Extended Phenytoin Sodium Capsules

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Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Extended Phenytoin Sodium Capsules monograph. The purpose for the revision is to add *Dissolution Test* 5 to accommodate the FDA approved specifications for the sponsor product.

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

The Extended Phenytoin Sodium Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement* to *USP 40–NF 35.*

Should you have any questions, please contact K. Kalyana Seela, Ph.D., Senior Scientific Liaison (kks@usp.org).

Extended Phenytoin Sodium Capsules

DEFINITION

Extended Phenytoin Sodium Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$).

IDENTIFICATION

- **A. INFRARED ABSORPTION—GENERAL** ⟨197⟩
  Sample: 300 mg of phenytoin sodium from the contents of Capsules in 50 mL of water in a separator. Add 10 mL of 3 N hydrochloric acid, and extract with three successive portions, measuring 100, 60, and 30 mL, respectively, of ether and chloroform (1:2). Evaporate the combined extracts, and dry the residue of phenytoin at 105° for 4 h.
  Acceptance criteria: The spectrum of the *Sample* corresponds to that of a similarly prepared USP Phenytoin RS.
- **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**
  Buffer: 0.05 M monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 3.5.
  Mobile phase: Methanol and *Buffer* (55:45)
  Standard solution: 0.6 mg/mL of USP Phenytoin RS in *Mobile phase*. [NOTE—Dissolve the required quantity of phenytoin in a small amount of methanol before diluting with *Mobile phase*.]
  Sample stock solution: Transfer the contents of 10 Capsules to a 250-mL volumetric flask. Add 150 mL of methanol, and sonicate for 20 min. Cool to room temperature, and dilute with methanol to volume.
  Sample solution: Nominally 0.6 mg/mL of phenytoin from the *Sample stock solution* in *Mobile phase*
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 229 nm
  Column: 4.6-mm × 25-cm; packing L1
  Flow rate: 1 mL/min
  Injection volume: 10 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Column efficiency: NLT 3000 theoretical plates
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of phenytoin from the *Sample solution*
r_S = peak response of phenytoin from the *Standard solution*
C_S = concentration of USP Phenytoin RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of phenytoin in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of phenytoin sodium, 274.25
M_{r2} = molecular weight of phenytoin, 252.27

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩
  Test 1
  Medium: Water; 900 mL
  Apparatus 1: 50 rpm
  Times: 30, 60, and 120 min
  Mobile phase: Methanol and water (70:30)
  Standard solution: Dissolve USP Phenytoin RS in methanol, and dilute with water to obtain a concentration similar to that of the *Sample solution*.
  Sample solution: Pass a portion of the solution under test through a suitable filter.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 229 nm
  Column: 4.6-mm × 25-cm; packing L1
  Flow rate: 1 mL/min
  Injection volume: 10 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Column efficiency: NLT 3200 theoretical plates
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2}) \times V \times (100/L)$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Phenytoin RS in the *Standard solution* (mg/mL)
M_{r1} = molecular weight of phenytoin sodium, 274.25
M_{r2} = molecular weight of phenytoin, 252.27
V = volume of *Medium*, 900 mL
L = label claim (mg/Capsule)

Tolerances (for products labeled as 30-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 40% (Q) in 30 min, 56% (Q') in 60 min, and NLT 65% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to *Table 1*.

Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is within the range between Q – 15% and Q – 5%, is within the range Q' ± 10%, and is NLT Q'' + 5% at the stated *Times*.
S_2	6	Average of 12 units ($S_1 + S_2$) is within the range between Q – 10% and Q, is within the range Q' ± 8%, and is NLT Q''; no unit is outside the range between Q – 20% and Q + 10%, no unit is outside the range Q' ± 18%, and no unit is less than Q'' – 10% at the stated *Times*.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is within the range between Q – 10% and Q, is within the range Q' ± 8%, and is NLT Q''; NMT 2 units are outside the range between Q – 20% and Q + 10%, and no unit is outside the range Q – 30% and Q + 20%; NMT 2 units are outside the range Q' ± 18%, and no unit is outside the range Q' ± 25%; NMT 2 units are less than Q'' – 10%, and no unit is less than Q'' – 20% at the stated *Times*.

