Add the following:

▪Divalproex Sodium Extended-Release Tablets

DEFINITION

Divalproex Sodium Extended-Release Tablets contain an amount of divalproex sodium equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of valproic acid ($C_8H_{16}O_2$).

IDENTIFICATION

• **A.** 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: 0.5 g of citric acid monohydrate and 0.4 g of dibasic sodium phosphate in 1 L of water

Mobile phase: Methanol and *Buffer* (11:9). Adjust with phosphoric acid to a pH of 5.0.

Diluent: *Buffer*, adjusted with phosphoric acid to a pH of 2.0

Standard stock solution: 2.5 mg/mL of USP Valproic Acid RS in methanol

Standard solution: 1.0 mg/mL of USP Valproic Acid RS from the *Standard stock solution* in *Diluent*

Sample stock solution: Transfer an amount of powder (from NLT 20 Tablets) to a suitable volumetric flask to obtain a nominal concentration of 2.5 mg/mL of valproic acid. Dissolve in 50% of the flask volume of methanol by shaking for 1 h. Dilute with methanol to volume, and pass through a suitable filter.

Sample solution: 1.0 mg/mL of valproic acid from the filtrate of the *Sample stock solution* in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 15-cm; 4-µm packing L11

Flow rate: 0.7 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for valproic acid

Relative standard deviation: NMT 2.0% for valproic acid

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of valproic acid in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% of valproic acid

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

Test 1

Acid stage medium: 0.1 N of hydrochloric acid; 500 mL

Buffer stage medium: 21.6 g of sodium dodecyl sulfate, 6.9 g of sodium dihydrogen phosphate monohydrate, and 0.12 g of sodium hydroxide in 1 L of water. Adjust with diluted sodium hydroxide or phosphoric acid to a pH of 5.5; 900 mL.

Apparatus 2: 100 rpm, with three prong sinkers only for 250-mg Tablets, ●if necessary● (RB 1-Sep-2011)

Times: 45 min in the *Acid stage medium*; 3, 12, and 24 h in the *Buffer stage medium*

Analysis: After 45 min in the *Acid stage medium*, withdraw a sample from the solution, and immediately filter. Replace the *Acid stage medium* with the *Buffer stage medium*, and run the test for the times specified.

Buffer: 1.42 g of dibasic sodium phosphate and 0.5 mL of glacial acetic acid in 1 L of water. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Methanol and *Buffer* (13:7)

Standard stock solution: 2.5 mg/mL of USP Valproic Acid RS in methanol

Standard solution: 0.15 mg/mL of USP Valproic Acid RS from the *Standard stock solution* in the *Buffer stage medium*. [NOTE—Add 40% of the flask volume of methanol before diluting with *Buffer stage medium* to volume.]

Sample solution: Pass a portion of the solution under test through a suitable filter of 20-µm pore size. Use the *Sample solution* from the *Acid stage medium* as is. Dilute the *Sample solution* from the *Buffer stage medium* with methanol by a factor of 2.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 15-cm; 10-µm packing L11

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 80 µL

Run time: 6 min

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Sample solutions* from the *Acid stage medium*, *Buffer stage medium*, and *Standard solution*

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved in the *Acid stage medium*:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V_A = volume of the *Acid stage medium*, 500 mL

Calculate the concentration of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the time interval, *t*, in mg/mL:

$$C_t = (r_U/r_S) \times (C_S \times D_U) \times 2$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)
D_U = dilution factor of the *Sample solution* in the *Buffer stage medium*, 2

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) in the *Buffer stage medium* at the first time interval:

$$\text{Result} = C_1 \times V_B \times (100/L)$$

C_1 = concentration of valproic acid in the *Buffer stage medium* at the first time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the second time interval:

$$\text{Result} = [C_2 \times (V_B - V_S)] + (C_1 \times V_S) \times (100/L)$$

C_2 = concentration of valproic acid in the *Buffer stage medium* at the second time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
V_S = volume of the sample taken at each time interval (mL)
C_1 = concentration of valproic acid in the *Buffer stage medium* at the first time interval (mg/mL)
L = label claim (mg/Tablet)

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the n^{th} time interval:

$$\text{Result} = C_n \times [V_B - (n-1) \times V_S] + [(C_1 + C_2 + ...+ C_{n-1}) \times V_S] \times (100/L)$$

C_n = concentration of valproic acid in the *Buffer stage medium* at the n^{th} time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
V_S = volume of the sample taken (mL)
C_1 = concentration of valproic acid dissolved in the first time interval in the *Buffer stage medium* (mg/mL)
C_2 = concentration of valproic acid dissolved in the second time interval in the *Buffer stage medium* (mg/mL)
C_{n-1} = concentration of valproic acid dissolved in the $(n-1)^{th}$ time interval in the *Buffer stage medium* (mg/mL)
L = label claim (mg/Tablet)

Tolerances

Acid stage: •NMT•(RB 1-Sep-2011) 10% of the labeled amount of valproic acid ($C_8H_{16}O_2$) is dissolved.

