C_S = concentration of USP Alpha Tocopherol RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of Vitamin E as *d*- or *dl*-alpha tocopherol in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–120.0% of the labeled amount of Vitamin E as *d*- or *dl*-alpha tocopherol ($C_{29}H_{50}O_2$)▲*USP36*

- **ALPHA TOCOPHERYL ACETATE:** Proceed as directed in the *Assay* for *Alpha Tocopherol*. For the *Standard solution* and *Sample solution*, substitute alpha tocopheryl acetate for alpha tocopherol, and substitute USP Alpha Tocopheryl Acetate RS for USP Alpha Tocopherol RS.
Acceptance criteria: 95.0%–120.0%

Change to read:

- **ALPHA TOCOPHERYL ACID SUCCINATE**
▲Internal standard solution, System suitability solution, Chromatographic system, System suitability, and **Analysis:** Proceed as directed in the *Assay* for *Alpha Tocopherol.*
Standard solution: Transfer 30.0 mg of USP Alpha Tocopheryl Acid Succinate RS into a 20-mL vial. Add 2.0 mL of methanol, 1.0 mL of 2,2-dimethoxypropane, and 0.1 mL of hydrochloric acid to the vial. Cap tightly, and sonicate. Allow to stand in the dark for 1 h ± 5 min. Remove from the dark, uncap, and evaporate just to dryness on a steam bath with the aid of a stream of nitrogen. Add 3.0 mL of *Internal standard solution*, and mix on a vortex mixer to dissolve.
Sample solution
For the Preparation in liquid form: Transfer a portion of Preparation, equivalent to 30.0 mg of Vitamin E (*d*- or *dl*-alpha tocopheryl acid succinate), into a 20-mL vial. Add 2.0 mL of methanol, 1.0 mL of 2,2-dimethoxypropane, and 0.1 mL of hydrochloric acid to the vial. Cap tightly, and sonicate. Allow to stand in the dark for 1 h ± 5 min. Remove from the dark, uncap, and evaporate just to dryness on a steam bath with the aid of a stream of nitrogen. Add 3.0 mL of *Internal standard solution*, and mix on a vortex mixer to dissolve.
For the Preparation in solid form: Transfer a portion of Preparation, equivalent to 30 mg of Vitamin E (*d*- or *dl*-alpha tocopheryl acid succinate), into a flask suitable for refluxing. Add 5 mL of water, and heat on a water bath at 60° for 10 min. Add 25 mL of alcohol, and reflux for 30 min. Cool, and transfer to a separator with the aid of 50 mL of water and 50 mL of ether. Shake vigorously, allow the layers to separate, and collect each layer in individual separators. Extract the aqueous layer with two 25-mL portions of ether, combining the extracts with the original ether layer. Wash the combined extract with one 25-mL portion of water, filter the ether solutions through 1 g of anhydrous sodium sulfate, and with the aid of a stream of nitrogen evaporate the ether solution on a water bath, controlled at a temperature that will not cause the ether solution to boil over. Remove the container from the water bath when 5 mL remains. Quantitatively transfer the remains into a 20-mL vial, and complete the evaporation without the application of heat. Add 2.0 mL of methanol, 1.0 mL of 2,2- dimethoxypropane, and 0.1 mL of hydrochloric acid to the vial. Cap tightly, and sonicate. Allow to stand in the dark for 1 h ± 5 min. Remove from the dark, uncap, and evaporate just to dryness on a steam bath with the aid of a stream of nitrogen. Add 3.0 mL of *Internal standard solution*, and mix on a vortex mixer to dissolve. ▲*USP36*
Acceptance criteria: 95.0%–120.0%

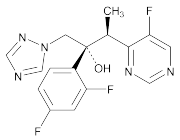
SPECIFIC TESTS

- **ACIDITY** (for liquid forms of Vitamin E Preparation)
Diluent: Alcohol and ether (1:1), neutralized to phenolphthalein with 0.1 N sodium hydroxide
Sample solution: Dissolve 1 g of Preparation in 25 mL of *Diluent*.
Analysis: To 25 mL of the *Sample solution*, add 0.5 mL of phenolphthalein TS, and titrate with 0.10 N sodium hydroxide until the solution remains faintly pink after shaking for 30 s.
Acceptance criteria: NMT 1.0 mL of 0.10 N sodium hydroxide is required.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, protected from light. Protect Preparation containing *d*- or *dl*-alpha tocopherol with a blanket of inert gas.
- **LABELING:** Label it to indicate the chemical form of Vitamin E present, and to indicate whether the *d*- or the *dl*-form is present, excluding any different forms that may be introduced as a minor constituent of the vehicle. Designate the quantity of Vitamin E present.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Alpha Tocopherol RS
USP Alpha Tocopheryl Acetate RS
USP Alpha Tocopheryl Acid Succinate RS

Voriconazole



$C_{16}H_{14}F_3N_5O$ 349.31

4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1*H*-1,2,4-triazol-1-ylmethyl)-, (α*R*,β*S*)-; (α*R*,β*S*)-α-(2,4-Difluorophenyl)-5-fluoro-β-methyl-α-(1*H*-1,2,4-triazol-1-ylmethyl)-4-pyrimidineethanol [137234-62-9].

