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Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension

» Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension is a sterile suspension of Penicillin G Benzathine and Penicillin G Procaine or, when labeled for veterinary use only, of Penicillin G Benzathine and penicillin G procaine, in Water for Injection. It may contain one or more suitable buffers, preservatives, and suspending agents. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amounts of penicillin G benzathine and penicillin G procaine.

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

Labeling—Where it is intended for veterinary use only, it is so labeled.

USP Reference standards ⟨11⟩—
USP Penicillin G Benzathine RS
USP Penicillin G Potassium RS
USP Procaine Hydrochloride RS

Change to read:

Identification—

A: ▲Mix a portion of it with methanol to obtain a solution containing about 3000 Penicillin G Units per mL. Apply 20 µL of this test solution and 20 µL of a Standard solution of USP Penicillin G Benzathine RS in methanol containing 2.5 mg per mL to a suitable thin-layer chromatographic plate (see *Chromatography ⟨621⟩*) coated with a 0.25-mm layer of chromatographic silica gel, and allow the spots to dry. Using an unlined developing chamber, develop the chromatogram in a solvent system consisting of a mixture of methanol, acetonitrile, and ammonium hydroxide (70:30:3) 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 uniformly with a spray reagent prepared as follows. Dissolve 20 g of tartaric acid and 1.7 g of bismuth subnitrate in 80 mL of water. Add 2.5 mL of this solution, 2.5 mL of potassium iodide solution (4 in 10), and 10 g of tartaric acid to 50 mL of water, and mix. Examine the chromatograms: the principal spot obtained from the test solution corresponds in R_F value to that obtained from the Standard solution. The spot obtained from the test solution, corresponding in R_F value to that obtained from the Standard solution, is completely resolved from a second spot, produced by penicillin G procaine.▲ (ERR 1-Dec-2022)

B: It responds to the *Identification* test under *Penicillin G Procaine*.

Crystallinity ⟨695⟩ (where it is prepared from penicillin G procaine and is labeled as intended for veterinary use only)—Dilute a portion of the Injectable Suspension, equivalent to about 300,000 Penicillin G Units, with water to obtain a volume of 10 mL, and centrifuge. Remove and discard the supernatant fluid. Resuspend the residue in 10 mL of water, and centrifuge. Remove and discard the supernatant fluid. Dry the residue in a vacuum desiccator. The dried residue meets the requirements.

pH ⟨791⟩: between 5.0 and 7.5.

Limit of soluble penicillin G and procaine (where it is prepared from penicillin G procaine and is labeled for veterinary use only)—

Mobile phase—Dissolve 4 g of sodium 1-hexanesulfonate and 5.44 g of monobasic potassium phosphate in 760 mL of water, adjust with phosphoric acid to a pH of 2.5, dilute with acetonitrile to 1000 mL, and mix. Pass through a filter having a 0.5-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

pH 6.0 Phosphate buffer—Dissolve 16 g of monobasic potassium phosphate and 4 g of dibasic sodium phosphate in water, dilute with water to 200 mL, adjust with phosphoric acid or 1 N sodium hydroxide to a pH of 6.0.

Diluent—Transfer 60 mL of butyl alcohol, 100 mL of acetonitrile, and 10 mL of *pH 6.0 Phosphate buffer* to a 500-mL volumetric flask, dilute with water to volume, and mix.

Standard solution—Transfer about 24 mg of USP Penicillin G Potassium RS, accurately weighed, and about 8 mg of USP Procaine Hydrochloride RS, accurately weighed, to a 100-mL volumetric flask, add 12 mL of butyl alcohol and 20 mL of acetonitrile, and shake to dissolve. Add 2 mL of *pH 6.0 Phosphate buffer* and mix and bring to volume with water.

Test solution—Centrifuge about 20 mL of the Suspension. Remove the supernatant fluid, and pass it through a filter having a 5-µm or finer porosity. Transfer 5.0 mL of the clear filtrate to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

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Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a 204-nm detector and a 4-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 0.3%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of penicillin G ($C_{16}H_{18}N_2O_4S$) in the *Test solution* by the formula:

$$(334.40/372.48)(C)(r_U/r_S)$$

in which 334.40 and 372.48 are the molecular weights of penicillin G and penicillin G potassium respectively; C is the concentration, in mg per mL, of USP Penicillin G Potassium RS in the *Standard solution;* and r_U and r_S are the responses of the penicillin G peaks in the chromatograms of the *Test solution* and the *Standard solution*, respectively: not more than 1% is found. Calculate the percentage of procaine ($C_{13}H_{20}N_2O_2$) in the *Test solution* by the formula:

$$(236.32/272.78)(C)(r_U/r_S)$$

in which 236.32 and 272.78 are the molecular weights of procaine and procaine hydrochloride, respectively; C is the concentration, in mg per mL, of USP Procaine Hydrochloride RS in the *Standard solution*; and r_U and r_S are the responses of the procaine peaks in the chromatograms of the *Test solution* and the *Standard solution*, respectively: not more than 1% is found.