Buffer stage: See *Table 1*.

Table 1

Time (h)	Amount Dissolved (Tablets labeled to contain 500 mg of valproic acid)	Amount Dissolved (Tablets labeled to contain 250 mg of valproic acid)
3	10%–30%	10%–30%
9	35%–55%	35%–60%
12	45%–70%	45%–75%
24	NLT 75%	NLT 75%

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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

Acid stage medium: 0.1 N of hydrochloric acid; 500 mL

Buffer stage concentrate: 15.53 g/L of monobasic sodium phosphate monohydrate, 5.45 g/L of sodium hydroxide, and 48.65 g of sodium lauryl sulfate per L in water (final pH approximately 11); 400 mL

Buffer stage medium: Mix 400 mL of *Buffer stage concentrate* with 500 mL of *Acid stage medium* to a pH of 5.5 ± 0.05. •[NOTE—If necessary, adjust the pH of the *Buffer stage concentrate* with 1 N hydrochloric acid or 1 N sodium hydroxide to assure that the final pH of the mixture of media is 5.5.• (RB 1-Sep-2011) Retain this solution to dilute the solutions prepared later.

Apparatus 2: 100 rpm, with wire helix sinkers

Times: 45 min in the *Acid stage medium*; 3, 9, 12, and 21 h in the *Buffer stage medium*

Procedure: After 45 min in *Acid stage medium*, stop and lift the paddles from the vessels. Do not perform an analysis of the *Acid stage medium*. Transfer 400 mL of •*Buffer stage concentrate*•(RB 1-Sep-2011) to the vessels containing the *Acid stage medium*, and run the test for the times specified.

Buffer: 3.5 g/L of monobasic sodium phosphate monohydrate in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and *Buffer* (1:1)

Standard stock solution: 28 mg/mL of USP Valproic Acid RS in a suitable volumetric flask. Dissolve with 20% of the flask volume of 1 N sodium hydroxide, and dilute with water to volume. Dilute this solution with *Buffer stage medium* to obtain a final concentration of about 2.8 mg/mL.

Standard solutions: Prepare a series of dilutions in *Buffer stage medium* from the *Standard stock solution* in the concentrations of 0.028, 0.11, 0.22, 0.50, and 0.70 mg/mL.

Sample solution: Withdraw 10 mL of the solution under test, and pass through a suitable filter of 35-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Samples: 0.028, 0.11, 0.22, 0.50, and 0.70 mg/mL of the *Standard solutions*

Suitability requirements

Tailing factor: NMT 2.0, using the 0.50 mg/mL of *Standard solution*

Table 2

		3 h	9 h	12 h	21 h
L1	Individual Tablets	10%–27%	35%–70%	44%–92%	NLT 87%
L2	Average	10%–27%	35%–70%	44%–92%	NLT 87%
L2	Individual Tablets	0%–37%	25%–80%	34%–102%	NLT 77%
L3	Average	10%–27%	35%–70%	44%–92%	NLT 87%
L3	Individual Tablets	NMT 2 Tablets are outside the range of 0%–37% and no individual Tablet is outside the range of 0%–47%	NMT 2 Tablets are outside the range of 25%–80% and no individual Tablet is outside the range of 15%–90%	NMT 2 Tablets are outside the range of 34%–102% and no individual Tablet is outside the range of 24%–112%	NMT 2 Tablets release less than 77% and no individual Tablet releases less than 67%

Relative standard deviation: NMT 2.0%
Correlation coefficient: NLT 0.999, using the five concentrations of the *Standard solution*

Analysis

Samples: *Sample solutions*

From the standard curve, determine the amount of valproic acid ($C_8H_{16}O_2$) dissolved at each time interval using the response of each *Sample solution*.

