internal standard for the *Assay preparation* and the *Standard preparation,* respectively.

Phenylephrine Bitartrate

$C_9H_{13}NO_2 \cdot C_4H_6O_6$ 317.3

R-2-(Methylamino)-1-(3-hydroxyphenyl)ethanol-, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1) (salt).

(–)-1-(3-Hydroxyphenyl)-2-methylaminoethanol, hydrogen tartrate.

(–)-3 Hydroxy-α-[(methylamino)methyl]benzenemethanol, hydrogen tartrate.

1-*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol, hydrogen tartrate [17162-39-9].

» Phenylephrine Bitartrate contains not less than 99.0 percent and not more than 100.5 percent of $C_9H_{13}NO_2 \cdot C_4H_6O_6$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—**
USP Norphenylephrine Hydrochloride RS
USP Phenylephrine Hydrochloride RS

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The alkaline filtrate from the test for *Specific rotation* responds positively to the test for *Tartrate* ⟨191⟩.

Specific rotation ⟨781S⟩**:** between –53° and –57° for the prepared sample.

Test solution—Prepare a sample solution of about 240 mg per mL in water. Make the solution slightly alkaline by adding concentrated ammonium hydroxide dropwise. Rub the wall of the vessel with a glass rod so that the base precipitates out. Filter the base under suction, wash with a little water and acetone, and dry at 105° for 2 hours. Prepare and measure a 50 mg per mL solution of base precipitate in 1 M hydrochloric acid.

pH ⟨791⟩**:** between 3.0 and 4.0 in 10% w/v aqueous solution.

Loss on drying ⟨731⟩**—**Dry at 105° to a constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Chromatographic purity—

Buffer solution—Dissolve 3.25 g of 1-octanesulfonic acid sodium salt monohydrate in 1 L of water. Adjust slowly with 3 M phosphoric acid to a pH of 2.8.

Solution A—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (9:1).

Solution B—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (9:1).

Diluent—Prepare a mixture of *Solution A* and *Solution B* (8:2).

System suitability solution—Dissolve accurately weighed quantities of USP Phenylephrine Hydrochloride RS and USP Norphenylephrine Hydrochloride RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 1.0 mg per mL and 0.9 μg per mL, respectively.

Blank solution—Prepare a solution containing 0.8 mg per mL L(+)-tartaric acid in *Diluent*.

Test solution—Transfer 78 mg of Phenylephrine Bitartrate, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4-mm × 5.5-cm column that contains packing L1. The column and injection port temperatures are maintained at 45 ± 2°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	93	7	equilibration
0–10	93→70	7→30	linear gradient
10–10.1	70→93	30→7	linear gradient
10.1–18	93	7	equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between norphenylephrine and (–)-phenylephrine is not less than 1.5; the tailing factor of (–)-phenylephrine is less than 1.8; and the relative standard deviation for replicate injections is not more than 5%.

Procedure—Separately inject equal volumes (about 4 μL) of the *Blank solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Phenylephrine Bitartrate taken by the formula:

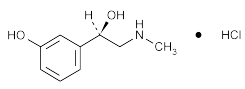
$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks. [NOTE—Examine the chromatogram of the *Blank solution* for peaks and disregard any corresponding peaks observed in the chromatogram of the *Test solution.*] The limits of impurities are specified in the accompanying table.

Compound	Approximate Relative Retention Time	Limit (%)
Phenylephrine	1.0	—
Norphenylephrine	0.9	0.2
Phenylephrone	1.2	0.1
Benzylphenylephrine	2.9	0.2
Benzylphenylephrone	3.1	0.1
Individual unknown impurity	—	0.1
Total impurity	—	0.5

Assay—Transfer about 280 mg of Phenylephrine Bitartrate, accurately weighed, to a 100-mL beaker, and dissolve by stirring in 60 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank determination (see *Titrimetry* ⟨541⟩), and make the necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 31.73 mg of $C_9H_{13}NO_2 \cdot C_4H_6O_6$.

Phenylephrine Hydrochloride



$C_9H_{13}NO_2 \cdot HCl$ 203.67

Benzenemethanol, 3-hydroxy-α-[(methylamino)methyl]-, hydrochloride (*R*)-.

(–)-*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride [61-76-7].

» Phenylephrine Hydrochloride contains not less than 97.5 percent and not more than 102.5 percent of $C_9H_{13}NO_2 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at 25°, excursions permitted between 15°and 30°.

USP Reference standards ⟨11⟩**—**
USP Phenylephrine Hydrochloride RS

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: A solution (1 in 100) responds to the tests for *Chloride* ⟨191⟩.

Melting range ⟨741⟩**:** between 140° and 145°.

Specific rotation ⟨781S⟩**:** between –42° and –47.5°.

Test solution: 50 mg per mL, in water.

Loss on drying ⟨731⟩**—**Dry it at 105° for 2 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.2%.

Sulfate ⟨221⟩**—**A solution of 50 mg in 25 mL of water shows no more turbidity than corresponds to 0.10 mL of 0.020 N sulfuric acid (0.20%).

