

BRIEFING

Oxaliplatin: This monograph was posted on the USP Website as a draft USP Pending Standard for public comment. No comments were received. The MD-ODD Expert Committee reviewed the draft and approved the monograph as an Authorized USP Pending Standard. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Thermo Electron Corporation ODS Hypersil brand of L1 column. The typical retention time observed for oxaliplatin is about 8 minutes. The related compounds are monitored by four chromatographic procedures. These procedures are based on analyses performed with the following columns:

1. *Limit of oxalic acid:* Thermo Electron Corporation BDS Hypersil C18 brand of L1 column.
2. *Limit of (SP-4-2)-di aqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum:* Thermo Electron Corporation BDS Hypersil C18 brand of L1 column.
3. *Limit of oxaliplatin related compound C, oxaliplatin related compound F, and unspecified impurities:* Thermo Electron Corporation ODS Hypersil brand of L1 column.
4. *Limit of oxaliplatin related compound D:* Daicel Chemical Industries Chiralcel OC-H brand of L## column.

An authorized version of this monograph was posted on the USP Website in February 29, 2008. The following corrections are made:

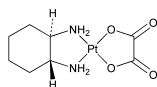
1. *Limit of oxaliplatin related compound C, oxaliplatin related compound F, and unspecified impurities* line 10 under *Identification solution:* Change “{C₆H₁₄N₄O₆Pt, 433.28}” to {C₆H₁₄I₂N₂Pt, 563.08}.
2. *Assay*, line 8 under *System suitability solution:* Change “{C₆H₁₄N₄O₆Pt, 433.28}” to {C₆H₁₄Cl₂N₂Pt, 380.17}

(MD-ODD: F. Mao; MSA: R. Tirumalai) RTS—C43046

Add the following:

■ **Oxaliplatin**

v. 1.1 Authorized September 20, 2007



C₈H₁₄N₂O₄Pt 397.29

[*SP-4-2-(1R-trans)*]-[1,2-cyclohexanediamine-*N,N'*][ethanedioato(2-)-*O,O'*]platinum.

cis-[(1*R,2R*)-1,2-Cyclohexanediamine-*N,N'*][oxalato(2-)-*O,O'*]platinum [61825-94-3].

» Oxaliplatin contains not less than 98.0 percent and not more than 102.0 percent of C₈H₁₄N₂O₄Pt, calculated on the dried basis.

Packaging and storage—Preserve in tight, polyethylene containers. Store at room temperature.

USP Reference standards <11>—*USP Endotoxin RS. USP Oxaliplatin RS. USP Oxaliplatin Related Compound A RS. USP Oxaliplatin Related Compound B RS. USP Oxaliplatin Related Compound C RS. USP Oxaliplatin Related Compound D RS. USP Oxaliplatin Related Compound F RS. USP Oxaliplatin System Suitability RS.*

Identification—

A: *Infrared Absorption* <197K>.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Bacterial endotoxins <85>—The level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Oxaliplatin is used can be met. Where the label states that Oxaliplatin must be subjected to further processing during the preparation of dosage forms, the level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Oxaliplatin is used can be met.

Microbial limits <61>—The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

Acidity—Dissolve 100 mg in 50 mL of carbon dioxide-free water, add 0.5 mL of phenolphthalein TS: the solution is colorless, and not more than 0.60 mL of 0.01 M sodium hydroxide is required to change the color of the solution to pink.

Loss on drying <731>—Dry about 1 g at 100° to 105° for 2 hours: it loses not more than 0.5% of its weight.

Specific rotation <781S>: between +74.5° and +78.0°, on the dried basis.

Test solution: 5 mg per mL, in water, at 20°.

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Limit of silver—

Standard stock solution—Dilute quantitatively, and stepwise if necessary, a commercially available silver nitrate atomic absorption standard solution containing about 1.000 g of silver per L with 0.5 M nitric acid to obtain a solution having a known concentration of 5.0 µg per mL.

