sion of the residue: it exhibits maxima only at the same wavelengths as that of a similar preparation of USP Glycine RS .

Bacterial endotoxins ⟨85⟩**—**It contains not more than 0.5 Endotoxin Unit per mL.

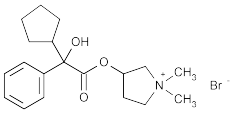
pH ⟨791⟩: between 4.5 and 6.5, determined potentiometrically on a portion to which 0.3 mL of saturated potassium chloride has been added for each 100 mL.

Other requirements—It meets the requirements under *Injections* ⟨1⟩, except that the container in which the solution is packaged may be designed to empty rapidly and may exceed 1000 mL in capacity.

Assay—Dilute an accurately measured volume of Irrigation, equivalent to about 150 mg of glycine, with water to 25 mL, and add 10 mL of formaldehyde TS, previously adjusted to a pH of 9.0, and 5 drops of mixed indicator solution (prepared by dissolving 75 mg of phenolphthalein and 25 mg of thymol blue in a mixture of equal volumes of alcohol and water to make 100 mL). Titrate with 0.1 N sodium hydroxide VS until the yellow color disappears and a faint violet color appears. Each mL of 0.1 N sodium hydroxide is equivalent to 7.507 mg of glycine ($C_2H_5NO_2$).

Glycopyrrolate

Change to read:



$C_{19}H_{28}BrNO_3$ 398.33

Pyrrolidinium, 3-[▲(*SR*)-▲*USP35*(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, ▲[*RS*-]▲*USP35* bromide; ▲(*RS*)-[3-(*SR*)-Hydroxy-1,1-dimethylpyrrolidinium bromide] α-cyclopentylmandelate▲*USP35* [596-51-0].

DEFINITION

Change to read:

Glycopyrrolate ▲▲*USP35* contains NLT 98.0% and NMT ▲102.0%▲*USP35* of $C_{19}H_{28}BrNO_3$, ▲calculated on the dried basis.▲*USP35*

IDENTIFICATION

• **A. Infrared Absorption** ⟨197K⟩

Change to read:

• **B.** ▲The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲*USP35*

• **C. Identification Tests—General,** *Bromide* ⟨191⟩
Sample solution: 25 mg/mL
Acceptance criteria: Meets the requirements

ASSAY

Change to read:

• **Procedure**
▲**Buffer:** Prepare a solution of 1.0 g of anhydrous sodium sulfate and 200 mg of sodium 1-hexanesulfonate monohydrate in 650 mL of water. To this solution add 3.0 mL of 1 N sulfuric acid, and mix.
Mobile phase: Acetonitrile, methanol, and *Buffer* (20:15:65)
Standard solution: 0.1 mg/mL of USP Glycopyrrolate RS in *Mobile phase*
Sample solution: 0.1 mg/mL of Glycopyrrolate in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 222 nm
Column: 4.6-mm × 15-cm; 5-μm packing L1
Column temperature: 40°
Flow rate: 1.2 mL/min
Injection size: 50 μL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 1.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of glycopyrrolate ($C_{19}H_{28}BrNO_3$) in the portion of Glycopyrrolate taken:

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

r_U = peak response of Glycopyrrolate from the *Sample solution*
r_S = peak response of glycopyrrolate from the *Standard solution*
C_S = concentration of USP Glycopyrrolate RS in the *Standard solution* (mg/mL)
C_U = concentration of Glycopyrrolate in the *Sample solution* (mg/mL)
Acceptance criteria: 98.0%–102.0% on the dried basis ▲*USP35*

IMPURITIES

• **Residue on Ignition** ⟨281⟩**:** NMT 0.3%

Delete the following:

▲• **Ordinary Impurities** ⟨466⟩
Standard solutions: 0.05, 0.25, 0.5, and 1.0 mg/mL in alcohol
Sample solution: 50 mg/mL in alcohol
Eluant: A mixture of ethyl acetate, water, and anhydrous formic acid (74:16:10)
Adsorbent: Chromatographic silica gel
Application volume: 5 μL
Visualization: Dry the plate at 105 ° for 15 min, followed by Visualization Technique 3; then air-dry the developed plate at room temperature for 2 h.
Acceptance criteria: The intensity of any secondary spot of the *Sample solution* corresponds to NMT 0.5%, and the sum of the intensities of all secondary spots of the *Sample solution* corresponds to NMT 2.0%. ▲*USP35*

