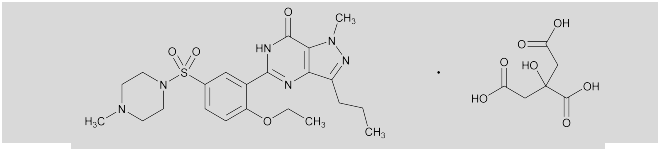
Add the following:

▪Sildenafil Citrate



$C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$ 666.70

Piperazine, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1); 1-[[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate (1:1) [171599-83-0].

Sildenafil

$C_{22}H_{30}N_6O_4S$ 474.58

[139755-83-2].

DEFINITION

Sildenafil Citrate contains NLT 98.0% and NMT 102.0% of sildenafil citrate ($C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

• **A. INFRARED ABSORPTION** ⟨197K⟩

ASSAY

• **PROCEDURE**

Buffer: Dilute 7 mL of triethylamine with water to 1 L. Stir, and adjust with phosphoric acid to a pH of 3.0 ± 0.1.

Mobile phase: *Buffer*, methanol, and acetonitrile (58:25:17)

Standard solution: 0.028 mg/mL of USP Sildenafil Citrate RS in *Mobile phase*

Sample solution: 0.028 mg/mL of Sildenafil Citrate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 290 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 0.85% for six replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of sildenafil citrate ($C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$) in the portion of the sample taken:

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

r_U = peak response of sildenafil from the *Sample solution*

r_S = peak response of sildenafil from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **HEAVY METALS,** *Method II* ⟨231⟩**:** NMT 20 ppm

• **RESIDUE ON IGNITION** ⟨281⟩

Sample: NLT 0.5 g

Acceptance criteria: NMT 0.1%

• **LIMIT OF IMIDAZOLE**

Diluent: Methanol, water, and ammonium hydroxide (15:5:1)

Standard solution 1: 0.035 mg/mL of USP Imidazole RS in *Diluent*

Standard solution 2: 0.0175 mg/mL of USP Imidazole RS in *Diluent* from *Standard solution 1*

Sample solution: 17.5 mg/mL of Sildenafil Citrate in *Diluent*

System suitability solution: Mix equal volumes of *Sample solution* and *Standard solution 1*.

Chromatographic system

(See *Chromatography* ⟨621⟩, *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.2-mm layer of chromatographic silica gel mixture with a particle size of 2–10 µm (HPTLC plates)

Application volume: 10 µL. [NOTE—Apply as 6-mm bands.]

Developing solvent system: Methylene chloride, ethyl acetate, alcohol, and ammonium hydroxide (50:30:20:1)

System suitability

Sample: *System suitability solution*

Suitability requirements: The chromatogram shows two clearly separated zones.

Analysis:

Samples: *Standard solution 2* and *Sample solution*

Develop the plate over a distance of about two-thirds of the length of the plate. Dry at 100° for about 15 min, and cool. Expose the plate to iodine vapor until the plate is light brown, and examine the plate under UV light at 254 nm. [NOTE—The retardation factors for citrate, imidazole, and sildenafil are about 0, 0.25, and 0.4, respectively.]

Acceptance criteria: Any spot corresponding to imidazole in the *Sample solution* is not more intense than the principal spot from *Standard solution 2* (0.1%).

• **ORGANIC IMPURITIES**

Buffer, **Mobile phase**, and **Chromatographic system:** Proceed as directed in the *Assay*, except to run the chromatograph for 3 times the retention time of sildenafil.

Identification solution: 7.5 µg/mL of USP Sildenafil Related Compound A RS in *Mobile phase*

System suitability solution: Dissolve 70 mg of Sildenafil Citrate in 1 mL of a solution of hydrogen peroxide and anhydrous formic acid (2:1). Allow to stand for at least 10 min to generate sildenafil *N*-oxide, and then dilute with *Mobile phase* to 250 mL.

Sample solution: 0.7 mg/mL of Sildenafil Citrate in *Mobile phase*

Diluted sample solution: 1.4 µg/mL of sildenafil citrate in *Mobile phase* from the *Sample solution*

Sensitivity solution: 0.35 µg/mL of sildenafil citrate in *Mobile phase* from the *Diluted sample solution*

System suitability

Samples: *Diluted sample solution*, *Sensitivity solution*, and *System suitability solution*

[NOTE—The relative retention times for sildenafil, sildenafil *N*-oxide, and sildenafil related compound A are about 1.0, 1.2, and 1.7, respectively.]

Suitability requirements

Resolution: NLT 2.5 between sildenafil *N*-oxide and sildenafil, *System suitability solution*

Tailing factor: NMT 1.5 for the sildenafil peak, *Diluted sample solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Identification solution*, *Diluted sample solution*, and *Sample solution*

[NOTE—Identify sildenafil related compound A from the *Identification solution*.]

