Suitability requirements
Resolution: NLT 2.4 between acetaminophen and oxycodone
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of oxycodone ($C_{18}N_{21}NO_4$) in the portion of Tablets taken:

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

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

Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) in the portion of Tablets taken:

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

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

Acceptance criteria: 90.0%–110.0% of the labeled amount of oxycodone ($C_{18}H_{21}NO_4$), and 90.0%–110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$)

PERFORMANCE TESTS

- **DISSOLUTION,** *Procedure for a Pooled Sample* ⟨**711**⟩
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 45 min
Sample solution: Sample per *Dissolution* ⟨711⟩. Dilute with *Medium* as needed.
Analysis: Determine the amounts of oxycodone ($C_{18}H_{21}NO_4$) and acetaminophen ($C_8H_9NO_2$) dissolved, using the procedure in the *Assay*, and making any necessary volumetric adjustments, including adjusting the solution under test to a pH of about 5.5 before injecting.
Tolerances: NLT 75% (*Q*) of the labeled amounts of oxycodone ($C_{18}H_{21}NO_4$) and acetaminophen ($C_8H_9NO_2$) is dissolved.

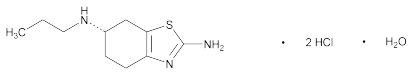
Change to read:

- **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩**:** ■Meet the requirements■2S *(USP35)*

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.
- **LABELING:** The Tablets may be labeled to indicate the content of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) equivalent. Each mg of oxycodone is equivalent to 1.116 mg of oxycodone hydrochloride.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Acetaminophen RS
USP Oxycodone RS

Pramipexole Dihydrochloride



$C_{10}H_{17}N_3S \cdot 2HCl \cdot H_2O$ 302.26
Benzothiazole-2,6-diamine, 4,5,6,7-tetrahydro-*N*⁶-propyl-, dihydrochloride, monohydrate, (*S*)-;
(*S*)-2-Amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate [191217-81-9].

DEFINITION

Pramipexole Dihydrochloride contains NLT 98.0% and NMT 102.0% of $C_{10}H_{19}Cl_2N_3S$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨**197A**⟩ or ⟨**197M**⟩
Wavelength range: ⟨197A⟩, 3800 cm^{-1} to 650 cm^{-1}; ⟨197M⟩, 4000 cm^{-1} to 600 cm^{-1}
- **B.** The retention time of the major peak in the *Sample solution* corresponds to that of pramipexole (*S*-enantiomer) in the *System suitability solution* in the test for *Enantiomeric Purity*.
- **C. IDENTIFICATION TESTS—GENERAL,** *Chloride* ⟨**191**⟩
Sample: 1 mg/mL of Pramipexole Dihydrochloride in water
Acceptance criteria: Meets the requirements of the silver nitrate precipitate test

ASSAY

- **PROCEDURE**
Solution A: Dissolve 9.1 g of potassium dihydrogen phosphate and 5.0 g of sodium 1-octanesulfonate monohydrate in 1 L of water. Adjust with phosphoric acid to a pH of 3.0.
Solution B: Acetonitrile and *Solution A* (1:1)
Diluent: Acetonitrile and *Solution A* (1:4)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	60	40
15	20	80
15.1	60	40
20	60	40

System suitability solution: 1.5 mg/mL of USP Pramipexole Dihydrochloride RS and 0.8 mg/mL of USP Pramipexole Related Compound A RS in *Diluent*
Standard solution: 1.5 mg/mL of USP Pramipexole Dihydrochloride RS in *Diluent*
Sample solution: 1.5 mg/mL of Pramipexole Dihydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)

