Doxorubicin Hydrochloride Injection

DEFINITION

Doxorubicin Hydrochloride Injection is a sterile solution of Doxorubicin Hydrochloride in Sterile Water for Injection made isoosmotic with Sodium Chloride, Dextrose, or other suitable added substances. It contains NLT 90.0% and NMT 115.0% of the labeled amount of doxorubicin hydrochloride ($C_{27}H_{29}NO_{11} \cdot HCl$).

IDENTIFICATION

- **A.** The retention time of the doxorubicin peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV spectrum of the doxorubicin peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **PROCEDURE**

[NOTE—Protect solutions containing doxorubicin from light.]

Solution A: •0.1% trifluoroacetic acid TS• (IRA 1-Mar-2017)

Solution B: Acetonitrile, methanol, and trifluoroacetic acid (800:200:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
15	25	75
16	25	75
16.1	90	10
18	90	10

Diluent: *Solution A* and *Solution B* (50:50)

System suitability solution: 0.1 mg/mL each of USP Doxorubicin Hydrochloride RS and USP Epirubicin Hydrochloride RS in *Diluent*

Standard solution: 0.1 mg/mL of USP Doxorubicin Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.1 mg/mL of doxorubicin hydrochloride in *Diluent* from Injection

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 254 nm. For *Identification B*, use a diode array detector in the range of 190–400 nm.

Column: 2.1-mm × 10-cm; 1.7-µm packing L1

Temperatures

Autosampler: 4°

Column: 35°

Flow rate: 0.5 mL/min

Injection volume: 2 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between doxorubicin and epirubicin, *System suitability solution*

Tailing factor: 0.8–1.5, *Standard solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of doxorubicin hydrochloride ($C_{27}H_{29}NO_{11} \cdot HCl$) in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak response of doxorubicin from the *Sample solution*

r_S = peak response of doxorubicin from the *Standard solution*

C_S = concentration of USP Doxorubicin Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of doxorubicin hydrochloride in the *Sample solution* (mg/mL)

P = potency of doxorubicin in USP Doxorubicin Hydrochloride RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–115.0%

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

[NOTE—Protect solutions containing doxorubicin from light.]

Mobile phase, Diluent, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: •0.008 mg/mL each of USP Doxorubicin Hydrochloride RS and 0.012 mg/mL of USP Doxorubicinone RS in *Diluent*. [NOTE—It may be necessary to first dissolve in acetonitrile, using NMT 5% of the final volume, before diluting with *Diluent*.]• (IRA 1-Mar-2017)

Sample solution: Nominally 0.4 mg/mL of doxorubicin hydrochloride in *Diluent* from Injection

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between doxorubicin and epirubicin, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of doxorubicinone in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

r_U = peak response of doxorubicinone from the *Sample solution*

r_S = peak response of doxorubicinone from the *Standard solution*

C_S = concentration of USP Doxorubicinone RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of doxorubicin hydrochloride in the *Sample solution* (mg/mL)

P = potency of doxorubicinone in USP Doxorubicinone RS (mg/mg)

•• (IRA 1-Mar-2017)

Calculate the percentage of any individual unspecified degradation product in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak response of each degradation product from the *Sample solution*
r_S = peak response of doxorubicin from the *Standard solution*
C_S = concentration of USP Doxorubicin Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of doxorubicin hydrochloride in the *Sample solution* (mg/mL)
P = potency of doxorubicin in USP Doxorubicin Hydrochloride RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Acceptance criteria: See *Table 2*.

●**Table 2**

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Doxorubicin	1.0	—
Epirubicin[a]	1.05	—
Doxorubicinone[b]	1.08	3.0
Daunorubicinone[c,d]	1.35	—
Any other individual degradation product	—	2.0
Total impurities	—	5.0

[a] For resolution measurement only. Not to be reported; not to be included in total impurities.
[b] (8*S*,10*S*)-6,8,10,11-Tetrahydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione.
[c] (8*S*,10*S*)-8-Acetyl-6,8,10,11-tetrahydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione.
[d] The acceptance criteria of this impurity, if present, would fall under the acceptance criteria for "any other individual degradation product" and is included in the total impurities.

● (IRA 1-Mar-2017)

SPECIFIC TESTS

- **pH** ⟨**791**⟩**:** 2.5–4.5
- **Sterility Tests** ⟨**71**⟩**,** *Test for Sterility of the Product to Be Examined, Membrane Filtration***:** It meets the requirements when tested as directed, the entire contents of all the containers being collected aseptically.
- **Bacterial Endotoxins Test** ⟨**85**⟩
  Sample solution: 1.1 mg/mL of doxorubicin hydrochloride prepared from Injection in *Sterile Water for Injection*
  Acceptance criteria: NMT 2.2 USP Endotoxin Units/mg of doxorubicin hydrochloride
- **Other Requirements:** It meets the requirements in *Injections and Implanted Drug Products* ⟨1⟩.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in single-dose or multiple-dose containers, preferably of Type I glass, protected from light. Store in a refrigerator. Injection may be packaged in multiple-dose containers not exceeding 100 mL in volume.

Change to read:

- **USP Reference Standards** ⟨**11**⟩
- ●
  ● (IRA 1-Mar-2017)
  USP Doxorubicin Hydrochloride RS
  USP Doxorubicinone RS
  (8*S*,10*S*)-6,8,10,11-Tetrahydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione.
  $C_{21}H_{18}O_9$ 414.36
  USP Endotoxin RS
  USP Epirubicin Hydrochloride RS