Limit of ketones—Dissolve 200 mg in 1 mL of water, add 2 drops of sodium nitroferricyanide TS, then add 1 mL of 1 N sodium hydroxide, followed by 0.6 mL of glacial acetic acid: the color of the final solution is not deeper than that obtained in a control solution prepared with 1 mL of dilute acetone (1 in 2000).

Chromatographic purity—

Standard preparations—Dissolve an accurately weighed quantity of USP Phenylephrine Hydrochloride RS in methanol to obtain a solution having a known concentration of 1 mg per mL. Quantitatively dilute with methanol to obtain *Standard preparations* having the following compositions:

Standard Preparation	Dilution	Concentration (µg RS per mL)	Percentage (%, for comparison with test specimen)
A	(1 in 2)	500	1.0
B	(1 in 4)	250	0.5
C	(1 in 10)	100	0.2
D	(1 in 20)	50	0.1

Test preparation—Dissolve an accurately weighed quantity of Phenylephrine Hydrochloride in methanol to obtain a solution containing 50 mg per mL.

Procedure—Apply separately 5 µL of the *Test preparation* and 5 µL of each *Standard preparation* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Position the plate in a chromatographic chamber and develop the chromatograms in a solvent system consisting of a mixture of *n*-butyl alcohol, water, and formic acid (7:2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate in warm, circulating air. Examine the plate under short-wavelength UV light. Then spray the plate with a saturated solution of *p*-nitrobenzenediazonium tetrafluoroborate followed by sodium carbonate solution (1 in 10). Compare the intensities of any secondary spots observed in the chromatogram of the *Test preparation* with those of the principal spots in the chromatograms of the *Standard preparations:* the sum of the intensities of secondary spots obtained from the *Test preparation* corresponds to not more than 1.0% of related compounds, with no single impurity corresponding to more than 0.5%.

Chloride content—Dissolve about 300 mg, accurately weighed, in 5 mL of water. Add 5 mL of glacial acetic acid and 50 mL of methanol, then add eosin Y TS, and titrate with 0.1 N silver nitrate VS. Each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of Cl. Not less than 17.0% and not more than 17.7% of Cl is found, calculated on the dried basis.

Assay—Dissolve about 100 mg of Phenylephrine Hydrochloride, accurately weighed, in 20 mL of water contained in an iodine flask, add 50.0 mL of 0.1 N bromine VS, then add 5 mL of hydrochloric acid, and immediately insert the stopper. Shake the flask, and allow to stand for 15 minutes. Introduce quickly 10 mL of potassium iodide solution (1 in 10), allow to stand for 5 minutes, shake thoroughly, remove the stopper, and rinse it and the neck of the flask with a small quantity of water into the flask. Titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached, signaled by the color change of the solution from reddish-brown to faint yellow. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 0.1 N bromine is equivalent to 3.395 mg of $C_9H_{13}NO_2 \cdot HCl$.

Phenylephrine Hydrochloride Injection

» Phenylephrine Hydrochloride Injection is a sterile solution of Phenylephrine Hydrochloride in Water for Injection. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_9H_{13}NO_2 \cdot HCl$.

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

USP Reference standards ⟨11⟩**—**
USP Endotoxin RS
USP Phenylephrine Hydrochloride RS

Identification—Concentrate or dilute, if necessary, a suitable volume of Injection to a concentration of about 10 mg per mL. Apply 2 µL of this solution and of a Standard solution of USP Phenylephrine Hydrochloride RS, containing about 10 mg per mL, at points about 2.5 cm from the bottom edge of a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel. Dry the spots in a current of warm air, and develop the chromatogram in a suitable chromatographic chamber with a mixture of methanol, water, and ammonium hydroxide (72:25:3) until the solvent front has moved about 12 cm. Dry the plate in warm air, and spray it with alcoholic potassium hydroxide TS. Dry at 60° for 15 minutes, and spray the plate with *p*-nitroaniline TS: the reddish orange spot obtained from the test solution corresponds in color, size, and intensity to that obtained from the Standard solution.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 25.0 USP Endotoxin Units per mg of phenylephrine hydrochloride.

pH ⟨791⟩: between 3.0 and 6.5.

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

Assay—

Mobile phase—Prepare and filter a mixture of methanol and water (1:1) containing 1.1 g of sodium 1-octanesulfonate per liter, adjusted with 3 M phosphoric acid to a pH of 3.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Dilution solvent—Prepare a mixture of methanol and water (1:1), adjusted with 3 M phosphoric acid to a pH of 3.0.

System suitability solution—Dissolve about 50 mg each of USP Phenylephrine Hydrochloride RS and USP Epinephrine Bitartrate RS in 5 mL of water, dilute with *Dilution solvent* to 25.0 mL, and mix. Further dilute 5.0 mL of the resulting solution with *Dilution solvent* to 25.0 mL, and mix to obtain a solution having a concentration of about 0.4 mg of phenylephrine hydrochloride and 0.4 mg of epinephrine bitartrate per mL.

Standard preparation—Dissolve about 50 mg of USP Phenylephrine Hydrochloride RS, accurately weighed, in 10 mL of