Standard solutions—Pipet 0.5, 1, 2, 3, and 4 mL of the *Standard stock solution* to separate 100-mL volumetric flasks. Dilute quantitatively with 0.5 M nitric acid to obtain solutions having known concentrations of about 0.025, 0.05, 0.1, 0.15, and 0.2 µg per mL, respectively.

Test solution—Transfer 0.5 g of Oxaliplatin, accurately weighed, to a 50-mL volumetric flask. Add 20 mL of nitric acid, and decompose samples by heating to approximately 80° until the liquid is clear. Cool down to ambient temperature, and dilute quantitatively with water to obtain a solution having a known concentration of about 10 mg of decomposed oxaliplatin per mL.

Procedure (see *Spectrophotometry and Light-Scattering* (851))—Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at the silver emission line of 328.1 nm with a suitable atomic absorption spectrophotometer equipped with a silver hollow-cathode lamp and an oxidizing air-acetylene flame, using 0.5 M nitric acid as the blank. Plot the absorbances of the *Standard solutions* versus their concentrations, in µg per mL, of silver, and draw the straight line best fitting the five plotted points. Calculate the linearity between the responses of the *Standard solutions* and their concentrations. The resulting correlation coefficient should be not less than 0.99. From the graph obtained, determine the concentration of silver, in µg per mL, in the *Test solution*. [NOTE—The instrument-calculated standard curve and the concentration of silver, in µg per mL, in the *Test solution* are equivalent to those obtained by the manual process.] Calculate the ppm of silver in the portion of Oxaliplatin taken by the formula:

$$50 \frac{C}{W}$$

in which *C* is the concentration, in µg per mL, of silver in the *Test solution*; and *W* is the weight, in g, of Oxaliplatin taken for the *Test solution*. Not more than 5 ppm of silver is found.

Limit of oxalic acid—

Mobile phase—Add 1.36 g of potassium dihydrogen phosphate to 8 mL of a 400 g per L solution of tetrabutylammonium hydroxide, and dilute with water to 1000 mL. Mix 80 volumes of this solution and 20 volumes of acetonitrile, and adjust with phosphoric acid to a pH of 6.0.

Standard stock solution—Dissolve an accurately weighed quantity of USP Oxaliplatin Related Compound A RS in water to obtain a solution having a known concentration of about 0.06 mg per mL. [NOTE—USP Oxaliplatin Related Compound A RS is dihydrate oxalic acid (C₂H₂O₄ · 2H₂O 126.07).]

Standard solution—Dilute the *Standard stock solution* quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 1.5 µg per mL.

System suitability solution—Dissolve suitable quantities of sodium nitrate in water, and dilute quantitatively to obtain a solution having a known concentration of about 0.05 mg per mL. Pipet 2 mL of this solution and 25 mL of the *Standard stock solution* into a 100-mL volumetric flask, and dilute with water to volume.

Test solution—Dissolve an accurately weighed quantity of Oxaliplatin in water to obtain a solution having a known concentration of about 2 mg per mL. [NOTE—Inject the *Test solution* immediately after preparation.]

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. The column temperature is maintained at 40°. Chromatograph 20 µL of the *System suitability solution*, and record the peak areas as directed for *Procedure*: the relative retention times are about

2.1 for sodium nitrate and 4.0 for oxalic acid; and the resolution, *R*, between the peaks of oxalic acid and sodium nitrate is not less than 9. Chromatograph the *Standard solution*, and record the peak areas as directed for *Procedure*: the relative standard deviation of the oxalic acid peak for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, allow the chromatogram to run for about 12 minutes, and record the chromatograms. Calculate the percentage of oxalic acid in the portion of Oxaliplatin taken by the formula:

$$100(90.03/126.07)(C_s/C_v)(r_u/r_s)$$

in which 90.03 and 126.07 are the molecular weights of oxalic acid and USP Oxaliplatin Related Compound A RS, respectively; C_s is the concentration, in mg per mL, of oxaliplatin related compound A in the *Standard solution*; C_v is the concentration, in mg per mL, of Oxaliplatin in the *Test solution*; r_u is the oxalic acid area in the *Test solution*; and r_s is the oxalic acid area in the *Standard solution*: not more than 0.1% of oxalic acid is found.

