 and 200 mg/Capsule: 60 min

Tier 2

Medium A: Water adjusted with hydrochloric acid or sodium hydroxide to a pH of 3.0, and degas. Dissolve a suitable amount of pepsin in the deaerated pH 3.0 water to give the pepsin activity of 100,000 USP Units/L; 450 mL. Use immediately.

Medium B: 30 g/L of sodium lauryl sulfate in water, adjusted with hydrochloric acid or sodium hydroxide to a pH of 3.0; 450 mL

Medium: *Medium A* and *Medium B* (1:1); 900 mL

Apparatus 2: 100 rpm, with sinkers. [NOTE—A suitable sinker is available from QLA Quality Lab, www.qla-llc.com, catalog number CAPWHT-02.]

Times

For 50 and 100 mg/Capsule: 10 min for *Medium A*; then an additional 20 min for *Medium A* with the addition of *Medium B*, for a total of 30 min

For 150 and 200 mg/Capsule: 10 min for *Medium A*; then an additional 50 min for *Medium A* with the addition of *Medium B*, for a total of 60 min

Dissolution procedure: Perform the test using the conditions in *Tier 1*. In the presence of cross-linking, repeat the test with new Capsules using the conditions in *Tier 2* as follows. Drop a Capsule in 450 mL of equilibrated *Medium A*, and at 10 min while continuing to stir, add 450 mL of pre-equilibrated *Medium B*. Continue dissolution for an additional 20 min for 50 and 100 mg/Capsule, and an additional 50 min for 150 and 200 mg/Capsule.

Mobile phase: Acetonitrile, water, and phosphoric acid (15: 85: 0.1)

Standard solution A: 0.11 mg/mL of USP Thalidomide RS prepared as follows. Transfer a suitable amount of USP Thalidomide RS to an appropriate volumetric flask, add acetonitrile equivalent to 10% of the final flask volume, and sonicate to dissolve. Dilute with *Medium* from *Tier 1* to volume.

Standard solution B: 0.11 mg/mL of USP Thalidomide RS prepared as follows. Transfer a suitable amount of USP Thalidomide RS to an appropriate volumetric flask, add acetonitrile equivalent to 10% of the final flask volume, and sonicate to dissolve. Dilute with *Medium* from *Tier 2* to volume.

Sample solution: Pass a portion of the solution under test through a suitable PVDF filter of 0.45-µm pore size, discard at least 10 mL, and use the filtrate for analysis.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 237 nm

Column: 4.6-mm × 5-cm; 2.6-µm packing L1

Column temperature: 45°

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Samples: *Standard solution A* or *Standard solution B*. Use *Standard solution A* for *Tier 1* and *Standard solution B* for *Tier 2*.

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0% for 6 injections

Analysis

Samples: *Standard solution A* or *Standard solution B*. Use *Standard solution A* for *Tier 1* and *Standard solution B* for *Tier 2*.

Calculate the percentage of the labeled amount of thalidomide ($C_{13}H_{10}N_2O_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = peak response of thalidomide from the *Sample solution*
r_S = peak response of thalidomide from *Standard solution A* or *Standard solution B*
C_S = concentration of USP Thalidomide RS in *Standard solution A* or *Standard solution B* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Capsule)

Tolerances: NLT 75% (Q) of the labeled amount of thalidomide ($C_{13}H_{10}N_2O_4$) is dissolved.▲ (TBD)

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

ADDITIONAL REQUIREMENTS

- **MICROBIAL ENUMERATION TESTS** ⟨61⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨62⟩**:** The total aerobic microbial count does not exceed 10^3 cfu/g, and the total combined molds and yeasts count does not exceed 10^2 cfu/g. It meets the requirements of the tests for absence of *Escherichia coli*.
- **PACKAGING AND STORAGE:** Preserve in tight containers, protected from light, and store at controlled room temperature. Do not repackage.

Add the following:

▲- **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.▲ (TBD)
- **USP REFERENCE STANDARDS** ⟨11⟩
USP Thalidomide RS