
INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

- The list of new USP Reference Standards that have become available
- The list of assays or tests that are adopted but held in abeyance pending availability of required USP Reference Standards
- Newly adopted (official) revisions to the *USP–NF* that become official before the official date of the next *Supplement* or that were not ready for adoption by the closing date for the upcoming *Supplement*. (The official date for these revisions is stated on the next page.)
- Errata

Readers should review this section to determine if they are affected by any of the changes.

Symbols—New text is enclosed in symbols and set off from the current official text as shown in the following example:
•new text•

Where the symbols appear together with no enclosed text, such as ••, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the issue of a given *PF* volume.

Errata—Errata are considered to be text, erroneously published in the *USP–NF* or its *Supplements*, that do not accurately reflect the intended official requirements of the Council of Experts. At the end of the *Interim Revision Announcement* section in this publication is a list of errata and corrections to the *USP–NF*. The page number indicates where the item is found in *USP–NF*. Errata lists are updated as necessary in each *Pharmacopeial Forum* and also appear on USP’s website (www.usp.org). Errata lists will be cumulative in future *Supplements*, and the corrected text will appear in the next annual edition of *USP–NF*.

INTERIM REVISION ANNOUNCEMENT	1465
MONOGRAPHS (USP)	1469
Vincristine Sulfate Injection	1469
Vincristine Sulfate for Injection	1470
ERRATA LIST FOR <i>USP 32–NF 27</i>	1473

INTERIM REVISION
ANNOUNCEMENT
to *USP 33* and to *NF 28 REISSUE*

*By authority of the United States Pharmacopeial Convention, Inc.
Prepared by the Council of Experts and published by the Board of Trustees*

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Released November 1, 2010

Official December 1, 2010

Interim Revision Announcement

Inquiries regarding *USP–NF* can be addressed to the USP Executive Secretariat, 12601 Twinbrook Parkway, Rockville, MD 20852, USA (execsec@usp.org).

New USP Reference Standards

The following USP Reference Standards, which were not available when the associated monograph was made official, have since become available. The respective official date of each *USP–NF* standard, test, or assay requiring the use of the following USP Reference Standards is indicated in parentheses after the name of the Reference Standard. Note that the official date is six months after the notice of availability for this Reference Standard was published in *PF*.

USP Amifostine RS (April 1, 2010)

USP Powdered *Echinacea Pallida* Extract RS (February 1, 2011)

Unavailable First-Time Official USP Reference Standards

The official dates of any *USP–NF* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards. This listing was updated as of August 16, 2010. Please refer to the current USP Catalog for a more up-to-date availability list. The USP Catalog can be accessed online at <http://www.uspcatalog.com>.

USP Acarbose RS
USP Acarbose System Suitability Mixture RS
USP Albumin Human RS
USP Alteplase RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Aprotinin RS
USP Aprotinin System Suitability RS
USP Copolymer Polypropylene RS
USP Diethylstilbestrol Diphosphate RS
USP Eucatropine Hydrochloride RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Maritime Pine Extract RS
USP Menotropins RS
USP Sargramostim RS
USP Sincalide RS
USP Valrubicin Related Compound A RS

MONOGRAPHS (USP)

Vincristine Sulfate Injection

DEFINITION

Vincristine Sulfate Injection is a sterile solution of Vincristine Sulfate in Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of vincristine sulfate ($C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$).

[CAUTION—Handle Vincristine Sulfate Injection with great care because it is a potent cytotoxic agent.]

IDENTIFICATION

Change to read:

• **▲A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST**

(201)▲USP33

Standard solution: 10 mg/mL of USP Vincristine Sulfate RS in dichloromethane and methanol (3:1)

Sample solution: Transfer a volume of Injection, equivalent to 2 mg of vincristine sulfate, to a small centrifuge tube. For each mL of solution add 1 drop of ammonium hydroxide. Add 0.2 mL of dichloromethane. Place the cap on the tube, shake it vigorously for NLT 1 min, and centrifuge for 1 min. Carefully withdraw the dichloromethane layer, and transfer to a small stoppered vial.

