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Iodixanol Injection

DEFINITION
Iodixanol Injection is a sterile solution of Iodixanol in Water for Injection. It contains NLT 95.0% and NMT 105.0% of the labeled amount of iodixanol ($C_{35}H_{44}I_6N_6O_{15}$), as organically bound iodine. It may contain stabilizers and buffers. It contains no antimicrobial agents.

IDENTIFICATION
• **A.** The retention times of the two major peaks of the *Sample solution* correspond to those of *Standard solution B*, as obtained in *Organic Impurities, Procedure 2*.

ASSAY
• **PROCEDURE**
Sample solution: Transfer 2 mL of the Injection to a glass-stoppered, 125-mL conical flask, add 50 mL of 5% [sodium hydroxide](#) solution and 1.0 g of powdered [zinc](#), connect the flask to a reflux condenser, and reflux for 1 h. Cool the flask to room temperature, and rinse the condenser with 20 mL of [water](#), adding the rinsing to the refluxed solution. Filter the mixture, rinsing the flask and the filter with several small portions of [water](#), and adding the filtered rinsings to the filtrate. Add 20 mL of [glacial acetic acid](#) dilute with [water](#) to 200.0 mL, and transfer 100.0 mL of this solution to a 250-mL conical flask.
Analysis: Titrate with [0.1 N silver nitrate VS](#) using autotitration. Each mL of 0.1 N silver nitrate is equivalent to 25.84 mg of $C_{35}H_{44}I_6N_6O_{15}$.
[NOTE—The result must be corrected for any inorganic halides that may be present due to added stabilizers or buffers.]
Acceptance criteria: 95.0%–105.0%

IMPURITIES
• **ORGANIC IMPURITIES, PROCEDURE 1**
Solution A: [Acetonitrile](#) and [water](#) (1:1)
Solution B: [Water](#)
Blank solution: [Water](#)
Mobile phase: See [Table 1](#).

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	6	94
30	20	80
70	100	0
80	100	0
81	6	94
90	6	94

Standard stock solution A: 12.5 mg/mL of anhydrous iodixanol from [USP Iodixanol RS](#) in [water](#)
Standard stock solution B: 0.25 mg/mL of anhydrous iodixanol related compound C from [USP Iodixanol Related Compound C RS](#) in [water](#)
Standard stock solution C: 0.025 mg/mL of anhydrous iodixanol related compound D from [USP Iodixanol Related Compound D RS](#) in [water](#)
Standard solution A: 2.5 mg/mL of *Standard stock solution A* in [water](#)

Standard solution B: *Standard stock solution A, Standard stock solution B, Standard stock solution C, and [water](#) (5:2.5:2.5:15)*

Sample solution A: 25 mg/mL of iodixanol obtained from a volume of Injection in [water](#)

Sample solution B: 2.5 mg/mL of iodixanol obtained from a volume of Injection in [water](#)

Control solution: *Sample solution A, Standard stock solution B, and [water](#) (5:2.5:42.5)*

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-μm packing [L1](#)

Flow rate: 1 mL/min

Injection volume: 10 μL

System suitability

Samples: *Blank solution, Standard solution A, at least three replicates of Standard solution B, and Control solution*

Chromatograph the solutions as mentioned above. The chromatogram from *Standard solution A* exhibits two or three principal unresolved peaks. If the chromatogram exhibits two principal peaks, their relative areas are 60% and 40%. If the chromatogram exhibits three principal peaks, their relative areas are 60%, 38%, and 2%. The chromatogram from *Standard solution B* exhibits two resolved peaks due to iodixanol related compound D that elute before the iodixanol peaks and one iodixanol related compound C peak between the two principal iodixanol peaks. The area of the two iodixanol related compound D peaks is between 0.075% and 0.125% of the total area. Add the areas of the two isomer peaks for iodixanol related compound D from each of the three injections of *Standard solution B*, and calculate the relative standard deviation for the three summed areas: the relative standard deviation is NMT 5%. Measure the height of the iodixanol related compound C peak, and, if necessary, adjust the sensitivity of the amplifier to obtain a peak height between 80% and 100% of the full scale. Measure the height, *A*, above the baseline of the iodixanol related compound C peak and the height, *B*, above the baseline of the lowest part of the curve separating this peak from the first principal iodixanol peak: *A* is NLT 1.3*B*. In the chromatogram from the *Control solution*, iodixanol related compound C exhibits a measurable peak.

Analysis

Samples: *Blank solution, Sample solution A, and Sample solution B*

High-low chromatography: Where it is specified to proceed as directed for *High-low chromatography*, for the chromatogram from *Sample solution A*, calculate the percentage of each specified related compound in the portion of Injection taken:

$$\text{Result} = (10X)/(0.1Y + Z)$$

X = peak area for each of the specified related compounds from *Sample solution A*

Y = total area of all the peaks eluted before and after iodixanol from *Sample solution A*, disregarding any peaks due to injection noise or solvent

Z = sum of peak areas of iodixanol and any related compounds that are eluted together with, and between, the principal iodixanol peaks from *Sample solution B*

Iohexol: If iohexol is present, it exhibits two peaks, with retention times of 0.37 and 0.39 relative to the main iodixanol peak, in the chromatogram from *Sample solution A*. Draw a baseline at the height of the baseline from the *Blank solution*.

Calculate the total area of the two peaks and the percentage of iohexol in the portion of Injection taken as directed for *High-low chromatography*.

Iohexol related compound A¹: If iohexol related compound A is present, it elutes as a single peak with a retention time of 0.34 relative to the main iodixanol peak, in the chromatogram from *Sample solution A*. Draw a baseline at the height of the baseline from the *Blank solution*.

Calculate the area of the peak and the percentage of iohexol related compound A in the portion of Injection taken as directed for *High-low chromatography*.

Iodixanol related compound C: If iodixanol related compound C is present, only the first and larger peak, with a retention time of 1.07 relative to the main iodixanol peak, is seen between the two principal iodixanol peaks in the chromatogram from *Sample solution A*; the second iodixanol related compound C peak co-elutes with iodixanol. The area of the first and larger peak corresponds to 80% of the total area of iodixanol related compound C. Draw a vertical line through the minimum before the first and larger peak. Draw a horizontal baseline at the minimum after the first and larger peak.

Calculate the percentage of iodixanol related compound C in the portion of Injection taken:

$$\text{Result} = 12.5X_2/(0.1Y + Z)$$

*X*₂ = iodixanol related compound C peak area