DEFINITION

Voriconazole contains NLT 97.5% and NMT 102.0% of Voriconazole ($C_{16}H_{14}F_3N_5O$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨**197K**⟩
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of *System suitability solution A*, as obtained in the test for *Voriconazole Related Compound B*.

ASSAY

- **PROCEDURE**
Buffer: 1.9 g/L of ammonium formate in water. Adjust with formic acid to a pH of 4.0.
Mobile phase: Acetonitrile, methanol, and *Buffer* (15:30:55)

Standard solution: 25 µg/mL of USP Voriconazole RS in *Mobile phase*. [NOTE—Sonicate to dissolve, if necessary.]
Sample solution: 25 µg/mL of Voriconazole in *Mobile phase*. [NOTE—Sonicate to dissolve, if necessary.]
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 256 nm
Column: 3.9-mm × 15-cm; 4-µm packing L1
Column temperature: 35°
Flow rate: 1 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Column efficiency: NLT 3500 theoretical plates
Relative standard deviation: NMT 1.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of voriconazole ($C_{16}H_{14}F_3N_5O$) in the portion of Voriconazole 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 Voriconazole RS in the *Standard solution* (µg/mL)
C_U = concentration of voriconazole in the *Sample solution* (µg/mL)
Acceptance criteria: 97.5%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **HEAVY METALS,** *Method II* ⟨**231**⟩**:** NMT 10 ppm
- **RESIDUE ON IGNITION** ⟨**281**⟩**:** NMT 0.1%
- **VORICONAZOLE RELATED COMPOUNDS C AND D**

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability solution: 0.25 µg/mL of USP Voriconazole RS
Standard solution: 2.5 µg/mL each of USP Voriconazole RS, USP Voriconazole Related Compound C RS, and USP Voriconazole Related Compound D RS in *Mobile phase*. [NOTE—Sonicate to dissolve, if necessary.]
Sample solution: 500 µg/mL of Voriconazole in *Mobile phase*. [NOTE—Sonicate to dissolve, if necessary.]
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for the voriconazole peak, *Standard solution*
Column efficiency: NLT 3500 theoretical plates for the voriconazole peak, *Standard solution*
Relative standard deviation: NMT 10.0%, *System suitability solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of voriconazole related compound C and voriconazole related compound D in the portion of Voriconazole taken:

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

r_U = peak response of voriconazole related compound C or voriconazole related compound D from the *Sample solution*
r_S = peak response of voriconazole related compound C or voriconazole related compound D from the *Standard solution*
C_S = concentration of USP Voriconazole Related Compound C RS or USP Voriconazole Related Compound D RS in the *Standard solution* (µg/mL)
C_U = concentration of voriconazole in the *Sample solution* (µg/mL)
Calculate the percentage of any unspecified impurity in the portion of Voriconazole taken:

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

r_U = peak response of any individual impurity from the *Sample solution*
r_S = peak response of voriconazole from the *Standard solution*
C_S = concentration of USP Voriconazole RS in the *Standard solution* (µg/mL)
C_U = concentration of voriconazole in the *Sample solution* (µg/mL)
Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Voriconazole related compound C[a]	0.26	0.2
Voriconazole related compound D[b]	0.61	0.1
Voriconazole	1.0	—
Any unspecified impurity[c]	—	0.1
Total impurities[d]	—	0.5

[a] 1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone.
[b] (2*RS*,3*SR*)-2-(2,4-Difluorophenyl)-3-(pyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol.
[c] Disregard peaks less than 0.05%.
[d] Include voriconazole related compound B and voriconazole related compound F.

