

drying, pH, ampicillin content, concordance, crystallinity, and identity.

(b) The batch for potency, moisture, and pH.

(i) Samples required:

(a) The ampicillin trihydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*. Assay for potency by either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured representative portion of the sample into a suitable volumetric flask and dilute to volume with 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to give a convenient concentration. Mix well. Further dilute an aliquot with solution 3 to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2N hydrochloric acid to both the sample and working standard solutions after the addition of 0.01N iodine solution. Prepare the sample as follows: Reconstitute the drug as directed in the labeling. Place an accurately measured aliquot (usually a single dose) into an appropriately sized volumetric flask and dilute to volume with distilled water. Mix well. Further dilute with distilled water to the prescribed concentration.

(2) *Moisture*. Proceed as directed in § 436.201 of this chapter.

(3) *pH*. Proceed as directed in § 436.202 of this chapter, using the drug reconstituted as directed in the labeling.

[39 FR 18976, May 30, 1974, as amended at 49 FR 3459, Jan. 27, 1984; 49 FR 5096, Feb. 10, 1984; 50 FR 19919, May 13, 1985]

§ 440.107d Ampicillin trihydrate-probenecid for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality,*

and purity. Ampicillin trihydrate and probenecid for oral suspension is a dry mixture of ampicillin trihydrate and probenecid with suitable flavorings, lubricants, colorings, and suspending agents packaged in a single-dose container. When reconstituted as directed in the labeling, each single dose will contain ampicillin trihydrate equivalent to 3.5 grams of ampicillin and 1.0 gram of probenecid. Its ampicillin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of grams of ampicillin that it is represented to contain. Its probenecid content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of grams of probenecid that it is represented to contain. Its moisture content is not more than 5.0 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.5. The ampicillin trihydrate used conforms to the standards prescribed by § 440.7(a)(1). The probenecid used conforms to the standards prescribed by the U.S.P.

(2) *Labeling*. In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled "ampicillin-probenecid for oral suspension".

(3) *Requests for certification, samples*. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The ampicillin trihydrate used in making the batch for potency, loss on drying, pH, ampicillin content, concordance, crystallinity, and identity.

(b) The probenecid used in making the batch for all U.S.P. specifications.

(c) The batch for ampicillin content, probenecid content, moisture, and pH.

(ii) Samples required:

(a) The ampicillin trihydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of 10 immediate containers.

(b) *Tests and methods of assay*—(1) *Ampicillin content*—(i) *Sample preparation*. Reconstitute as directed in the labeling and mix well. Drain the suspension from the bottle for 30 seconds into a high-speed glass blender jar containing

sufficient sterile distilled water to obtain a total volume of 500 milliliters. Blend for 10 minutes.

(ii) *Assay procedures.* Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(a) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the aqueous solution with 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 0.1 microgram of ampicillin per milliliter (estimated).

(b) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, except in paragraph (d) of that section, add 3 drops of 1.2N hydrochloric acid to both the sample and working standard solutions after the addition of 0.01N iodine solution. Dilute an aliquot of the aqueous solution to the prescribed concentration.

(2) *Probenecid content*—(i) *Preparation of standard solution.* Transfer approximately 25 milligrams of U.S.P. probenecid reference standard, accurately weighed, to a 25-milliliter volumetric flask. Dissolve and dilute to volume with 1 percent aqueous sodium carbonate solution.

(ii) *Preparation of sample solution.* Reconstitute the sample as directed in the labeling and mix well. Drain the suspension from the bottle for 30 seconds into a 1,000-milliliter volumetric flask. Dilute to volume with 1 percent aqueous sodium carbonate solution, shake well, and filter through Whatman No. 6 filter paper. Discard the first 10-milliliter portion.

(iii) *Procedure.* Transfer 2.0 milliliters of the clear filtrate to a 125-milliliter separatory funnel and add 8.0 milliliters of 1.0N hydrochloric acid. Extract the solution with four 20-milliliter portions of chloroform, filtering each extract through a glass wool pledget into a 100-milliliter volumetric flask. Wash the pledget with chloroform, dilute to volume with chloroform and mix. Treat 2.0 milliliters of the standard solution in the same manner. Using a suitable spectrophotometer equipped with a 1-centimeter cell and chloroform washed with 1 percent aqueous sodium carbonate solution as a blank, determine the

absorbance of the sample and standard solutions at the peak near 257 nanometers.

(iv) *Calculations.* Calculate the probenecid content as follows:

$$\text{Grams probenecid per container} = \frac{\text{Absorbance of sample} \times \text{weight of standard in milligrams} \times \text{percent purity of standard}}{\text{Absorbance of standard} \times 25 \times 100}$$

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using the drug reconstituted as directed in the labeling.

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§ 440.107e Ampicillin trihydrate-probenecid capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ampicillin trihydrate-probenecid capsules are composed of ampicillin trihydrate and probenecid with or without one or more buffer substances, diluents, binders, lubricants, vegetable oils, colorings, and flavorings enclosed in a gelatin capsule. Each capsule contains ampicillin trihydrate equivalent to 389 milligrams of ampicillin and 111 milligrams of probenecid. Its ampicillin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of ampicillin that it is represented to contain. Its probenecid content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of probenecid that it is represented to contain. Its loss on drying is not less than 8.5 percent and not more than 13.0 percent. The ampicillin trihydrate used conforms to the standards prescribed by § 440.7(a)(1). The probenecid used conforms to the standards prescribed by the U.S.P.

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled "ampicillin-probenecid capsules".

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on: