r_S = peak response for irbesartan or hydrochlorothiazide from the *Standard solution*
C_S = concentration of irbesartan or hydrochlorothiazide in the *Standard solution*
L = label claim for irbesartan or hydrochlorothiazide (mg/Tablet)
V = volume of *Medium* (mL), 1000

Tolerances: NLT 80% (*Q*) of the labeled amounts of irbesartan ($C_{25}H_{28}N_6O$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) are dissolved.

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

Organic Impurities

- **PROCEDURE**

Buffer, Mobile phase, Acidified water, Extraction solution, System suitability solution, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of irbesartan related compound A in the portion of Tablets taken:

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

r_U = peak response of irbesartan related compound A from the *Sample solution*
r_S = peak response of irbesartan from the *Standard solution*
C_S = concentration of USP Irbesartan RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of irbesartan in the *Sample solution* (mg/mL)

Calculate the percentage of benzothiadiazine related compound A in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 1/F \times 100$$

r_U = peak response of benzothiadiazine related compound A from the *Sample solution*
r_S = peak response of hydrochlorothiazide from the *Standard solution*
C_S = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)
F = relative response factor (see *Impurity Table 1*)

Calculate the percentage of any other individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each other impurity in the *Sample solution*
r_T = sum of the peak responses excluding hydrochlorothiazide and benzothiadiazine related compound A from the *Sample solution*

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 1.5% (sum of all the individual unknown impurities, irbesartan related compound A, and benzothiadiazine related compound A)

Impurity Table 1

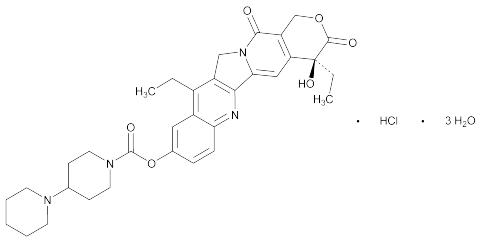
Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A	0.15	1.3	1.0
Hydrochlorothiazide	0.18	—	—
Irbesartan related compound A	0.86	1.0	0.3
Irbesartan	1.00	—	—
Any other individual, unidentified impurity	—	1.0	0.2

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Hydrochlorothiazide RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
1-Pentanoylamino-cyclopentanecarboxylic acid [2′-(*1H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amide.
$C_{25}H_{30}N_6O_2$ 446.54
USP Benzothiadiazine Related Compound A RS
4-Amino-6-chloro-1,3-benzenedisulfonamide.
$C_6H_8ClN_3O_4S_2$ 285.73

Irinotecan Hydrochloride



$C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ Anhydrous: 623.14
Trihydrate: 677.18

[1,4′-Bipiperidine]-1′-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl ester, monohydrochloride, trihydrate, (*S*)-; (+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4′-bipiperidine]-1′-carboxylate, monohydrochloride, trihydrate [136572-09-3].

DEFINITION

Irinotecan Hydrochloride contains NLT 98.0% and NMT 102.0% of $C_{33}H_{38}N_4O_6 \cdot HCl$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197K⟩**
- **B.** The retention time of the major peak of the *Sample solution* corresponds to the irinotecan (*S*-enantiomer) peak in the *Identification solution,* as obtained in the test for *Limit of Irinotecan Hydrochloride Enantiomer*.
- **C. IDENTIFICATION TESTS—GENERAL,** *Chloride* **⟨191⟩:** A 2-mg/mL solution meets the requirements of the tests.

ASSAY

- **PROCEDURE**

Solution A: 2.8 g/L of monobasic sodium phosphate monohydrate and 1.8 g/L of 1-octanesulfonic acid sodium salt monohydrate in water

Mobile phase: Acetonitrile, methanol, and *Solution A* (17:24:59)

Diluent: Use *Mobile phase* adjusted with diluted hydrochloric acid to a pH of 3.65 ± 0.15.

