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Penicillin G Procaine, Dihydrostreptomycin Sulfate, Chlorpheniramine Maleate, and Dexamethasone Injectable Suspension

» Penicillin G Procaine, Dihydrostreptomycin Sulfate, Chlorpheniramine Maleate, and Dexamethasone Injectable Suspension is a sterile suspension of Penicillin G Procaine and Dexamethasone in a solution of Sterile Dihydrostreptomycin Sulfate and Chlorpheniramine Maleate in Water for Injection. It contains one or more suitable buffers, preservatives, and dispersing or suspending agents. It may contain Procaine Hydrochloride in a concentration not exceeding 2.0 percent, and it may contain one or more suitable stabilizers. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amounts of Penicillin G Units and of dihydrostreptomycin ($C_{21}H_{41}N_7O_{12}$), and not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) and of dexamethasone ($C_{22}H_{29}FO_5$).

Packaging and storage—Preserve in single-dose or multiple-dose, tight containers, in a cool place.

Labeling—Label it to indicate that it is intended for veterinary use only.

USP Reference standards ⟨11⟩—

USP Chlorpheniramine Maleate RS
USP Dexamethasone RS
USP Dihydrostreptomycin Sulfate RS
USP Penicillin G Potassium RS
USP Penicillin G Procaine RS

Identification—

A: Transfer, with the aid of water, a portion of the Injectable Suspension, freshly mixed and free from air bubbles, equivalent to about 400,000 Penicillin G Units, to a separator, add 50 mL of chloroform, and shake by mechanical means for 15 minutes. Allow to separate, and filter the lower chloroform layer through about 4 g of anhydrous sodium sulfate supported on a pledget of glass wool, collecting the filtrate in a 100-mL volumetric flask. Repeat the extraction with two 25-mL portions of chloroform, combining the filtrates in the 100-mL volumetric flask. Dilute with chloroform to volume, and mix. [Note—Retain the aqueous phase for *Identification* test *B*.] Prepare a Standard solution of USP Penicillin G Procaine RS in chloroform containing about 4.5 mg per mL. Apply separately 10 µL of each solution to a 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 butanol, isopropyl alcohol, acetone, and water (4:4:2:2) 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. Expose the plate to iodine vapors in a closed chamber for about 15 minutes, and locate the spots: the R_F values and colors of the two principal spots obtained from the test solution correspond to those obtained from the Standard solution.

B: Dilute the aqueous phase retained from *Identification* test *A* with water to obtain a test solution containing about 5 mg of dihydrostreptomycin per mL. Prepare a Standard solution of USP Dihydrostreptomycin Sulfate RS in water containing 6.5 mg per mL. Apply separately 30 µL of each solution to a 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 *n*-propyl alcohol, water, pyridine, and glacial acetic acid (15:12:10:2) 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. Spray the plate with a reagent prepared by dissolving 2 g of ninhydrin in 100 mL of alcohol and adding 20 mL of glacial acetic acid, heat the plate at 110° for 10 minutes, and examine the chromatograms: the R_F value and color of the principal spot obtained from the test solution correspond to those obtained from the Standard solution.

C: The chromatogram of the *Assay preparation* obtained as directed in the *Assay for chlorpheniramine maleate* exhibits a major peak for chlorpheniramine, the retention time of which corresponds to that exhibited in the chromatogram of the *Standard preparation* similarly determined, both relative to the internal standard.

D: The chromatogram of the *Assay preparation* obtained as directed in the *Assay for dexamethasone* exhibits a major peak for dexamethasone, the retention time of which corresponds to that exhibited in the chromatogram of the *Standard preparation* similarly determined, both relative to the internal standard.

Bacterial Endotoxins Test ⟨85⟩ —It contains not more than 0.01 Endotoxin Unit per 100 Penicillin G Units.

pH ⟨791⟩: between 5.0 and 6.0.

Other requirements—It meets the requirements of the test for *Sterility* under *Penicillin G Procaine and Dihydrostreptomycin Sulfate Injectable Suspension*, and the requirements under *Injections and Implanted Drug Products* ⟨1⟩.

Assay for penicillin G—

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

Assay preparation—Dilute an accurately measured volume of Injectable Suspension, freshly mixed and free from air bubbles, quantitatively with *Buffer B.1* to yield a solution containing about 2000 Penicillin G Units per mL. Pipet 2 mL of this solution into each of two glass-stoppered, 125-mL conical flasks.

Procedure—Proceed as directed for *Procedure* under *Iodometric Assay—Antibiotics* ⟨425⟩, except in the *Blank Determination* to add 0.1 mL of 1.2 N hydrochloric acid immediately before the 10.0 mL of 0.01 N iodine VS. Calculate the quantity, in Penicillin G Units, in the portion of Injectable Suspension taken by the formula:

$$(L/2D)(F)(B - I)$$

in which L is the labeled quantity, in Penicillin G Units, in the volume of Injectable Suspension taken, and D is the concentration, in Penicillin G Units per mL, of the *Assay preparation*, on the basis of the labeled quantity in the portion of Injectable Suspension taken and the extent of dilution, and the other terms are as defined therein.