Chromatographic system

(See *Chromatography* (621), *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 20 μ L

Developing solvent system: Fresh ether, methanol, and methylamine solution (2 in 5) (19:2:1)

Spray reagent: Dissolve 2.0 g of ceric ammonium sulfate in 100 mL of water with heating and stirring, and slowly add 100 mL of phosphoric acid. Filter if necessary.

Analysis

Samples: *Standard solution* and *Sample solution*

Develop the chromatographic plate in a methanol prewash tank; for maximum sensitivity, dry it NMT 2 h before use. Score it about 15 cm above the points of application. Apply the *Standard solution* and the *Sample solution* about 2.5 cm from the lower edge of the plate, and dry thoroughly (a current of cool air may be used to help dry the spots). Place the plate in the nonequilibrated developing chamber that contains a paper liner around the back and sides and *Developing solvent system* to a depth of 2 cm. Remove the plate when the solvent moves to the scored line (about 80 min), and discard the solvent system. Dry the plate in a fume hood at room temperature, heat on a metal plate on a steam bath for 15 min, and spray the plate while still hot with *Spray reagent*. Continue heating the plate for 15 min to stabilize the spots.

Acceptance criteria: The R_f value and the color of the principal spot from the *Sample solution* correspond to those from the *Standard solution*.

Add the following:

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲USP33

ASSAY

• PROCEDURE

Solution A: Diethylamine and water (1:59). Adjust with phosphoric acid to a pH of 7.5.

Mobile phase: Methanol and *Solution A* (7:3)

System suitability solution: 1 mg/mL each of USP Vincristine Sulfate RS and USP Vinblastine Sulfate RS in water

Standard solution: 1 mg/mL of USP Vincristine Sulfate RS in water

Sample solution: Nominally 1 mg/mL from the Injection in water

Chromatographic system

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

Mode: LC

Detector: UV 297 nm

Precolumn: Porous silica gel packing

Guard column: 2- to 5-cm, packing L1

Column: 4.6-mm \times 25-cm, packing L7

Flow rate: 1.5 mL/min

Injection size: 10 μ L

System suitability

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

Suitability requirements

Resolution: NLT 4.0 between vincristine sulfate and vinblastine sulfate, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of vincristine sulfate ($C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$) in the portion of the Injection taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

C_U = nominal concentration of vincristine sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

Organic Impurities

• PROCEDURE

System suitability solution, Standard solution, and System suitability: Proceed as directed in the *Assay*.

Solution A: Diethylamine and water (3:197). Adjust with phosphoric acid to a pH of 7.5.

Solution B: Methanol

Solution C: Prepare a suitable dilution of any preservative present in the Injection, as identified in the labeling.

Mobile phase: See *Table 1*

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	38	62
12	38	62
27	8	92
29	38	62
34	38	62

Sample solution A: 1 mg/mL of vincristine sulfate from the Injection in water

Sample solution B: 0.04 mg/mL in water from the *Sample solution A*

Chromatographic system: Proceed as directed in the Assay, except to use a flow rate of 2 mL/min and an injection size of 200 μ L.

Analysis

Samples: *Solution C*, *Sample solution A*, and *Sample solution B*

Calculate the percentage of each impurity in the portion of Injection taken:

$$\text{Result} = [r_i / (\Sigma r_i + 25r_v)] \times 100$$

r_i = peak response of each impurity from the *Sample solution A*

r_v = peak response of vincristine from the *Sample solution B*

Calculate the percentage of total impurities in the portion of Injection taken:

$$\text{Result} = [(\Sigma r_i / (\Sigma r_i + 25r_v))] \times 100$$

The terms in the formula are as defined above.

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Vincristine	1.0	—
<i>N</i> -Desformylvincristine	1.4 \pm 0.1	3.0
Any other individual impurity	—	2.0
Total impurities	—	6.0

[NOTE—Make a suitable dilution of any preservative present in the Injection as identified in the labeling and determine the retention time. Disregard any peaks at these retention times for the calculations of any other individual impurity and total impurities.]

SPECIFIC TESTS

- **BACTERIAL ENDOTOXINS TEST (85):** It contains NMT 62.5 USP Endotoxin Units/mg of vincristine sulfate.
- **pH (791):** 3.5–5.5
- **STERILITY TESTS (71):** Meets the requirements
- **OTHER REQUIREMENTS:** It meets the requirements under *Injections (1)*, *Labeling*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in light-resistant glass containers and store in a refrigerator.

Change to read:

- **LABELING:** •The label states: "For Intravenous Use Only—Fatal If Given By Other Routes." •₆

Where labeled as containing more than 2 mg, it must also be labeled as a Pharmacy Bulk Package (see *Injections (1)*). The labeling directs that the drug be dispensed only in containers enclosed in an overwrap labeled as directed below. When packaged in a Pharmacy Bulk Package, it is exempt from the requirement under *Injections (1)* that the closure be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set, when it contains a suitable substance or mixture of substances to prevent the growth of microorganisms.

When dispensed, the container or syringe (holding the individual dose prepared for administration to the patient) must be enclosed in an overwrap bearing the statement: "Do Not Remove Covering Until Moment of Injection." •For Intravenous Use Only—Fatal If Given By Other Routes." •₆

• USP REFERENCE STANDARDS (11)

- USP Endotoxin RS
- USP Vinblastine Sulfate RS [Note—No loss on drying determination is needed.]
- USP Vincristine Sulfate RS

Vincristine Sulfate for Injection

DEFINITION

Vincristine Sulfate for Injection is a sterile mixture of Vincristine Sulfate with suitable diluents. It contains NLT 90.0% and NMT 110.0% of the labeled amount of vincristine sulfate ($C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$).

[CAUTION—Handle Vincristine Sulfate for Injection with great care because it is a potent cytotoxic agent.]

IDENTIFICATION

Change to read:

• **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST**

(201)_{▲USP33}

Standard solution: 10 mg/mL of USP Vincristine Sulfate RS in dichloromethane and methanol (3:1)

Sample stock solution: 25 mg/mL of vincristine sulfate from Injection in water

Sample solution: 10 mg/mL of vincristine sulfate from *Sample stock solution* in methanol

Chromatographic system

(See *Chromatography (621)*, *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 20 μ L

Developing solvent system: Fresh ether, methanol, and methylamine solution (2 in 5) (19:2:1)

Spray reagent: Dissolve 2.0 g of ceric ammonium sulfate in 100 mL of water with heating and stirring, and slowly add 100 mL of phosphoric acid. Filter if necessary.

Analysis: Develop blank plate in a methanol prewash tank; for maximum sensitivity, dry it NMT 2 h before use. Score it about 15 cm above the points of application. Apply the *Sample solution* and the *Standard solution* at points about 2.5 cm from the lower edge of the plate, and dry thoroughly (a current of cool air may be used to help dry the spots). Place the plate in the nonequilibrated developing chamber that contains a paper liner around the back and sides and *Developing solvent system* to a depth of about 2 cm. Remove the plate when the solvent moves to the scored line (about 80 min), and discard the solvent system. Dry the plate in a fume hood at room temperature, heat on a metal plate on a steam bath for about 15 min, and spray the plate while still hot with *Spray reagent*. Continue heating the plate for 15 min to stabilize the spots.

Acceptance criteria: The R_f value and the color of the principal spot from the *Sample solution* correspond to those from the *Standard solution*.

Add the following:

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay._{▲USP33}

ASSAY

• PROCEDURE

Solution A: Diethylamine and water (1:59). Adjust with phosphoric acid to a pH of 7.5.

Mobile phase: Methanol and *Solution A* (70:30)

System suitability solution: 1 mg/mL each of USP Vincristine Sulfate RS and USP Vinblastine Sulfate RS in water

Standard solution: 1 mg/mL of USP Vincristine Sulfate RS in water

Sample solution: 1 mg/mL of vincristine sulfate (from the Vincristine Sulfate for Injection) in water. [NOTE—Shake to mix.]

Chromatographic system

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

Mode: LC

Detector: UV 297 nm

Pre-column: Porous silica gel packing

Guard column: 2- to 5-cm, packing L1

Column: 4.6-mm × 25-cm, packing L7

Flow rate: 1.5 mL/min

Injection size: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 4.0 between vincristine sulfate and vinblastine sulfate, *System suitability solution*. [NOTE—For a particular column, the resolution may be increased by increasing the proportion of water in the *Mobile phase*.]