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Mode: LC
Detector: UV 264 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 40 ± 5°
Flow rate: 1.5 mL/min
Injection volume: 5 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for pramipexole related compound A and pramipexole are about 0.7 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 6.0 between pramipexole related compound A and pramipexole, *System suitability solution*
Tailing factor: NMT 2.0 for pramipexole, *System suitability solution*
Relative standard deviation: NMT 1.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{10}H_{19}Cl_2N_3S$ in the portion of Pramipexole Dihydrochloride taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Pramipexole Dihydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)
M_{r1} = molecular weight of pramipexole dihydrochloride, 284.26
M_{r2} = molecular weight of pramipexole dihydrochloride monohydrate, 302.26
Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.10%
- **HEAVY METALS,** *Method I* ⟨**231**⟩
Standard solution: *Standard Lead Solution*, 10 ppm
Sample solution: Ash 2 g of Pramipexole Dihydrochloride until an almost dry, carbonized mass is obtained. Cool the residue, add 2.0 mL of concentrated nitric acid and 5 drops of concentrated sulfuric acid, and carefully allow the fumes to evolve. Ignite at 500°–600° until the carbon is completely burned off. Cool the residue, add 4 mL of 6 M hydrochloric acid, cover the crucible, and digest on a boiling water bath for 15 min. Evaporate to dryness. Add one drop of concentrated hydrochloric acid and 10 mL of hot water, and digest for a further 2 min on the boiling water bath. Add 6 M ammonia solution dropwise until the solution is weakly alkaline, and adjust with 1 M acetic acid to a pH of 3.0–4.0. Filter the solution into a 25-mL volumetric flask, and dilute with water to 25 mL by washing the crucible and the filter.
Acceptance criteria: NMT 10 ppm
- **ORGANIC IMPURITIES**
Solution A, Solution B, Diluent, Mobile phase, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability solution: 7.5 µg/mL of USP Pramipexole Dihydrochloride RS and 3 µg/mL of USP Pramipexole Related Compound A RS in *Diluent*
Standard solution: 1.5 µg/mL of USP Pramipexole Dihydrochloride RS in *Diluent*
Sample solution: 1.5 mg/mL of Pramipexole Dihydrochloride in *Diluent*
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 6.0 between pramipexole related compound A and pramipexole, *System suitability solution*
Tailing factor: NMT 2.0 for pramipexole, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of any individual impurity in the portion of Pramipexole Dihydrochloride taken:

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

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of pramipexole from the *Standard solution*
C_S = concentration of USP Pramipexole Dihydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of pramipexole dihydrochloride monohydrate in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of pramipexole dihydrochloride, 284.26
M_{r2} = molecular weight of pramipexole dihydrochloride monohydrate, 302.26
Acceptance criteria
Individual impurities: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Pramipexole propionamide[a]	0.5	0.15
Pramipexole related compound A[b]	0.7	0.15
Pramipexole	1.0	—
N-Propylpramipexole[c]	1.4	0.15
Pramipexole dimer[d]	1.7	0.15
Any other unidentified individual impurity	—	0.10
Total impurities	—	0.5

[a] (*S*)-*N*-(2-Amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)propionamide.
[b] (*S*)-4,5,6,7-Tetrahydrobenzothiazole-2,6-diamine.
[c] (*S*)-2,6-Dipropylamino-4,5,6,7-tetrahydrobenzothiazole.
[d] $N^6,N^{6\prime}$-[2-Methylpentane-1,3-diyl]bis(4,5,6,7-tetrahydrobenzothiazole-2,6-diamine). This is a dimer of pramipexole (a mixture of four possible isomers).

SPECIFIC TESTS

Change to read:

- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** NLT 4.5% and NMT •7.0%• (RB 1-Dec-2011)
- **ENANTIOMERIC PURITY**
Mobile phase: *n*-Hexane, dehydrated alcohol, and diethylamine (850:150:1)
System suitability stock solution: 1 mg/mL each of USP Pramipexole Dihydrochloride RS and USP Pramipexole Related Compound D RS in dehydrated alcohol
System suitability solution: 0.01 mg/mL each of USP Pramipexole Dihydrochloride RS and USP Pramipexole Related Compound D RS from *System suitability stock solution* in *Mobile phase*
Standard stock solution: 2.0 mg/mL of USP Pramipexole Related Compound D RS in dehydrated alcohol