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the first time interval:

$$\text{Result} = (C_1 \times V_B) \times (100/L)$$

C_1 = concentration of valproic acid in the *Buffer stage medium* at the 3 h time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the n^{th} time interval:

$$\text{Result} = C_n \times [V_B - (n-1) \times V_S] + [(C_1 + C_2 + \ldots + C_{n-1}) \times V_B] \times (100/L)$$

C_n = concentration of valproic acid in the *Buffer stage medium* at the n^{th} time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
V_S = volume of the sample taken (mL)
C_1 = concentration of valproic acid dissolved in the first time interval in the *Buffer stage medium* (mg/mL)
C_2 = concentration of valproic acid dissolved in the second time interval in the *Buffer stage medium* (mg/mL)
C_{n-1} = concentration of valproic acid dissolved in the $(n-1)^{th}$ time interval in the *Buffer stage medium* (mg/mL)
L = label claim (mg/Tablet)

Tolerances: The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conform to the following acceptance table (*Table 2*).

• **Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Acid stage medium: 0.1 N hydrochloric acid; 250 mL (row 1)

Buffer stage medium: pH 6.8 buffer (6.8 g of monobasic potassium phosphate and 0.92 g of sodium hydroxide in 1 L of water. Adjust with phosphoric acid or sodium hydroxide to a pH of 6.8 ± 0.05; 250 mL (rows 2–4)

Apparatus 3: 30 dips/min, 20-mesh polypropylene screen on top and bottom; 30 s drip time

Time: 1 h in acid stage (row 1); 2, 12, and 24 h in buffer stage (rows 2–4)

Buffer: 0.25 g of citric acid monohydrate, 0.2 g of anhydrous dibasic sodium phosphate, 3.4 g monobasic potassium phosphate, and 0.85 g of sodium hydroxide in 1 L of water. Adjust with phosphoric acid to a pH of 3.0 ± 0.05.

Mobile phase: Acetonitrile and *Buffer* (30:70)

Acid stage standard stock solution: 1 mg/mL of USP Valproic Acid RS in *Acid stage medium*. Dissolve a suitable amount of USP Valproic Acid RS in a suitable volumetric flask in 10% of the flask volume of methanol to solubilize valproic acid. Dilute with *Acid stage medium* to volume.

Buffer stage standard stock solution: 1 mg/mL of USP Valproic Acid RS in *Buffer stage medium*. Dissolve a suitable amount of USP Valproic Acid RS in a suitable volumetric flask in 10% of the flask volume of methanol to solubilize valproic acid. Dilute with *Buffer stage medium* to volume.

Acid stage standard solution: (L/2500) mg/mL of valproic acid from *Acid stage stock solution* in *Acid stage medium*, where L is the Tablet label claim, in mg

Buffer stage standard solution: (L/700) mg/mL of valproic acid from *Buffer stage stock solution* in *Buffer stage medium*, where L is the Tablet label claim, in mg

Sample solutions: Centrifuge a portion of the solution under test at about 3000 rpm for about 20 min. Use the supernatant.

Chromatographic system

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

Mode: LC
Detector: UV 210 nm
Column: 3.9-mm × 15-cm; 5-µm packing L11
Flow rate: 2 mL/min
Injection volume: 100 µL for Tablets labeled to contain 250 mg; 50 µL for Tablets labeled to contain 500 mg

System suitability

Samples: *Acid stage standard solution* and *Buffer stage standard solution*

Suitability requirements

Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis

Samples: *Acid stage standard solution*, *Buffer stage standard solution*, *Acid stage sample solutions*, and *Buffer stage sample solutions*

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at each time point Q_i:

$$Q_1 = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_2 = [(r_U/r_S) \times (C_S/L) \times V \times 100] + Q_1$$

$$Q_{12} = [(r_U/r_S) \times (C_S/L) \times V \times 100] + Q_2$$

$$Q_{24} = [(r_U/r_S) \times (C_S/L) \times V \times 100] + Q_{12}$$

r_U = peak response of the *Sample solution* from the *Acid stage* or *Buffer stage* time points
r_S = peak response of the *Acid stage standard solution* or *Buffer stage standard solution*
C_S = concentration of valproic acid in the *Acid stage standard solution* or *Buffer stage standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of the *Acid stage medium* or *Buffer stage medium*, 250 mL

Tolerances: See *Table 3*.

Table 3

Time (h)	Amount Dissolved (Tablets labeled to contain 500 mg of valproic acid)	Amount Dissolved (Tablets labeled to contain 250 mg of valproic acid)
1	NMT 10%	NMT 10%
2	5%–25%	5%–25%
12	55%–75%	65%–85%
24	NLT 80%	NLT 80%

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩. ●(RB 1-Sep-2011)

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

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers 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 Valproic Acid RS■1S *(USP34)*