Limit of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum—[NOTE—Use suitable polypropylene containers for the preparation and injection of all solutions.]

Mobile phase—Dissolve 1.36 g of potassium dihydrogen phosphate and 1 g of sodium heptanesulfonate in 1000 mL of water. Mix 80 volumes of this solution and 20 volumes of acetonitrile, and adjust with phosphoric acid to a pH of 3.0 ± 0.05 .

Standard stock solution—Dissolve an accurately weighed quantity of USP Oxaliplatin Related Compound B RS in methanol, and dilute quantitatively with water to obtain a solution having a known concentration of about 0.05 mg per mL. [NOTE—USP Oxaliplatin Related Compound B RS {[SP-4-2-(1R-*trans*)]-(1,2-cyclohexanediamine-*N,N'*) dinitratoplati-

num(II), $C_6H_{14}N_4O_6Pt$, 433.28} is converted to (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum after dissolving in methanol and diluting with water.]

Standard solution—Dilute the *Standard stock solution* quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.75 µg per mL.

System suitability solution—Dissolve about 5 mg of USP Oxaliplatin Related Compound B RS in 25 mL of methanol and dilute to 100 mL with water. Adjust with 0.2 g per L of sodium hydroxide solution to a pH of 6.0. Heat for 4 hours at 70°, and allow to cool. [NOTE—The preparation of the *System suitability solution* forms diaquodiaminocyclohexaneplatinum dimer.]

Test solution—Dissolve an accurately weighed quantity of Oxaliplatin in water to obtain a solution having a known concentration of about 2 mg per mL. [NOTE—Inject the *Test solution* immediately after preparation.]

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. The column temperature is maintained at 40°. Chromatograph the *System suitability solution*, and record the peak areas as directed for *Procedure*: the relative retention times are about 2.4 for (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum and 3.4 for diaquodiaminocyclohexaneplatinum dimer; the resolution, *R*, between the (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum peak and the diaquodiaminocyclohexaneplatinum dimer peak is not less than 7. Chromatograph the *Standard solution*, and record the peak areas as directed for *Procedure*: the relative standard deviation of the (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum peak for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, allow the chromatogram to run for about 10

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minutes, and record the chromatograms. Calculate the percentage of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum in the portion of Oxaliplatin taken by the formula:

$$100(345.30/433.28)(C_s/C_v)(r_v/r_s)$$

in which 345.30 and 433.28 are the molecular weights of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum and USP Oxaliplatin Related Compound B, respectively; C_s is the concentration, in mg per mL, of oxaliplatin related compound B in the *Standard solution*; C_v is the concentration, in mg per mL, of Oxaliplatin in the *Test solution*; r_s is the (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum peak area in the *Test solution*; and r_s is the (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum peak area in the *Standard solution*: not more than 0.1% of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum is found.

Limit of oxaliplatin related compound C, oxaliplatin related compound F, and unspecified impurities—

Mobile phase and System suitability solution—Proceed as directed in the *Assay*.

Oxaliplatin related compound C standard stock solution—Dissolve an accurately weighed quantity of USP Oxaliplatin Related Compound C RS in water to obtain a solution having a known concentration of about 0.1 mg per mL. [NOTE—USP Oxaliplatin Related Compound C RS is [1*R*-trans-(1,2-cyclohexanediamine-*N,N'*)]-trans-dihydroxido-[oxalato(2-)-*O,O'*]platinum(IV) {C₆H₁₆N₂O₆Pt, 431.30}.]

Oxaliplatin related compound C standard solution—Dilute the *Standard stock solution* quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 2.0 µg per mL.

Oxaliplatin standard stock solution—Dissolve an accurately weighed quantity of USP Oxaliplatin RS in water to obtain a solution having a known concentration of about 0.1 mg per mL.

Standard solution—Dilute the *Oxaliplatin related compound C standard stock solution* and the *Oxaliplatin standard stock solution* quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 1.0 µg each per mL.