Tolerances (for products labeled as 100-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 45% (Q) in 30 min, 60% (Q') in 60 min, and NLT 70% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to *Table 2*.

Table 2

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is within the range between Q – 25% and Q – 5%, is equal to Q' ± 20%, and is NLT Q'' + 5% at the stated *Times*.
S_2	6	Average of 12 units ($S_1 + S_2$) is within the range between Q – 20% and Q, is within the range Q' ± 15%, and is NLT Q''; no unit is outside the range between Q – 30% and Q + 10%, no unit is outside the range Q' ± 25%, and no unit is less than Q'' – 10% at the stated *Times*.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is within the range between Q – 20% and Q, is within the range Q' ± 15%, and is NLT Q''; NMT 2 units are outside the range between Q – 30% and Q + 10%, and no unit is outside the range between Q – 40% and Q + 20%; NMT 2 units are outside the range Q' ± 25%, and no unit is outside the range Q' ± 35%; NMT 2 units are less than Q'' – 10%, and no unit is less than Q'' – 20% at the stated *Times*.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Proceed as directed in *Test 1*, except use *Apparatus 1* at 75 rpm and the following *Tolerances*.
Tolerances (for products labeled as 100-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 45% (Q) in 30 min, 65% (Q') in 60 min, and NLT 70% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to *Table 3*.

Table 3

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is within the range between Q – 25% and Q – 5%, is equal to Q' ± 20%, and is NLT Q'' + 5% at the stated *Times*.
S_2	6	Average of 12 units ($S_1 + S_2$) is within the range between Q – 25% and Q – 5%, is within the range of Q' – 20% and Q' + 10%, and is NLT Q''; no unit is outside the range between Q – 30% and Q + 5%, no unit is outside the range Q' – 25% and Q' + 20%, and no unit is less than Q'' –10% at the stated *Times*.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is within the range between Q – 25% and Q – 5%, is within the range of Q' – 20% and Q' + 10%, and is NLT Q''; NMT 2 units are outside the range between Q – 30% and Q + 5%; and no unit is outside the range of Q – 40% and Q + 15%; NMT 2 units are outside the range Q' – 25% and Q' + 20%, and no unit is outside the range Q' – 35% and Q' + 25%; NMT 2 units are less than Q'' – 10%; and no unit is less than Q'' – 20% at the stated *Times*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: Water; 900 mL
Apparatus 1: 75 rpm
Times: 30, 60, and 120 min
Determine the amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved by using the method described in *Test 1*.
Tolerances (for products labeled as 200- and 300-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 30% (Q) in 30 min, 50% (Q') in 60 min, and NLT 60% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to *Table 4*.

Table 4

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is within the range between Q – 20% and Q + 5%, is equal to Q' – 20% and Q' + 25%, and is NLT Q'' + 5% at the stated *Times*.
S_2	6	Average of 12 units ($S_1 + S_2$) is within the range between Q – 20% and Q, is within the range of Q' ± 20%, and is NLT Q''; no unit is outside the range between Q – 25% and Q + 10%, no unit is outside the range Q' ± 25%, and no unit is less than Q'' – 10% at the stated *Times*.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is within the range between Q – 20% and Q, is within the range of Q' ± 20%, and is NLT Q''; NMT 2 units are outside the range between Q – 25% and Q + 10%, and no unit is outside the range Q – 25% and Q + 15%; NMT 2 units are outside the range Q' ± 25%; and no unit is outside the range Q' ± 30%; NMT 2 units are less than Q'' – 10%; and no unit is less than Q'' – 20% at the stated *Times*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium, Apparatus 1, Times, and **Analysis:** Proceed as directed for *Test 1*.
Tolerances (for products labeled as 30-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 40% (Q) in 30 min, 56% (Q') in 60 min, and NLT 65% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to *Table 5*.