Standard solution: 1 mg/mL of USP Irinotecan Hydrochloride RS in *Diluent*

Sample solution: 1 mg/mL of Irinotecan Hydrochloride in *Diluent*

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 255 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection size: 15 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of irinotecan hydrochloride ($C_{33}H_{38}N_4O_6 \cdot HCl$) in the portion of Irinotecan Hydrochloride taken:

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

r_U = peak area from the *Sample solution*
r_S = peak area from the *Standard solution*
C_S = concentration of USP Irinotecan Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Irinotecan Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Heavy Metals,** *Method II* **⟨231⟩:** NMT 10 ppm
- **Limit of Irinotecan Hydrochloride Enantiomer**

Mobile phase: Hexane, dehydrated alcohol, and diethylamine (250:250:1)
Diluent: Dehydrated alcohol and diethylamine (250:1)
System suitability solution: 0.1 mg/mL each of USP Irinotecan Hydrochloride RS and USP Irinotecan Related Compound D RS in *Diluent*
Identification solution: 1 mg/mL of USP Irinotecan Hydrochloride RS in *Diluent*. [Note—This solution is used for *Identification* test *B*.]
Standard solution: 1.5 µg/mL of USP Irinotecan Related Compound D RS in *Diluent*
Sensitivity solution: 0.5 µg/mL of USP Irinotecan Related Compound D RS in *Diluent*, from the *Standard solution*
Sample solution: 1 mg/mL of Irinotecan Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 370 nm
Column: 4.6-mm × 25-cm; 10-µm packing L40
Flow rate: 1.0 mL/min
Injection size: 20 µL
System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
[Note—The relative retention times for irinotecan related compound D (*R*-enantiomer) and irinotecan (*S*-enantiomer) are 0.7 and 1.00, respectively.]
Suitability requirements
Resolution: NLT 2.5 between irinotecan related compound D and irinotecan, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Sensitivity: The irinotecan related compound D peak should be visible, *Sensitivity solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of irinotecan hydrochloride *R*-enantiomer in the portion of Irinotecan Hydrochloride taken:

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

r_U = peak area of irinotecan related compound D from the *Sample solution*
r_S = peak area of irinotecan related compound D from the *Standard solution*
C_S = concentration of USP Irinotecan Related Compound D RS in the *Standard solution* (mg/mL)
C_U = concentration of Irinotecan Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria
***R*-enantiomer:** NMT 0.15%
[Note—On the basis of the synthetic route, per form either *Organic Impurities Procedure 1* or *Organic Impurities Procedure 2*.]

- **Organic Impurities Procedure 1 (for Material Labeled as Produced by a Synthetic Process)**

Mobile phase, Diluent, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability stock solution: 0.01 mg/mL each of USP Irinotecan Related Compound B RS and USP Irinotecan Related Compound C RS in methanol
System suitability solution: 1.0 µg/mL each of USP Irinotecan Related Compound B RS and USP Irinotecan Related Compound C RS in *Diluent*, from *System suitability stock solution*
Standard solution: 2.0 µg/mL of USP Irinotecan Hydrochloride RS in *Diluent*
Sensitivity solution: 0.5 µg/mL of USP Irinotecan Hydrochloride RS in *Diluent*
System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
Suitability requirements
Resolution: NLT 1.1 between irinotecan related compound B and irinotecan related compound C, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*
Analysis
Samples: *Sample solution* and *Standard solution*
Calculate the percentage of each impurity in the portion of Irinotecan Hydrochloride taken:

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

r_U = peak area of each impurity from the *Sample solution*
r_S = peak area of irinotecan from the *Standard solution*
C_S = concentration of irinotecan hydrochloride in the *Standard solution* (mg/mL)
C_U = concentration of Irinotecan Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria
Individual impurities: See *Table 1*. [Note—Disregard any impurity peaks less than 0.05%.]

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Irinotecan related compound B	0.55	0.15
Irinotecan related compound C	0.60	0.10
Irinotecan hydrochloride	1.0	—
Any unspecified impurity	—	0.10
Total impurities	—	0.5

- **ORGANIC IMPURITIES PROCEDURE 2 (FOR MATERIAL LABELED AS PRODUCED BY A SEMI-SYNTHETIC PROCESS)**

Solution A: 2.72 g/L of monobasic potassium phosphate in water. Adjust with dilute phosphoric acid (1 in 20) to a pH of 3.5 ± 0.05.
Solution B: Acetonitrile and methanol (3:2)
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
40	30	70
45	30	70
50	80	20
55	80	20

Diluent: Acetonitrile, methanol, and *Solution A* (1:1:2)
System suitability solution: 0.1 mg/mL each of USP Irinotecan Hydrochloride RS and USP Irinotecan Related Compound A RS in *Diluent*
Standard solution: 1 µg/mL of USP Irinotecan Hydrochloride RS in *Diluent*
Sample solution: 1 mg/mL of Irinotecan Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection size: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 3.0 between irinotecan and irinotecan related compound A, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Irinotecan Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak area of each individual impurity from the *Sample solution*
r_S = peak area of irinotecan from the *Standard solution*
C_S = concentration of USP Irinotecan Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Irinotecan Hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor for each individual impurity (see *Table 3*)

Acceptance criteria
Individual impurities: See *Table 3*. [NOTE—Disregard any unspecified impurity peaks less than 0.05%.]