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of vincristine sulfate (C₄₆H₅₆N₄O₁₀ · H₂SO₄) in the portion of Vincristine Sulfate for Injection taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

C_U = nominal concentration of vincristine sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **UNIFORMITY OF DOSAGE UNITS, Content Uniformity (905)**

Buffer solution: Dissolve 6.3 g of ammonium formate in about 900 mL of water, adjust with formic acid to a pH of 5.0 while stirring, and dilute with water to 1000 mL.

Standard solution: 40 µg/mL of USP Vincristine Sulfate RS in *Buffer solution*

Sample solution: Between 40 and 50 µg/mL of vincristine sulfate in *Buffer solution*. [NOTE—Dissolve the contents of 1 container of Vincristine Sulfate for Injection in a suitable volume of *Buffer solution*.]

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: UV

Cell: 1 cm

Absorbance: 262 nm

Blank: *Buffer solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in mg, of C₄₆H₅₆N₄O₁₀ · H₂SO₄ in the container of Vincristine Sulfate for Injection taken:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times F$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Vincristine Sulfate RS in the *Standard solution* (µg/mL)

V = final volume of the *Sample solution*

F = unit conversion factor, 0.001 mg/µg

Acceptance criteria: Meets the requirements for solids

IMPURITIES

Organic Impurities

• **PROCEDURE**

Solution A: Diethylamine and water (3:197). Adjust with phosphoric acid to a pH of 7.5.

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	38	62
12	38	62
27	8	92
29	38	62
34	38	62

System suitability solution, Standard solution, and System suitability: Proceed as directed in the *Assay*.

Sample solution A: 1 mg/mL of vincristine sulfate from Vincristine Sulfate for Injection in water

Sample solution B: 0.04 mg/mL of vincristine sulfate from *Sample solution A*

Chromatographic system: Proceed as directed in the *Assay*, except to use a flow rate of 2 mL/min and an injection size of 200 µL.

Analysis

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

Calculate the percentage of each impurity in the portion of Vincristine Sulfate for Injection taken:

$$\text{Result} = [r_i/(\sum r_i + 25r_v)] \times 100$$

r_i = peak response of each impurity appearing after the solvent peak from *Sample solution A*

r_v = peak response of vincristine from *Sample solution B*

Calculate the percentage of total impurities in the portion of Vincristine Sulfate for Injection taken:

$$\text{Result} = [\sum r_i/(\sum r_i + 25r_v)] \times 100$$

The terms in the formula are as defined above.

Acceptance criteria

Individual impurities: NMT 2.0%

Total impurities: NMT 5.0%

SPECIFIC TESTS

- **STERILITY TESTS (71):** Meets the requirements
- **BACTERIAL ENDOTOXINS TEST (85):** It contains NMT 100.0 USP Endotoxin Units/mg of vincristine sulfate.
- **CONSTITUTED SOLUTION:** At the time of use, it meets the requirements for *Injections* (1), *Constituted Solutions*.
- **OTHER REQUIREMENTS:** It meets the requirements for *Injections* (1), *Labeling*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve as described in *Injections* (1), *Containers for Sterile Solids*, and store in a refrigerator.

Change to read:

- **LABELING:** • The label states, “For Intravenous Use Only—Fatal If Given By Other Routes”.•₆

Where labeled as containing more than 2 mg, it must also be labeled as a *Pharmacy Bulk Package* (see *Injections* (1)). The labeling directs that the drug be dispensed only in containers enclosed in an overwrap labeled as directed below. When packaged in a *Pharmacy Bulk Package*, it is exempt from the requirement under *Injections* (1) that the closure be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set, when it contains a suitable substance or mixture of substances to prevent the growth of microorganisms.

When dispensed, the container or syringe (holding the individual dose prepared for administration to the patient) must be enclosed in an overwrap bearing the statement, “Do Not Remove Covering Until Moment of Injection.” • For Intravenous Use Only—Fatal If Given By Other Routes.”•₆

- **USP REFERENCE STANDARDS** (11)
 - USP Endotoxin RS
 - USP Vinblastine Sulfate RS [Note—No loss on drying determination is needed for USP Vinblastine Sulfate RS.]
 - USP Vincristine Sulfate RS