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Standard solution: 1.5 µg/mL of USP Pramipexole Related Compound D RS in *Mobile phase* from *Standard stock solution*
Sample solution: 0.3 mg/mL, prepared by dissolving a suitable weighed quantity of Pramipexole Dihydrochloride in 25% of a flask volume of dehydrated alcohol and diluting with *Mobile phase* to volume
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; 10-µm packing L51
Flow rate: 1.5 mL/min
Injection volume: 75 µL
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for pramipexole related compound D (*R*-enantiomer) and pramipexole (*S*-enantiomer) are 0.5 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 5.0 between pramipexole related compound D and pramipexole, *System suitability solution*
Tailing factor: NMT 2.4 for pramipexole, *System suitability solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of pramipexole related compound D in the portion of Pramipexole Dihydrochloride taken:

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

r_U = peak response of pramipexole related compound D from the *Sample solution*
r_S = peak response of pramipexole related compound D from the *Standard solution*
C_S = concentration of pramipexole related compound D in the *Standard solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)
Acceptance criteria: NMT 1.0% of pramipexole related compound D

- **LIMIT OF PALLADIUM**

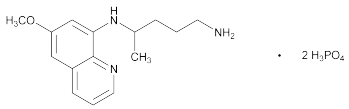
[NOTE—Perform this test if palladium is a known inorganic impurity.]
Diluent: 0.1 M hydrochloric acid
Standard solution: 40 µg/L of palladium in *Diluent*, from commercially available palladium standard solution for atomic absorption/inductively coupled plasma. [NOTE—Freshly prepare this solution as required on the day of use.]
Sample solution: To 0.5 g of Pramipexole Dihydrochloride in a 50-mL volumetric flask add 5.00 mL of 1 M hydrochloric acid, and dissolve with heating. Cool to room temperature, and dilute with water to volume.
Spectrometric conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩).
Mode: Atomic absorption spectrophotometry
Analytical wavelength: Palladium emission line at 247.6 nm
Lamp: Hollow cathode
Atomization source: Graphite furnace. [NOTE—Follow the manufacturer's recommended programming sequence.]
Sample size: 20 µL
Blank: *Diluent*
System suitability
Sample: *Standard solution*
Suitability requirements
Absorbance: NLT 0.034
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the concentration of palladium in the *Sample solution* by the standard addition method.
Acceptance criteria: NMT 5 µg/g

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from moisture and light.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Pramipexole Dihydrochloride RS. [NOTE—Supplied in monohydrate form.]
USP Pramipexole Related Compound A RS
(*S*)-4,5,6,7-Tetrahydrobenzothiazole-2,6-diamine.
$C_7H_{11}N_3S$ 169.25
USP Pramipexole Related Compound D RS
(*R*)-2-Amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole.
$C_{10}H_{17}N_3S$ 211.33

Primaquine Phosphate



$C_{15}H_{21}N_3O \cdot 2H_3PO_4$ 455.34
1,4-Pentanediamine, N^4-(6-methoxy-8-quinolinyl)-, (±)-, phosphate (1:2);
(±)-8-[(4-Amino-1-methylbutyl)amino]-6-methoxyquinoline phosphate (1:2) [63-45-6].

DEFINITION

Change to read:

Primaquine Phosphate contains •NLT 97.0% and NMT 102.0%• (RB 1-Jan-2012) of primaquine phosphate ($C_{15}H_{21}N_3O \cdot 2H_3PO_4$), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩**:** Meets the requirements
- **B.** The residue obtained by ignition meets the requirements of the test for pyrophosphate, as described in *Identification Tests—General* ⟨191⟩, *Phosphate*.
- **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **PROCEDURE**

▲Mobile phase: Acetonitrile, tetrahydrofuran, trifluoroacetic acid, and water (9: 1: 0.1: 90)
Standard solution: 0.4 mg/mL of USP Primaquine Phosphate RS in *Mobile phase*. [NOTE—Sonicate with intermittent shaking to dissolve, if necessary.]
System suitability stock solution: 0.4 mg/mL of USP Primaquine Related Compound A RS in *Mobile phase*
System suitability solution: Transfer 1.0 mL of the *System suitability stock solution* to a 10-mL volumetric flask, and dilute with *Standard solution* to volume.
Sensitivity solution: 0.2 µg/mL of USP Primaquine Phosphate RS from the *Standard solution*
Sample solution: 0.4 mg/mL in *Mobile phase*. [NOTE—Sonicate with intermittent shaking to dissolve, if necessary.]
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)

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