Identification solution—Dissolve suitable quantities of USP Oxaliplatin Related Compound F in methanol, sonicating and gently heating in a water bath if necessary, to obtain a solution having a known concentration of 0.1 mg per mL. Dilute this solution quantitatively with water to obtain a solution having a known concentration of about 1.0 µg per mL. [NOTE—USP Oxaliplatin Related Compound F RS is [SP-4-2-(1*R*-trans)]-(1,2-cyclohexanediamine-*N,N'*) diiodido-platinum(II) {C₆H₁₄I₂N₂Pt, 563.08}.]

Test solution—Dissolve an accurately weighed quantity of Oxaliplatin in water to obtain a solution having a known concentration of about 2 mg per mL. [NOTE—Inject the *Test solution* immediately after preparation.]

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 40°. Chromatograph the *System suitability solution*, and record the peak areas as directed for *Procedure*: the resolution, *R*, between the USP Oxaliplatin System Suitability RS peak and the oxaliplatin peak is not less than 2.0. Chromatograph the *Standard solution*, and record the peak areas as directed for *Procedure*: the relative standard deviations of the oxaliplatin related compound C and oxaliplatin peaks for replicate injections are not more than 10.0%. Chromatograph the *Identification solution*, and record the retention time of oxaliplatin related compound F for the purpose of peak identification. [NOTE—The relative retention times are about 0.6 for oxaliplatin related compound C, 0.9 for USP Oxaliplatin System Suitability RS, and 1.0 for Oxaliplatin.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Oxaliplatin related compound C standard solution*, the *Standard solution*, and the *Test solution* into the chromatograph, allow the chromatogram to run for about 35 minutes, and record the chromatograms. [NOTE—Disregard any peak with an area less than that of the peak due to oxaliplatin obtained from the *Standard solution*. Disregard any peak with a retention time of less than 2 minutes.] Calculate the percentage of oxaliplatin related compound C in the portion of Oxaliplatin taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of oxaliplatin related compound C in the *Oxaliplatin related compound C standard solution*; C_U is the concentration, in mg per mL, of Oxaliplatin in the *Test solution*; r_U is the oxaliplatin related compound C peak area in the *Test solution*; and r_S is the oxaliplatin related compound C peak area in the *Oxaliplatin related compound C standard solution*: not more than 0.1% of oxaliplatin related compound C is found. Calculate the percentage of oxaliplatin related compound F or any unspecified impurity in the portion of Oxaliplatin taken by the formula:

$$100(1F)(C_S/C_U)(r_U/r_S)$$

in which F is the relative response factor for oxaliplatin related compound F and any unspecified impurity ($F = 2.8$ for oxaliplatin related compound F; $F = 1.0$ for any unspecified impurity); C_S is the concentration, in mg per mL, of oxaliplatin in the *Standard solution*; C_U is the concentration, in mg per mL, of Oxaliplatin in the *Test solution*; r_U is the oxaliplatin related compound F or any unspecified impurity peak area in the *Test solution*; and r_S is the oxaliplatin peak area in the *Standard solution*: not more than 0.1% of oxaliplatin related compound F is found; not more than 0.1% of any single unspecified impurity is found; and not more than 0.1% of total unspecified impurities is found. The sum of

oxalic acid, (*SP-4-2*)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]platinum, oxaliplatin related compound C, oxaliplatin related compound F, and total unspecified impurities is not more than 0.30%.

Limit of oxaliplatin related compound D—

Mobile phase—Prepare a mixture of methanol and ethanol (70 : 30).

Oxaliplatin related compound D standard stock solution—Dissolve an accurately weighed quantity of USP Oxaliplatin Related Compound D RS in methanol to obtain a solution having a known concentration of about 50 µg per mL. [NOTE—USP Oxaliplatin Related Compound D RS is *cis*-[(1*S*,2*S*)-1,2-cyclohexanediamine-*N,N'*][oxalato(2-)-*O,O'*]platinum { $C_8H_{14}N_2O_4Pt$, 397.29}.]

Oxaliplatin related compound D standard solution—Dilute the *Oxaliplatin related compound D standard stock solution* quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 7.5 µg per mL.

Oxaliplatin standard stock solution—Dissolve an accurately weighed quantity of USP Oxaliplatin RS in methanol to obtain a solution having a known concentration of about 0.75 mg per mL.

