Add the following:

▪Alprazolam Extended-Release Tablets

DEFINITION
Alprazolam Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$).

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**
Mobile phase: Acetonitrile, water, and phosphoric acid (350:650:1)
Standard solution: 0.05 mg/mL of USP Alprazolam RS in methanol
Sample solution: Transfer an appropriate number of Tablets into a suitable volumetric flask to obtain a nominal concentration of about 0.05 mg/mL of alprazolam. Sonicate in 80% of the flask volume of methanol for 15 min, shake mechanically for 30 min, dilute with methanol to final volume, filter a portion of the solution, and discard the first 3 mL of filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 30°
Flow rate: 1 mL/min
Injection size: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for alprazolam
Efficiency: NLT 3000 theoretical plates for alprazolam
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of alprazolam ($C_{17}H_{13}ClN_4$), based on the label claim, 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 Alprazolam RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of alprazolam in the *Sample solution* (mg/mL)
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨**711**⟩
●**Test 1**●(RB 1-Aug-2011)
Medium: pH 6.0 phosphate buffer (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water; adjust with phosphoric acid or potassium hydroxide to a pH of 6.0 ± 0.1); 500 mL
Apparatus 1: 100 rpm
Time: 1, 4, 8, and 12 h
Mobile phase: Acetonitrile, tetrahydrofuran, and *Medium* (7:1:12)
Standard stock solution: 0.5 mg/mL of USP Alprazolam RS in acetonitrile
Standard solution: (*L*/500) mg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, where *L* is the label claim in mg/Tablet
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 254 nm
Column: 4.6-mm × 10-cm; 5-µm packing L7
Flow rate: 1 mL/min
Injection size: 100 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Column efficiency: NLT 3000 theoretical plates
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Alprazolam RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 500 mL
Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved		
	0.5-mg Tablet	2-mg Tablet	3-mg Tablet
1	NMT 25%	NMT 20%	NMT 20%
4	40%–60%	30%–55%	30%–55%
8	70%–90%	65%–90%	65%–90%
12	NLT 85%	NLT 85%	NLT 85%

The percentages of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) released 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*.
Medium: pH 6.0 phosphate buffer (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water; adjust with phosphoric acid or potassium hydroxide to a pH of 6.0 ± 0.1); 500 mL
Apparatus 1: 100 rpm
Time: 1, 4, 8, and 16 h
Mobile phase: Acetonitrile, tetrahydrofuran, and *Medium* (35:5:60)
Standard stock solution: 0.05 mg/mL of USP Alprazolam RS in methanol
Standard solution: (*L*/500) mg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, where *L* is the label claim in mg/Tablet
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 254 nm
Column: 4.6-mm × 7.5-cm; 5-µm packing L7
Flow rate: 1.3 mL/min
Injection size: 80 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved at each time point *i*, (Q_i):

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

$$Q_4 = [(r_U/r_S) \times (C_S/L) \times (V - V_S) \times 100] + [Q_1 \times (V_S/V)]$$

$$Q_8 = [(r_U/r_S) \times (C_S/L) \times (V - 2V_S) \times 100] + [Q_1 \times (V_S/V)] + [Q_4 \times V_S/(V - V_S)]$$

$$Q_{16} = [(r_U/r_S) \times (C_S/L) \times (V - 3V_S) \times 100] + [Q_1 \times V_S/V)] + [Q_4 \times V_S/(V - V_S)] + [Q_8 \times V_S/(V - 2V_S)]$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of alprazolam in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = initial volume of *Medium*, 500 mL
V_S = volume of the sample withdrawn at each time point (mL)

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved			
	0.5-mg Tablet	1-mg Tablet	2-mg Tablet	3-mg Tablet
1	NMT 25%	NMT 25%	NMT 20%	NMT 20%
4	45%–60%	40%–55%	30%–50%	25%–45%
8	70%–90%	65%–85%	55%–75%	50%–70%
16	NLT 85%	NLT 85%	NLT 85%	NLT 80%

The percentages of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) released at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩. ● (RB 1-Aug-2011)

● **Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: pH 6.0 phosphate buffer (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water; adjust with phosphoric acid or potassium hydroxide to a pH of 6.0 ± 0.1); 500 mL, deaerated.
Apparatus 1: 100 rpm
Times: 1, 4, and 8 h for Tablets labeled to contain 0.5 mg or 1 mg; 1, 4, 8, and 16 h for Tablets labeled to contain 2 mg or 3 mg
Mobile phase: Acetonitrile and *Medium* (40:60)
Standard stock solution: 0.5 mg/mL of USP Alprazolam RS in methanol
Standard solution: (L/500) mg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, where L is the label claim in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter of 1-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 10-cm; 3-µm or 5-µm packing L7
Flow rate: 1 mL/min
Injection size: 100 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 5.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved at each time point *i*, (Q_i):