Other requirements—It meets the requirements for *Bacterial endotoxins* and *Sterility* under *Penicillin G Procaine Injectable Suspension.* It meets also the requirements under *Injections and Implanted Drug Products ⟨1⟩*.

Assay for penicillin G procaine—

Standard preparations—Transfer about 14*k* mg of USP Procaine Hydrochloride RS, accurately weighed, to a 500-mL volumetric flask, and dissolve in 2 mL of 0.5 N sodium hydroxide, *k* being the ratio of the labeled number of Penicillin G Procaine Units to the labeled number of Penicillin G Benzathine Units in the Injectable Suspension. After 15 minutes, add 1 mL of 1.2 N hydrochloric acid, dilute with water to volume, and mix. This stock solution contains about 28*k* µg of USP Procaine Hydrochloride RS per mL. Transfer 1.0, 2.0, 3.0, 4.0, and 5.0 mL, respectively, of this stock solution to each of five 25-mL volumetric flasks. Transfer 4.0, 3.0, 2.0, and 1.0 mL of water to the first four flasks, respectively.

Assay preparation—Where the Injectable Suspension is represented as being in a single-dose container, withdraw all of the withdrawable contents, using a suitable hypodermic needle and syringe. Where the label states the quantities of penicillin G benzathine and penicillin G procaine in a given volume of Injectable Suspension, remove an accurately measured volume of the Injectable Suspension. For each 300,000 Penicillin G Benzathine Units in the specimen of Injectable Suspension taken, add 20 mL of 0.5 N sodium hydroxide, and mix. After 15 minutes, add 0.5 mL of 1.2 N hydrochloric acid for each mL of 0.5 N sodium hydroxide used, and dilute quantitatively with water to obtain a solution containing 36 Penicillin G Procaine Units per mL. Transfer 5.0 mL of this solution to a 50-mL volumetric flask.

Procedure—To each of the flasks containing the *Standard preparations* and the *Assay preparation*, and to a seventh 50-mL volumetric flask containing 5.0 mL of water to provide the blank, add 0.5 mL of 4 N hydrochloric acid, 1.0 mL of sodium nitrite solution (1 in 1000), 1.0 mL of ammonium sulfamate solution (1 in 200), and 1.0 mL of N-(1-naph thyl)ethylenediamine dihydrochloride solution (1 in 1000), mixing and allowing 2 minutes to elapse after each addition. Dilute the contents of each flask with water to volume, and mix. Concomitantly determine the absorbances of the solutions from the *Standard preparations* and the *Assay preparation* at the wavelength of maximum absorbance at about 550 nm, with a suitable spectrophotometer, using the blank to set the instrument at zero. Plot the absorbance values of solutions from the *Standard preparations* versus concentration, in mg per mL, of procaine hydrochloride in the solutions from the *Standard preparations*, and draw the straight line best fitting the five plotted points. From the graph so obtained, determine the concentration (C), in mg per mL, of procaine hydrochloride in the solution from the *Assay preparation.* Calculate the quantity, in Penicillin G Procaine Units in each container or in each mL of the Injectable Suspension taken by the formula:

$$(588.73/272.78)(1009.1)(CL/D)$$

in which 588.73 and 272.78 are the molecular weights of penicillin G procaine monohydrate and procaine hydrochloride, respectively; 1009.1 is the theoretical potency, in Penicillin G Units, in each mg of penicillin G procaine; L is the labeled amount, in Penicillin G Procaine Units in each container or in each mL of Injectable Suspension taken; and D is the concentration, in Penicillin G Procaine Units per mL, of the solution from the *Assay preparation*, on the basis of the labeled amount in each container or in each mL of Injectable Suspension taken and the extent of dilution.

Assay for penicillin G benzathine—

Standard preparation—Using USP Penicillin G Potassium RS, prepare as directed for *Standard preparation* under *Iodometric Assay—Antibiotics ⟨425⟩*.

Assay preparation—Where the Injectable Suspension is represented as being in a single-dose container, withdraw all of the withdrawable contents, using a suitable hypodermic needle and syringe. Where the label states the quantities of penicillin G benzathine and penicillin G

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