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
7-Desethyl irinotecan[a]	0.82	0.77	0.15
Irinotecan	1.00	—	—
Irinotecan related compound A[b]	1.15	1.4	0.15
11-Ethyl irinotecan[c]	1.27	0.63	0.15
Camptothecin[d]	1.35	1.4	0.15
Irinotecan related compound B[e]	1.50	1.3	0.15
7-Ethylcamptothecin[f]	1.76	1.2	0.15
7,11-Diethyl-10-hydroxy-camptothecin[g]	2.05	0.65	0.15
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.50

[a] (*S*)-4-Ethyl-4-hydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione-9-yl (1,4′-bipiperidine)-1′-carboxylate.
[b] (*S*)-4-Ethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.
[c] (*S*)-4,8,11-Triethyl-4-hydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione-9-yl (1,4′-bipiperidine)-1′-carboxylate.
[d] (*S*)-4-Ethyl-4-hydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.
[e] (*S*)-4,11-Diethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.
[f] (*S*)-4,11-Diethyl-4-hydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.
[g] (*S*)-4,8,11-Triethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.

SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS ⟨61⟩ and TESTS FOR SPECIFIED MICROORGANISMS ⟨62⟩:** The total aerobic microbial count does not exceed 1000 cfu/g, and the total combined molds and yeasts count does not exceed 100 cfu/g.
- **WATER DETERMINATION,** *Method I* **⟨921⟩:** Between 7.0% and 9.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **LABELING:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Irinotecan Hydrochloride RS
USP Irinotecan Related Compound A RS
(*S*)-4-Ethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-b]quinoline-3,14(4*H*,12*H*)-dione.
$C_{20}H_{16}N_2O_5$ 364.35
USP Irinotecan Related Compound B RS
(*S*)-4,11-Diethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.
$C_{22}H_{20}N_2O_5$ 392.40
USP Irinotecan Related Compound C RS
(*S*)-9-[(1,4′-Bipiperidine)-1′-carbonyloxy]-4-methyl-11-ethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline hydrochloride.
$C_{32}H_{36}N_4O_6 \cdot HCl$ 609.11
USP Irinotecan Related Compound D RS
(*R*)-9-[(1,4′-Bipiperidine)-1′-carbonyloxy]-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline hydrochloride, trihydrate.
$C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3\ H_2O$ 677.18

Iron Dextran Injection

» Iron Dextran Injection is a sterile, colloidal solution of ferric hydroxide in complex with partially hydrolyzed Dextran of low molecular weight, in Water for Injection. It contains not less than 95.0 percent and not more than 105.0 per cent of the labeled amount of iron. It may contain not more than 0.5 per cent of phenol as a preser vative.

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of T ype I or T ype II glass.

USP Reference standards ⟨11⟩**—**
USP Endotoxin RS

Identification—To 1 mL of Injection on a watch glass add 2 drops of ammonium hydroxide: no precipitate is formed. Add 2 mL of hydrochloric acid, mix, and add 2 mL of ammonium hydroxide: a brown precipitate is formed.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 0.50 USP Endotoxin Unit per mg of iron.

Acute toxicity—Select five mice each weighing between 18 and 25 g, maintained on an adequately balanced diet. Inject a dose of Injection, equivalent to 200 mg of iron per kg of body weight, into a tail vein at a rate not exceeding 0.1 mL per second. Keep the mice under obser vation for 48 hours after the injection. If none of the mice show outward symptoms of toxicity, the requirements of the test are met. If any of the mice die within the obser vation period, select four groups of ten mice each weighing between 18 and 25 g. Inject, intravenously, all mice of one group with one of the following doses of Injection: 375, 500, 750, or 1000 mg of iron per kg of body weight. Observe the mice for 7 days, and record the number of deaths in each group. If more than 16 mice die, calculate the LD_{50} as directed under *Design and Analysis of Biological Assays* ⟨111⟩: the LD_{50} is not less than 500 mg of iron per kg of body weight.

Absorption from injection site—Prepare a site over the semitendinosus muscle of one leg of each of two rabbits by clipping the fur and disinfecting the exposed skin. Inject each site with a dose of 0.4 mL per kg of body weight in the following manner. Place the needle in the distal end of the semitendinosus muscle at an angle such as to ensure that the full length of the needle is used, then pass it through the sartorius and vastus medialis muscles. House the rabbits separately. Seven days after the injection, sacrifice the rabbits and dissect the treated legs to examine the muscles: no heavy black deposit of unabsorbed iron compounds is obser ved, and the tissue is only lightly colored.

pH ⟨791⟩: between 4.5 and 7.0.