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

$$Q_4 = [(r_U/r_S) \times (C_S/L) \times (V - V_S) \times 100] + [Q_1 \times (V_S/V)]$$

$$Q_8 = [(r_U/r_S) \times (C_S/L) \times (V - 2V_S) \times 100] + [Q_1 \times (V_S/V)] + [Q_4 \times V_S/(V - V_S)]$$

$$Q_{16} = [(r_U/r_S) \times (C_S/L) \times (V - 3V_S) \times 100] + [Q_1 \times V_S/V)] + [Q_4 \times V_S/(V - V_S)] + [Q_8 \times V_S/(V - 2V_S)]$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of alprazolam in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = initial volume of *Medium*, 500 mL
V_S = volume of the sample withdrawn at each time point (mL)

Tolerances: See *Table 3*.

Table 3

Time (h)	Amount Dissolved			
	0.5-mg Tablet	1-mg Tablet	2-mg Tablet	3-mg Tablet
1	15%–35%	10%–30%	10%–30%	5%–25%
4	50%–75%	45%–65%	30%–55%	25%–50%
8	NLT 75%	NLT 70%	60%–80%	50%–75%
16	—	—	NLT 85%	NLT 80%

The percentages of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) released at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩. ● (RB 1-Aug-2011)

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**
Buffer: 5.4 g/L of monobasic potassium phosphate (KH_2PO_4) in water. Adjust with phosphoric acid to a pH of 3.4.
Solution A: Acetonitrile, methanol, and *Buffer* (27:10:63)
Solution B: Acetonitrile, methanol, and *Buffer* (7:3:10)
System suitability solution: 1 µg/mL each of USP Chlordiazepoxide Related Compound A RS, USP Alprazolam Related Compound A RS, and USP Nordazepam RS; and 0.4 µg/mL of USP Alprazolam RS in methanol
Standard solution: 0.4 µg/mL of USP Alprazolam RS in methanol

Sample solution: From NLT 20 Tablets ground to a fine powder, transfer an amount of powder to a suitable flask to obtain a nominal concentration of 0.2 mg/mL of alprazolam in methanol. [NOTE—Sonicate for 15 min to dissolve the contents.] Filter a portion, and discard the first 1 mL of filtrate.
Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	95	5
22	95	5
25	15	85
60	15	85
60.1	95	5
70	95	5

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Flow rate: 1.5 mL/min
Injection size: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times are listed in *Table 5*.]
Suitability requirements
Resolution: NLT 1.5 between nordazepam and alprazolam; NLT 1.5 between chlordiazepoxide related compound A and alprazolam related compound A, *System suitability solution*
Tailing factor: NMT 2.0 for the alprazolam peak, *System suitability solution*
Relative standard deviation: NMT 5%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

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

r_U = peak response of the impurity from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Alprazolam RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of alprazolam in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 5*)

Acceptance criteria See *Table 5*.

Table 5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Chlordiazepoxide related compound A[a,e]	0.36	1.0	—
USP Alprazolam Related Compound A RS[b]	0.45	0.7	0.5
Nordazepam[c,e]	0.8	1.0	—
Alprazolam	1.0	—	—
2-Amino-5-chlorobenzophenone	1.8	0.9	0.5
Amino-derivative[d]	2.2	1.2	0.5
Any other individual degradation product	—	1.0	0.2
Total impurities	—	—	2.0

[a] α-Chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide.
[b] 2-(2-Acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine.
[c] 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (reported as unspecified impurity).
[d] 7-Chloro-1-methyl-5-phenyl[1,2,4]triazolo[4,3-a]quinolin-4-amine.
[e] If present meets the requirement for any other individual degradation product.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at room temperature.

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.• (RB 1-Aug-2011)

- **USP REFERENCE STANDARDS** ⟨11⟩
USP Alprazolam RS
USP Alprazolam Related Compound A RS
2-(2-Acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine.
USP Chlordiazepoxide Related Compound A RS
7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide.
$C_{15}H_{11}ClN_2O_2$ 286.72
USP Nordazepam RS■1S *(USP34)*