Oxaliplatin standard solution—Dilute the *Oxaliplatin standard stock solution* quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 37.5 µg per mL.

Standard solution—Transfer 2 mL of *Oxaliplatin related compound D standard solution* and 40 mL of *Oxaliplatin standard stock solution* into a 50-mL volumetric flask, and dilute with methanol to volume.

System suitability solution I—Transfer 5 mL of *Oxaliplatin standard solution* and 4 mL of *Oxaliplatin related compound D standard stock solution* into a 50-mL volumetric flask, and dilute with methanol to volume.

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System suitability solution II—Dilute the Oxaliplatin related compound D standard solution quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.6 µg per mL.

Test solution—Dissolve an accurately weighed quantity of Oxaliplatin in methanol to obtain a solution having a known concentration of about 0.6 mg per mL.

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L##. The flow rate is about 0.3 mL per minute. The column temperature is maintained at between 36° and 40°. Chromatograph the *System suitability solution I*, and record the peak areas as directed for *Procedure*: the relative retention time is about 1.2 for oxaliplatin related compound D; and the resolution, *R*, between the oxaliplatin related compound D peak and the oxaliplatin peak is not less than 1.5. Chromatograph the *System suitability solution II*, and record the peak areas as directed for *Procedure*: the relative standard deviation of oxaliplatin related compound D peak for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, allow the chromatogram to run for about 26 minutes, and record the chromatograms. Calculate the percentage of oxaliplatin related compound D in the portion of Oxaliplatin taken by the formula:

$$100(C_S/C_V)(r_V/r_S)$$

in which C_S is the concentration, in mg per mL, of oxaliplatin related compound D in the *Standard solution*; C_V is the concentration, in mg per mL, of Oxaliplatin in the *Test solution*; r_V is the oxaliplatin related compound D peak area in the *Test solution*; and r_S is the oxaliplatin related compound D peak area in the *Standard solution*: not more than 0.1% of oxaliplatin related compound D is found.

Assay—

Acidified water—Adjust water with phosphoric acid to a pH of 3.0.

Mobile phase—Prepare a mixture of *Acidified water* and acetonitrile (99 : 1).

Standard preparation—Dissolve an accurately weighed quantity of USP Oxaliplatin RS in water to obtain a solution having a known concentration of about 0.1 mg per mL.

System suitability solution—Dissolve suitable quantities of USP Oxaliplatin System Suitability RS in methanol to obtain a solution having a known concentration of about 0.1 mg per mL. Transfer 1 mL of this solution and 1 mL of the *Standard preparation* into a 10-mL volumetric flask, and dilute with water to volume. [NOTE—USP Oxaliplatin System Suitability RS is [SP-4-2-(1*R*-*trans*)]-(1,2-cyclohexanediamine-*N,N'*) dichloridoplatinum(II) {C₆H₁₄Cl₂N₂Pt, 380.17}.]

Assay preparation—Dissolve an accurately weighed quantity of Oxaliplatin in water to obtain a solution having a known concentration of about 0.1 mg per mL.

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 40°. Chromatograph the *System suitability solution*, and record the peak areas as directed for *Procedure*: the resolution, *R*, between the USP Oxaliplatin System Suitability RS peak and the oxaliplatin peak is not less than 2.0. Chromatograph the *Standard preparation*, and record the peak areas as directed for *Procedure*: the relative standard deviation of the oxaliplatin peak for replicate injections is not more than 2.0%; and the tailing factor is not greater than 1.5.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, allow the chromatogram to run for about 12 minutes, record the chromatograms, and measure the areas

for oxaliplatin peaks. Calculate the quantity, in percent, of $C_8H_{14}N_2O_4Pt$ in the portion of Oxaliplatin taken by the formula:

$$100(C_s/C_u)(r_u/r_s)$$

in which C_s is the concentration, in mg per mL, of USP Oxaliplatin RS in the *Standard preparation*; C_u is the concentration of Oxaliplatin in the *Assay preparation*; and r_u and r_s are the peak areas obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■