Nonvolatile residue—Using a "to contain" pipet, transfer 1.0 mL onto 3 to 5 g of sand spread in a shallow layer in a stainless steel dish, the dish and sand having been previously dried and weighed. Rinse the pipet, with several small portions of water, onto the sand. Evaporate on a steam bath to dr yness, continue the drying in an oven at 105 ° for 15 hours, and weigh: the weight of the residue for Injection labeled to contain 50 mg of iron per mL is not less than 28.0% and not more than 32.0%, that for Injection labeled to contain 75 mg of iron per mL is not less than 35.0% and not more than 40.0%, and that for Injection labeled to contain 100 mg of iron per mL is not less than 37.0% and not more than 43.0%.

Chloride content—Using a "to contain" pipet, transfer 10.0 mL of Injection into a 150-mL beaker, rinsing the pipet into the beaker with several small portions of water. Add 50 mL of water and 2 mL of nitric acid, mix, and titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically with silver-glass electrodes. Each mL of 0.1 N silver nitrate consumed is equivalent to 3.545 mg of chloride (Cl). The chloride content of Injection labeled to contain 50 mg of iron per mL is not less than 0.48% and not more than 0.68%, and that of Injection labeled to contain either 75 mg or 100 mg of iron per mL is not less than 0.8% and not more than 1.1%.

Limit of phenol—Proceed as directed for *Phenol* under *Antimicrobial Agents—Content* ⟨341⟩: not more than 0.5% is found.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay for iron—

Iron stock solution—Transfer an accurately weighed quantity of about 350 mg of ferrous ammonium sulfate hexahydrate to a 1000-mL volumetric flask, add water to dissolve, dilute with water to volume, and mix to obtain a solution having a concentration of 50 µg of iron per mL.

Calcium chloride solution—Transfer 2.64 g of calcium chloride dihydrate to a 1000-mL volumetric flask, add 500 mL of water, and swirl to dissolve. Add 5.0 mL of hydrochloric acid, and dilute with water to volume.

Standard preparations—To separate 100-mL volumetric flasks transfer 2.0, 4.0, 6.0, 8.0, and 10.0 mL, respectively, of *Iron stock solution*. Dilute each flask with *Calcium chloride solution* to volume, and mix to obtain *Standard preparations* having known concentrations of 1.0, 2.0, 3.0, 4.0 and 5.0 µg of iron per mL.

Assay preparation—Using a "to contain" pipet, transfer an accurately measured volume of Injection, equivalent to about 100 mg of iron, to a 200-mL volumetric flask. Dilute with *Calcium chloride solution* to volume, and mix. Pipet 2.0 mL of this solution into a 250-mL volumetric flask, dilute with *Calcium chloride solution* to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparations* and the *Assay preparation* at the iron emission line of 248.3-nm with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with an iron hollow-cathode lamp and an air–acetylene flame, using the *Calcium chloride solution* as the blank. Plot the absorbance of each *Standard preparation* versus concentration, in µg per mL, of iron, and draw the straight line best fitting the five plotted points. From the graph so obtained, determine the concentration, in µg per mL, of iron in the *Assay preparation*. Calculate the quantity, in mg, of iron in each mL of the Injection taken by the formula:

$$25C / V$$

in which C is the concentration, in µg per mL, of iron in the *Assay preparation;* and V is the volume of Injection taken.

Iron Sorbitex Injection

» Iron Sorbitex Injection is a sterile solution of a complex of iron, Sorbitol, and Citric Acid that is stabilized with the aid of Dextrin and an excess of Sorbitol. It contains not less than 94.0 per cent and not more than 104.0 per cent of the labeled amount of iron.

Packaging and storage—Preserve in single-dose containers, preferably of Type I glass.

Labeling—Label it to indicate its expiration date, which is not more than 24 months after date of manufacture.

USP Reference standards ⟨11⟩**—**
USP Endotoxin RS

Identification—

A: To 1 mL of Injection add 5 mL of water and 1 mL of ammonium hydroxide: no precipitate is formed.

B: To 1 mL of Injection add 0.1 mL of 3 N hydrochloric acid and 0.5 mL of potassium ferrocyanide TS: a dark blue precipitate is formed.