- **VORICONAZOLE RELATED COMPOUND F**

Sodium hydroxide solution: 470 g/L of sodium hydroxide in water
Mobile phase: Methanol, water, and *Sodium hydroxide solution* (500: 1500: 0.175). [NOTE—Minimize the carbonate formation in the *Mobile phase* by degassing methanol and water before mixing.]
Suppressant solution: 12 mM of sulfuric acid in water
Chloride stock solution: 85 µg/mL of sodium chloride in water
Standard stock solution: 250 µg/mL of USP Voriconazole Related Compound F RS. Dissolve in 50% of the final volume with methanol, and dilute with *Mobile phase* to volume.
Standard solution: 5 µg/mL of USP Voriconazole Related Compound F RS from the *Standard stock solution* in a mixture of methanol and *Mobile phase* (50:50)
System suitability solution A: 5 µg/mL of USP Voriconazole Related Compound F RS from the *Standard stock solution* and 1.7 µg/mL of USP Sodium Chloride RS in a mixture of methanol and *Mobile phase* (50:50)
System suitability solution B: 2.5 µg/mL of USP Voriconazole Related Compound F RS from the *Standard solution* in *Mobile phase*
Sample solution: 5 mg/mL of Voriconazole. Dissolve in 50% of the final volume with methanol, and dilute with *Mobile phase* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: Ion chromatography/LC
Detector: Conductivity with anion suppressor
Column: 4-mm × 5-cm guard column and 4-mm × 25-cm analytical column; both packing L46

Column temperature: 40°
Flow rate: 1 mL/min
Flow rate (for anion suppressor): 2 mL/min
Injection size: 20 µL
System suitability
Samples: *System suitability solution A* and *System suitability solution B*
[NOTE—The relative retention times for acetate ion (for information only), voriconazole related compound F, and chloride ion are 0.47, 1.0, and 1.5, respectively.]
Suitability requirements
Resolution: NLT 3.5 between the voriconazole related compound F and chloride peaks, *System suitability solution A*
Tailing factor: NMT 2.0, *System suitability solution B*
Relative standard deviation: NMT 10.0%, *System suitability solution B*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of voriconazole related compound F in the portion of Voriconazole taken:

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

r_U = peak response of voriconazole related compound F from the *Sample solution*
r_S = peak response of voriconazole related compound F from the *Standard solution*
C_S = concentration of USP Voriconazole Related Compound F RS in the *Standard solution* (µg/mL)
C_U = concentration of voriconazole in the *Sample solution* (µg/mL)
Acceptance criteria: NMT 0.1%

- **VORICONAZOLE RELATED COMPOUND B**

Initially dissolve the Standard and sample materials in 4% of the final volume of acetonitrile.
Buffer: 0.8 g/L of ammonium acetate. Adjust with glacial acetic acid to a pH of 5.0.
Mobile phase: Acetonitrile and *Buffer* (18:82)
System suitability solution A: 500 µg/mL of USP Voriconazole RS and 2.5 µg/mL of USP Voriconazole Related Compound B in *Mobile phase*.
System suitability solution B: 0.25 µg/mL of USP Voriconazole Related Compound B RS in *Mobile phase*
Standard solution: 2.5 µg/mL of USP Voriconazole Related Compound B RS in *Mobile phase*
Sample solution: 500 µg/mL of Voriconazole in *Mobile phase*.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 256 nm
Column: 4.6-mm × 25-cm; 5-µm packing L45
Column temperature: 30°
Flow rate: 1 mL/min
Injection size: 20 µL
System suitability
Samples: *System suitability solution A* and *System suitability solution B*
[NOTE—The relative retention times for voriconazole and voriconazole related compound B are 1.0 and 1.4, respectively.]
Suitability requirements
Resolution: NLT 4.0 between the voriconazole and voriconazole related compound B peaks, *System suitability solution A*
Tailing factor: NMT 2.0 for the voriconazole related compound B peak, *System suitability solution A*
Relative standard deviation: NMT 10.0%, *System suitability solution B*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of voriconazole related compound B in the portion of Voriconazole taken:

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

r_U = peak response of voriconazole related compound B from the *Sample solution*
r_S = peak response of voriconazole related compound B from the *Standard solution*
C_S = concentration of USP Voriconazole Related Compound B RS in the *Standard solution* (µg/mL)
C_U = concentration of voriconazole in the *Sample solution* (µg/mL)
Acceptance criteria: NMT 0.2%