Calculate the percentage of sildenafil related compound A and any other unspecified individual impurity in the portion of Sildenafil Citrate taken:

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

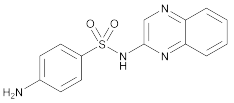
r_U = peak response of sildenafil related compound A or any other unspecifed impurity from the *Sample solution*
r_S = peak response of sildenafil from the *Diluted sample solution*
C_S = concentration of the *Diluted sample solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria
Sildenafil related compound A: NMT 0.3%
Any other unspecified individual impurity: NMT 0.10%
Total unspecified impurities: NMT 0.3%
Total impurities: NMT 0.5%. Disregard any peak less than 0.05%.

SPECIFIC TESTS
• **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** NMT 2.5%

ADDITIONAL REQUIREMENTS
• **PACKAGING AND STORAGE:** Preserve in air-tight containers, and store at room temperature.
• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Imidazole RS
$C_3H_4N_2$ 68.08
USP Sildenafil Citrate RS
USP Sildenafil Related Compound A RS
5-[2-Ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-(2-methylpropyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one.
$C_{23}H_{32}N_6O_4S$ 488.60■2S (USP35)

Sulfaquinoxaline



$C_{14}H_{12}N_4O_2S$ 300.34
N^1-2-Quinoxalinylsulfanilamide [59-40-5].

DEFINITION
Sulfaquinoxaline contains NLT 98.0% and NMT 101.0% of $C_{14}H_{12}N_4O_2S$, calculated on the dried basis.

IDENTIFICATION
• **A. INFRARED ABSORPTION** ⟨**197K**⟩
• **B. ULTRAVIOLET ABSORPTION** ⟨**197U**⟩
Sample solution: 10 µg/mL in 0.01 N sodium hydroxide
Acceptance criteria: Meets the requirements

Delete the following:

■• **C.**
Sample: 4 mg
Analysis: Dissolve the *Sample* in 2 mL of 2 N hydrochloric acid, add 0.2 mL of 10 mg/mL sodium nitrite solution, and allow to stand for 2 min. Add the solution to 1 mL of 2-naphthol TS.
Acceptance criteria: An orange-red precipitate is formed.■2S (USP35)

ASSAY

Change to read:

• **PROCEDURE**
Mobile phase: 2 g/L of monobasic ammonium phosphate in a mixture of acetonitrile, glacial acetic acid, tetrahydrofuran, ammonium hydroxide, and water (400:10:5:2:583). Pass through a filter of 0.5-µm or finer pore size.
Standard solution: ■0.06 mg/mL■2S (USP35) of USP Sulfaquinoxaline RS in 0.01 N sodium hydroxide
Sample solution: ■0.06 mg/mL■2S (USP35) of Sulfaquinoxaline in 0.01 N sodium hydroxide
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4-mm × 25-cm; packing L1
Flow rate: 1 mL/min
Injection size: 15 µL
System suitability
Sample: *Standard solution*
Suitability requirements
■■2S (USP35)
Tailing factor: NMT 1.2
Relative standard deviation: ■NMT 1.0%■2S (USP35)
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of sulfaquinoxaline ($C_{14}H_{12}N_4O_2S$) in the portion of Sulfaquinoxaline 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 Sulfaquinoxaline RS in the *Standard solution* (mg/mL)
C_U = concentration of Sulfaquinoxaline in the *Sample solution* (mg/mL)
Acceptance criteria: 98.0%–101.0% on the dried basis

IMPURITIES
• **RESIDUE ON IGNITION** ⟨**281**⟩**:** NMT 0.1%
• **HEAVY METALS,** *Method II* ⟨**231**⟩**:** 20 ppm
• **ORGANIC IMPURITIES**
Sample solution: 4 mg/mL, prepared as follows. Dissolve 400 mg of Sulfaquinoxaline in 4 mL of 1 N sodium hydroxide, dilute with methanol to 100 mL, and mix.
Standard solution A: 0.12 mg/mL of USP Sulfaquinoxaline Related Compound A RS in methanol
Standard solution B: 0.04 mg/mL of sulfanilamide in methanol
Chromatographic system
(See *Chromatography* ⟨621⟩, *Thin-Layer Chromatography*.)
Mode: TLC
Adsorbent: 0.25-mm layer of chromatographic silica gel mixture
Application volume: 5 µL
Developing solvent system: Chloroform, methanol, and ammonium hydroxide (60:40:20)
Analysis: Separately apply each solution to the TLC plate, and proceed as directed in the chapter. When the solvent front has moved about three-fourths the length of the plate, remove the plate from the chamber, mark the solvent front, allow it to air-dry, and examine the plate under short-wavelength UV light.
Acceptance criteria: No spot corresponding to sulfaquinoxaline related compound A in the chromatogram of the *Sample solution* is more intense than the principal spot in the chromatogram of *Standard solution A* (NMT 3.0%); and no spot, other than the principal spot and the sulfaquinoxaline related