Table 5

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is within the range between Q – 10% and Q, is within the range Q' – 9% and Q' + 7%, and is NLT Q'' + 5% at the stated *Times*.
S_2	6	Average of 12 units ($S_1 + S_2$) is within the range between Q – 8% and Q + 2%, is within the range Q' – 9% and Q' + 7%, and is NLT Q''; no unit is outside the range between Q – 20% and Q + 10%, no unit is outside the range Q' – 19% and Q' + 17%, and no unit is less than Q'' – 10% at the stated *Times*.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is within the range between Q – 8% and Q + 2%, is within the range Q' – 9% and Q' + 7%, and is NLT Q''; NMT 2 units are outside the range between Q – 20% and Q + 10%, and no unit is outside the range Q – 30% and Q + 20%; NMT 2 units are outside the range Q' – 19% and Q' + 17%, and no unit is outside the range Q' – 26% and Q' + 24%; NMT 2 units are less than Q'' – 10%, and no unit is less than Q'' – 20% at the stated *Times*.

• **Test 5:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.
Medium, Apparatus 1, Times, and **Analysis:** Proceed as directed for *Test 1*.
Tolerances (for products labeled as 100-mg Capsules): The percentage of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) dissolved is NMT 45% (Q) in 30 min, 65% (Q') in 60 min, and NLT 80% (Q'') in 120 min. The requirements are met if the quantities dissolved from the Capsules tested conform to *Table 6*.

Table 6

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is within the range between Q – 25% and Q – 5%, is between Q' + 20% and Q' – 15%, and is NLT Q'' + 5% at the stated *Times*.
S_2	6	Average of 12 units ($S_1 + S_2$) is within the range between Q – 25% and Q – 5%, is within the range Q' ± 15%, and is NLT Q''; no unit is outside the range between Q – 30% and Q + 10%, no unit is outside the range Q' + 25% and Q' – 20%, and no unit is less than Q'' – 10% at the stated *Times*.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is within the range between Q – 25% and Q – 5%, is within the range Q' ± 15%, and is NLT Q''; NMT 2 units are outside the range between Q – 30% and Q + 10%, and no unit is outside the range Q – 35% and Q + 20%; NMT 2 units are outside the range between Q' + 25% and Q' – 20%, and no unit is outside the range Q' + 30% and Q' – 25%; NMT 2 units are less than Q'' – 10%, and no unit is less than Q'' – 20% at the stated *Times*.

• (RB 1-Oct-2016)
• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**
Buffer, Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Standard solution: 600 µg/mL of USP Phenytoin RS, 3 µg/mL of USP Phenytoin Related Compound A RS, and 3 µg/mL of USP Phenytoin Related Compound B RS in methanol
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for phenytoin related compound A, phenytoin related compound B, and phenytoin are 0.38, 0.45, and 1.0, respectively.]
Suitability requirements
Resolution: NLT 8 between phenytoin related compound B and phenytoin; NLT 1.5 between phenytoin related compound A and phenytoin related compound B
Tailing factor: NMT 2.0 for the phenytoin peak
Relative standard deviation: NMT 2.0% for phenytoin; NMT 5.0% for phenytoin related compound A or phenytoin related compound B
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each phenytoin related compound in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of phenytoin related compound A or phenytoin related compound B from the *Sample solution*
r_S = peak response of phenytoin related compound A or phenytoin related compound B from the *Standard solution*
C_S = concentration of the corresponding analyte in the *Standard solution* (µg/mL)
C_U = nominal concentration of phenytoin in the *Sample solution* (µg/mL)

Calculate the percentage of any individual unspecified degradation product in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each unspecified degradation product from the *Sample solution*
r_S = peak response of phenytoin from the *Standard solution*
C_S = concentration of USP Phenytoin RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of phenytoin in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 7*.

Table 7

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Phenytoin related compound A	0.38	0.5
Phenytoin related compound B	0.45	1.0
Phenytoin	1.0	—
Any individual, unspecified degradation product	—	0.2

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Protect from moisture. Store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Phenytoin RS
  USP Phenytoin Related Compound A RS
  Diphenylglycine.
  $C_{14}H_{13}NO_2$ 227.26
  USP Phenytoin Related Compound B RS
  Diphenylhydantoic acid.
  $C_{15}H_{14}N_2O_3$ 270.29