

sample for test as follows: Use a sufficient number of containers to yield 3 milligrams of dactinomycin. Reconstitute by adding 1.1 milliliters of sterile water for injection to each container. Aseptically pool the resultant solutions from each container. Dilute an accurately measured portion with sufficient diluent 1 to give a concentration of 0.2 milligram of dactinomycin per milliliter.

(4) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(5) *pH.* Reconstitute as directed in the labeling and proceed as directed in § 436.202 of this chapter.

[39 FR 19145, May 30, 1974, as amended at 44 FR 10379, Feb. 20, 1979; 46 FR 16685, Mar. 13, 1981; 46 FR 46313, Sept. 18, 1981; 49 FR 6093, Feb. 17, 1984; 49 FR 15074, Apr. 17, 1984; 49 FR 24018, June 11, 1984; 50 FR 1504, Jan. 11, 1985; 50 FR 19676, May 10, 1985]

§ 450.222 Daunorubicin hydrochloride for injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Daunorubicin hydrochloride for injection is a freeze-dried powder whose components are daunorubicin hydrochloride and mannitol. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of daunorubicin that it is represented to contain. It is sterile. It is nonpyrogenic. It contains no depressor substances. Its moisture content is not more than 3.0 percent. When reconstituted as directed in the labeling, its pH is not less than 4.5 and not more than 6.5. It passes the identity test. The daunorubicin hydrochloride used conforms to the standards prescribed by § 450.22(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(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 daunorubicin hydrochloride used in making the batch for potency, moisture, pH, crystallinity, and identity.

(b) The batch for potency, sterility, pyrogens, depressor substances, moisture, pH, and identity.

(ii) Samples required:

(a) The daunorubicin hydrochloride used in making the batch: 14 packages, each containing approximately 40 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 34 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay.* Daunorubicin hydrochloride is toxic. It must be handled with care in the laboratory. Solutions should not be pipetted by mouth. Transfer all dry powders in a suitable hood. Wear rubber gloves, protective gowns, head coverings, and protective eye goggles when handling dry powders. If the substance contacts the skin, wash with soap and water. Dispose of all waste material by dilution with larger volumes of sodium hypochlorite solution.

(1) *Daunorubicin content (high-pressure liquid chromatography).* Proceed as directed in § 436.322 of this chapter, preparing the sample and standard solutions and calculating the daunorubicin content as follows:

(i) *Preparation of working standard solution.* Accurately weigh approximately 25 milligrams of the daunorubicin working standard and dissolve in 25 milliliters of the internal standard solution prepared as directed in § 436.322(b)(3) of this chapter.

(ii) *Preparation of sample solution.* Prepare the sample solution by rinsing the contents of the vial into an appropriate-sized volumetric flask with a sufficient amount of internal standard solution prepared as directed in § 436.322(b)(3) of this chapter, to obtain a concentration of 1.0 milligram of daunorubicin per milliliter.

(iii) *Calculations.* Calculate the daunorubicin content as follows:

$$\text{Daunorubicin content per vial} = \frac{R_u \times W_s \times V \times P}{R_s \times 25 \times 1,000}$$

in milligrams

where:

$$R_u = \frac{\text{Area of the daunorubicin sample peak}}{\text{Area of the internal standard peak}}$$

$$R_s = \frac{\text{Area of the daunorubicin standard peak}}{\text{Area of the internal standard peak}}$$

W_s = Weight of the daunorubicin working standard in milligrams;

V = Volume in milliliters of the internal standard solution added to the vials;

P = Potency of the daunorubicin working standard in micrograms per milligram.

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens*. Proceed as directed in § 436.32(a) of this chapter, using a solution containing 2.25 milligrams of daunorubicin per milliliter.

(4) *Depressor substances*. Proceed as directed in § 436.35 of this chapter.

(5) *Moisture*. Proceed as directed in § 436.201 of this chapter, using the sample preparation method described in paragraph (d)(4) of that section.

(6) *pH*. Proceed as directed in § 436.202 of this chapter, using the sample obtained after reconstituting the drug as directed in the labeling.

(7) *Identity*. The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the daunorubicin working standard.

[45 FR 75198, Nov. 14, 1980, as amended at 50 FR 47214, Nov. 15, 1985]

§ 450.224 Doxorubicin hydrochloride injectable dosage forms.

§ 450.224a Doxorubicin hydrochloride for injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Doxorubicin hydrochloride for injection is a freeze-dried powder whose components are doxorubicin hydrochloride and lactose. It may also contain methylparaben. Its doxorubicin hydrochloride content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of doxorubicin hydrochloride that it is

represented to contain. It is sterile. It contains not more than 2.2 U.S.P. endotoxin units per milligram of doxorubicin hydrochloride. Its moisture content is not more than 4.0 percent. When reconstituted as directed in the labeling, its pH is not less than 4.5 and not more than 6.5. It passes the identity test. The doxorubicin hydrochloride used conforms to the standards prescribed by § 450.24(a)(1).

(2) *Labeling*. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(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 doxorubicin hydrochloride used in making the batch for doxorubicin hydrochloride content, residue solvents, depressor substances, moisture, pH, crystallinity, identity, and total related impurities.

(b) The batch for doxorubicin hydrochloride content, sterility, bacterial endotoxins, moisture, pH, and identity.

(ii) Samples required:

(a) The doxorubicin hydrochloride used in making the batch: 14 packages, each containing approximately 40 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 34 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*. Doxorubicin hydrochloride is toxic. It must be handled with care in the laboratory. Solutions should not be pipetted by mouth. Transfer all dry powders in a suitable hood while wearing rubber gloves. If the substance contacts the skin, wash with soap and water. Dispose of all waste material by dilution with large volumes of sodium hypochlorite (bleach) solution.