Add the following:

▲• **Organic Impurities**
Buffer: Prepare a solution of 1.0 g of anhydrous sodium sulfate and 200 mg of sodium 1-hexanesulfonate monohydrate in 650 mL of water. To this solution add 3.0 mL of 1 N sulfuric acid, and mix.
Diluent: Prepare a solution of 1.0 g of anhydrous sodium sulfate, 6.8 g of monobasic potassium phosphate, and 200 mg of sodium 1-hexanesulfonate monohydrate in 650 mL of water. To this solution add 3.0 mL of 1 N sulfuric acid, 150 mL of methanol, and 200 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.8.

Solution A: Acetonitrile, methanol, and *Buffer* (20:15:65)
Solution B: Acetonitrile, methanol, and *Buffer* (50:15:35)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
10	100	0
25	10	90
35	10	90
37	100	0
45	100	0

Standard solution: 1.5 µg/mL each of USP Glycopyrrolate RS, USP Glycopyrrolate Related Compound A RS, USP Glycopyrrolate Related Compound B RS, and USP Glycopyrrolate Related Compound C RS in *Diluent*. Sonicate, if necessary, to facilitate dissolution.
Sample solution: 1.0 mg/mL of Glycopyrrolate in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 222 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1 mL/min
Injection size: 50 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between glycopyrrolate and glycopyrrolate related compound B
Tailing factor: NMT 2.0 for the glycopyrrolate peak
Relative standard deviation: NMT 6.0% for each peak
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of glycopyrrolate related compounds A, B, and C in the portion of Glycopyrrolate taken:

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

r_U = peak response of each related compound from the *Sample solution*
r_S = peak response of the corresponding related compound from the *Standard solution*
C_S = concentration of the corresponding related compound in the *Standard solution* (mg/mL)
C_U = concentration of Glycopyrrolate in the *Sample solution* (mg/mL)

Calculate the percentage of any other individual impurity in the portion of Glycopyrrolate taken:

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

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of glycopyrrolate from the *Standard solution*
C_S = concentration of USP Glycopyrrolate RS in the *Standard solution* (mg/mL)
C_U = concentration of Glycopyrrolate in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
5-Nitroisophthalic acid[a]	0.45	0.15
Glycopyrrolate	1.00	—
Glycopyrrolate base[b]	1.14	0.15
Cyclopentylmandelic acid[c]	2.68	0.15
Any other individual impurity	—	0.10
Total impurities	—	0.50

[a] Glycopyrrolate related compound A.
[b] Glycopyrrolate related compound B.
[c] Glycopyrrolate related compound C.

▲*USP35*

Add the following:

▲• **LIMIT OF ERYTHRO ISOMER**
Buffer: 2.8 g/L of monobasic sodium phosphate in water. Adjust with a sodium hydroxide solution (1 in 10) to a pH of 6.50 ± 0.05.
Mobile phase: Methanol, acetonitrile, and *Buffer* (50:10:40)
System suitability solution: 40 µg/mL each of USP Glycopyrrolate Erythro Isomer RS and USP Glycopyrrolate RS in *Mobile phase*
Standard solution: 10 µg/mL of USP Glycopyrrolate RS in *Mobile phase*
Sample solution: 500 µg/mL of Glycopyrrolate in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 222 nm
Column: 4.0-mm × 25-cm; 5-µm packing L45
Column temperature: 30°
Flow rate: 1 mL/min
Injection size: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.2 between the erythro isomer and glycopyrrolate, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 6.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of erythro isomer in the portion of Glycopyrrolate taken:

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

r_U = peak response of the erythro isomer from the *Sample solution*
r_S = peak response of glycopyrrolate from the *Standard solution*
C_S = concentration of USP Glycopyrrolate RS in the *Standard solution* (mg/mL)
C_U = concentration of Glycopyrrolate in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Erythro isomer (*R, R/S, S*-glycopyrrolate)[a]	0.89	0.4
Glycopyrrolate	1.00	—

[a] USP Glycopyrrolate Erythro Isomer RS.

▲*USP35*

SPECIFIC TESTS

Delete the following:

▲• **MELTING RANGE OR TEMPERATURE,** *Class I* ⟨**741**⟩**:** 193°–198°, but the range between beginning and end of melting does not exceed 2°.▲*USP35*

• **LOSS ON DRYING** ⟨**731**⟩**:** Dry at 105° for 3 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in tight containers. ▲Store at room temperature. ▲*USP35*

Change to read:

• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Glycopyrrolate RS
▲USP Glycopyrrolate Related Compound A RS
5-Nitrobenzene-1,3-dicarboxylic acid.
$C_8H_5NO_6$ 211.13
USP Glycopyrrolate Related Compound B RS
1-Methylpyrrolidin-3-yl-2-cyclopentyl-2-hydroxy-2-phenylacetate.
$C_{18}H_{25}NO_3$ 303.40
USP Glycopyrrolate Related Compound C RS
2-Cyclopentyl-2-hydroxy-2-phenylacetic acid.
$C_{13}H_{16}O_3$ 220.26
USP Glycopyrrolate Erythro Isomer RS
(*RS*)-3-[(*RS*)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy]-1,1-dimethylpyrrolidinium bromide.
$C_{19}H_{28}BrNO_3$ 398.33

▲*USP35*

Glycopyrrolate Injection

» Glycopyrrolate Injection is a sterile solution of Glycopyrrolate in Water for Injection. It contains not less than 93.0 per cent and not more than 107.0 percent of the labeled amount of glycopyrrolate ($C_{19}H_{28}BrNO_3$).

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of Type I glass.

USP Reference standards ⟨11⟩**—**
USP Endotoxin RS
USP Glycopyrrolate RS

Identification—

Spray reagent—Dissolve 2 g of bismuth subnitrate in a solution consisting of 100 mL of water and 25 mL of glacial acetic acid (*Solution A*). Dissolve 40 g of potassium iodide in 100 mL of water (*Solution B*). Add 10 mL of *Solution A* and 10 mL of *Solution B* to a solution consisting of 100 mL of water and 20 mL of glacial acetic acid, and mix.

Procedure—Pipet an amount of Injection equivalent to about 1 mg of glycopyrrolate into a 10-mL volumetric flask, dilute with water to volume, and mix to obtain the test solution. Prepare a Standard solution of USP Glycopyrrolate RS in water containing about 0.1 mg of glycopyrrolate per mL. Apply 30 µL of the test solution and 30 µL of the Standard solution to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of butyl alcohol, glacial acetic acid, and water (3:1:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, and allow to air-dry. Spray the plate with *Spray reagent*, and allow to air-dry: the R_F value and color of the principal spot obtained from the test solution correspond to those obtained from the Standard solution.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 555.5 USP Endotoxin Units per mg of glycopyrrolate.

pH ⟨791⟩: between 2.0 and 3.0.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase—Dissolve 1.0 g of anhydrous sodium sulfate and 200 mg of sodium 1-pentanesulfonate in 615 mL of water in a 1000-mL volumetric flask. Add 3.0 mL of 1 N sulfuric acid, 235 mL of acetonitrile, and 150 mL of methanol, and mix. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Glycopyrrolate RS in *Mobile phase*, and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 0.2 mg per mL.

Resolution solution—Prepare a solution of benzaldehyde in *Mobile phase* containing about 0.5 mg per mL. Transfer 2.0 mL of this solution to a 25-mL volumetric flask, dilute with *Standard preparation* to volume, and mix.

Assay preparation—Dilute a volume of Injection, quantitatively if necessary, with *Mobile phase* to obtain a solution having a concentration of about 0.2 mg of glycopyrrolate per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 222-nm detector and a 3.9-mm × 30-cm column containing packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed under *Procedure:* the resolution, *R,* between the benzaldehyde and glycopyrrolate peaks is not less than 3.0. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 35 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of glycopyrrolate ($C_{19}H_{28}BrNO_3$) in each mL of the Injection taken by the formula:

$$C(L / D)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Glycopyrrolate RS in the *Standard preparation; L* is the labeled quantity, in mg per mL, of glycopyrrolate in the Injection; *D* is the concentration, in mg per mL, of glycopyrrolate in the *Assay preparation,* on the basis of the labeled quantity and the extent of dilution; and r_U and r_S are the glycopyrrolate peak responses