

(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.

(1) *Doxorubicin hydrochloride content (high-performance liquid chromatography).* Proceed as directed in § 450.24(b)(1), preparing the sample solution and calculating the doxorubicin hydrochloride content as follows:

(i) *Sample solution.* Dilute an accurately measured volume of sample equivalent to not less than 2 milligrams of doxorubicin hydrochloride, quantitatively with mobile phase to obtain a solution containing 0.1 milligram of doxorubicin hydrochloride per milliliter (estimated).

(ii) *Calculations.* Calculate the milligrams of doxorubicin hydrochloride per milliliter of sample as follows:

$$\text{Milligrams of doxorubicin hydrochloride per milliliter} = \frac{A_U \times P_S \times d}{A_S \times 1,000}$$

where:

A_U = Area of the doxorubicin hydrochloride peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_S = Area of the doxorubicin hydrochloride peak in the chromatogram of the doxorubicin hydrochloride working standard;

P_S = Doxorubicin hydrochloride activity in the doxorubicin hydrochloride working standard solution in micrograms per milliliter; and

d = Dilution factor of the sample.

(2) [Reserved]

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

(4) *Bacterial endotoxins.* Proceed as directed in the United States Pharmacopeia (U.S.P.) Bacterial Endotoxin Test, using a test solution prepared by diluting doxorubicin hydrochloride injection with sterile water for injection

to obtain a concentration of 1.1 milligrams of doxorubicin hydrochloride per milliliter. The specimen under test contains not more than 2.2 U.S.P. endotoxin units per milligram of doxorubicin hydrochloride.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

(6) *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 doxorubicin hydrochloride working standard.

[53 FR 37292, Sept. 26, 1988, as amended at 59 FR 9641, Mar. 1, 1994]

§ 450.230 Idarubicin hydrochloride for injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Idarubicin hydrochloride for injection is a lyophilized mixture of idarubicin hydrochloride and lactose. Its idarubicin hydrochloride content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of idarubicin hydrochloride that it is represented to contain. It is sterile. It contains not more than 8.93 U.S.P. endotoxin units per milligram of idarubicin hydrochloride. Its moisture content is not more than 4.0 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.0. It passes the identity test. The idarubicin hydrochloride used conforms to the standards prescribed by § 450.30(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 idarubicin hydrochloride used in making the batch for idarubicin hydrochloride content, solvent residues, moisture, pH, crystallinity, related individual thin layer chromatography and high-performance liquid chromatography (HPLC) impurities, total impurities, and identity.

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

(ii) Samples required if requested by the Director, Center for Drug Evaluation and Research:

(A) The idarubicin 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.* Idarubicin hydrochloride is toxic. It must be handled with care in the laboratory. Transfer all dry powders into a suitable hood while wearing rubber gloves. Avoid inhaling fine particles of powder. Solutions should not be pipetted by mouth. If the substance contacts the skin, wash with soap and water. Dispose of all waste material by dilution with large volumes of dilute sodium hypochlorite (bleach) solution.

(1) *Idarubicin hydrochloride content (HPLC).* Proceed as directed in § 450.30(b)(1), preparing the sample solution and calculating the idarubicin hydrochloride as follows:

(i) *Sample solution.* Prepare the sample solution by rinsing the contents of the vial into an appropriate-sized volumetric flask with sufficient diluent to obtain a concentration of 0.5 milligram of idarubicin hydrochloride per milliliter (estimated).

(ii) *Calculations.* Calculate the idarubicin hydrochloride content per vial as follows:

$$\begin{array}{l} \text{Micrograms of} \\ \text{plicamycin} \\ \text{per milligram} \end{array} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - m)}$$

where:

A_u =Area of the idarubicin hydrochloride peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s =Area of the idarubicin hydrochloride peak in the chromatogram of the idarubicin hydrochloride working standard;

P_s =Idarubicin hydrochloride activity in the idarubicin hydrochloride working standard solution in micrograms per milliliter; and

d =Dilution factor of the sample.

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

(3) *Bacterial endotoxins.* Proceed as directed in the U.S.P. Bacteria endotoxin test. The specimen under test contains not more than 8.93 U.S.P. endotoxin units per milligram of idarubicin hydrochloride.

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

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using the sample obtained after reconstituting the drug as directed in the labeling, except use distilled water instead of saline.

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

[58 FR 26665, May 4, 1993]

§ 450.240 Plicamycin for injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Plicamycin for injection is a dry mixture of plicamycin and mannitol with or without a suitable buffer substance. Each immediate container contains 2.5 milligrams of plicamycin. Its plicamycin content is satisfactory if it contains not less than 90 percent and not more than 110 percent of the number of milligrams of plicamycin that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 2.0 percent. It contains no depressor substances. Its pH when reconstituted as directed in the labeling is not less than 5.0 and not more than 7.5. It passes the identity test for plicamycin. The plicamycin used conforms to the standards prescribed by § 450.40(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter. In addition, each package shall bear on its label or labeling the following as indicated:

(i) On the outside wrapper or container the statement "Store below 10° C. (50° F.)".