Assay for dihydrostreptomycin—Proceed as directed for the turbidimetric assay for dihydrostreptomycin under *Antibiotics—Microbial Assays* ⟨81⟩, using an accurately measured volume of Injectable Suspension, freshly mixed and free from air bubbles, diluted quantitatively with water to yield a *Test Dilution* having a concentration of dihydrostreptomycin assumed to be equal to the median dose level of the Standard.

Assay for chlorpheniramine maleate—

Internal standard solution—Prepare a solution of brompheniramine maleate in water having a concentration of about 7 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Chlorpheniramine Maleate RS in water to obtain a stock solution having a known concentration of about 6 mg per mL. Transfer 5.0 mL of this solution to a 50-mL centrifuge tube. Add 5.0 mL of *Internal standard solution*, and adjust with sodium hydroxide solution (1 in 2) to a pH of about 10. Add 25.0 mL of hexanes, place the cap on the tube, shake for about 2 minutes, and centrifuge. Use the upper hexanes layer as the *Standard preparation*.

Assay preparation—Transfer an accurately measured volume of Injectable Suspension, freshly mixed and free from air bubbles, equivalent to about 30 mg of chlorpheniramine maleate, to a 50-mL centrifuge tube. Proceed as directed under *Standard preparation*, beginning with "Add 5.0 mL of *Internal standard solution*." Use the upper hexanes layer as the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, and contains a 4-mm × 1.8-m glass column packed with 1.2% liquid phase G16 and 0.5% potassium hydroxide on 100- to 120-mesh support S1A. The column is maintained isothermally at about 180°, and the injection port and the detector block are maintained at about 200°. Dry nitrogen is used as the carrier gas at a flow rate of about 50 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between the analyte and internal standard peaks is not less than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 1.5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.75 for chlorpheniramine and 1.0 for brompheniramine. Calculate the quantity, in mg, of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) in each mL of the Injectable Suspension taken by the formula:

$$5(C/V)(R_U/R_S)$$

in which C is the concentration of USP Chlorpheniramine Maleate RS in the stock solution used to prepare the *Standard preparation*, V is the volume, in mL, of Injectable Suspension taken, and R_U and R_S are the peak response ratios of the chlorpheniramine maleate peak to the internal standard peak obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Assay for dexamethasone—

Mobile phase—Prepare a suitable filtered mixture of water and acetonitrile (2:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Dissolve about 30 mg of beclomethasone in 2 mL of methanol in a 50-mL volumetric flask, dilute with methylene chloride to volume, and mix.

Standard preparation—Transfer about 25 mg of USP Dexamethasone RS, accurately weighed, to a 50-mL volumetric flask. Add about 1 mL of methanol, swirl to dissolve, dilute with methylene chloride to volume, and mix. Transfer 5.0 mL of this solution to a suitable flask, and add 5.0 mL of *Internal standard solution*. Heat the flask on a steam bath, and evaporate under a stream of nitrogen just to dryness. Add 10.0 mL of methanol to the flask, and swirl to dissolve the residue. This *Standard preparation* contains about 0.25 mg of USP Dexamethasone RS and 0.3 mg of beclomethasone per mL.

Assay preparation—Transfer an accurately measured volume of Injectable Suspension, freshly mixed and free from air bubbles, equivalent to about 2.5 mg of dexamethasone, to a separator containing 50 mL of 0.1 N hydrochloric acid, add 5.0 mL of *Internal standard solution*, and extract with four 25-mL portions of methylene chloride, combining the extracts in a second separator. Wash the combined extracts with 50 mL of sodium bicarbonate solution (1 in 20), filtering the lower methylene chloride layer through about 4 g of anhydrous sodium sulfate supported on a cotton pledget previously washed with methylene chloride, and collecting the filtrate in a suitable flask. Wash the aqueous layer with 25 mL of methylene chloride, and filter the lower methylene chloride layer through the same filter, collecting the filtrate in the same flask. Heat the flask on a steam bath, and evaporate under a stream of nitrogen just to dryness. Add 10.0 mL of methanol, and swirl to dissolve the residue.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4-mm × 30-cm column that contains packing L1. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the resolution, *R,* of the analyte and the internal standard peaks is not less than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.8 for dexamethasone and 1.0 for beclomethasone. Calculate the quantity, in mg, of dexamethasone ($C_{22}H_{29}FO_5$) in each mL of the Injectable Suspension taken by the formula:

$$10(C/V)(R_U/R_S)$$

in which C is the concentration, in mg per mL, of USP Dexamethasone RS in the *Standard preparation*, V is the volume, in mL, of Injectable Suspension taken, and R_U and R_S are the peak response ratios of the dexamethasone peak to the internal standard peak obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
PENICILLIN G PROCAINE, DIHYDROSTREPTOMYCIN SULFATE, CHLORPHENIRAMINE MALEATE, AND DEXAMETHASONE INJECTABLE SUSPENSION	Ying Han Associate Science & Standards Liaison	BIO42020 Biologics Monographs 4 - Antibiotics
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	BIO42020 Biologics Monographs 4 - Antibiotics

Chromatographic Database Information: Chromatographic Database

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