SPECIFIC TESTS

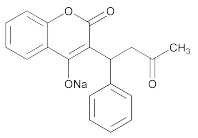
- **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** Where the label states that Voriconazole is sterile or that it must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.2 USP Endotoxin Units/mg of voriconazole.
- **STERILITY TESTS ⟨71⟩:** Where the label states that Voriconazole is sterile, it meets the requirements.
- **WATER DETERMINATION,** *Method I* **⟨921⟩:** NMT 0.4%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at room temperature.
- **LABELING:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Endotoxin RS
USP Voriconazole RS
USP Voriconazole Related Compound B RS
(2*S*,3*R*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol.
$C_{16}H_{14}F_3N_5O$ 349.31
USP Voriconazole Related Compound C RS
1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone.
$C_{10}H_7N_3OF_2$ 223.18
USP Voriconazole Related Compound D RS
(2*RS*,3*SR*)-2-(2,4-Difluorophenyl)-3-(pyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol.
$C_{16}H_{15}F_2N_5O$ 331.32
USP Voriconazole Related Compound F RS
{(1*RS*,4*SR*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl}methanesulfonic acid.
$C_{10}H_{16}O_4S$ 232.30

Warfarin Sodium



$C_{19}H_{15}NaO_4$ 330.31
2*H*-1-Benzopyran-2-one, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-, sodium salt.
3-(α-Acetonylbenzyl)-4-hydroxycoumarin sodium salt [129-06-6].

» Warfarin Sodium is an amorphous solid or a crystalline clathrate. The clathrate form consists principally of warfarin sodium and isopropyl alcohol, in a 2:1 molecular ratio; it contains not less than 8.0 percent and not more than 8.5 percent of isopropyl alcohol. Warfarin Sodium contains not less than 97.0 percent and not more than 102.0 percent of $C_{19}H_{15}NaO_4$, calculated on the anhydrous basis for the amorphous form or on the anhydrous and isopropyl alcohol-free basis for the crystalline form.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Labeling—Label it to indicate whether it is the amorphous or the crystalline form.

USP Reference standards ⟨11⟩**—**
USP Warfarin RS
USP Warfarin Related Compound A RS
3-(*o*-Hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one.
$C_{18}H_{16}O_2$ 264.33

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Standard specimen—Use USP Warfarin RS.

Test specimen—Dissolve about 100 mg in 25 mL of water, and adjust with hydrochloric acid to a pH of less than 3, using short-range pH indicator paper. Stir the mixture, and allow the precipitate to coagulate. Filter the mixture, and retain the filtrate for *Identification* test C. Wash the precipitate with four 5-mL portions of water, and dry in vacuum over phosphorus pentoxide for 4 hours. Use the warfarin obtained to prepare the *Test specimen*.

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

C: The filtrate obtained in *Identification* test *A* meets the requirements of the flame test for *Sodium* ⟨191⟩.

pH ⟨791⟩: between 7.2 and 8.3, in a solution (1 in 100).

Water, *Method I* ⟨921⟩: not more than 4.5% for the amorphous form; not more than 0.3% for the crystalline clathrate form.

Heavy metals ⟨231⟩**—**Dissolve 4.0 g in 45 mL of water, add 5 mL of glacial acetic acid, stir until the precipitate agglomerates, filter, and use 25 mL of the filtrate, employing glacial acetic acid, if necessary, to make the pH adjustment: the limit is 0.001%.

Absorbance in alkaline solution—Dissolve 1.25 g, accurately weighed, in 10 mL of sodium hydroxide solution (1 in 20), filter through a membrane filter, and within 15 minutes determine the absorbance of the solution in a 1-cm cell at 385 nm, with a suitable spectrophotometer, using sodium hydroxide solution (1 in 20) as the blank: the absorbance does not exceed 0.1.

Chromatographic purity—

Solvent mixture—Prepare a mixture of water and methanol (75:25).

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and glacial acetic acid (68:32:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer an accurately weighed quantity of about 24 mg of USP Warfarin RS and 24 mg of USP Warfarin Related Compound A RS to a 200-mL volumetric flask, add 4.0 mL of 0.1 N sodium hydroxide, 50 mL of methanol, and dissolve. Dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 200-mL volumetric flask, dilute with *Solvent mixture* to volume, and mix. Transfer 20.0 mL of this solution to a 50-mL volumetric flask, dilute with *Solvent mixture* to volume, and mix.

Test solution—Transfer an accurately weighed quantity of about 80 mg of Warfarin Sodium to a 100-mL volumetric flask, dissolve in and dilute with *Solvent mixture* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 25-cm column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the chromatogram as directed for *Procedure:* the resolution, *R,* between warfarin and warfarin related compound A is not less than 3; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all of the peaks. The relative retention times of warfarin and warfarin related compound A are 1.0 and about 1.2, respectively. Calculate the percentage of each impurity in the portion of Warfarin Sodium taken by the formula:

$$10{,}000(C / M)(r_i / r_S)$$

in which *C* is the concentration, in mg per mL, of warfarin sodium in the *Standard solution; M* is the quantity, in mg, of warfarin sodium taken to prepare the *Test solution;* r_i is the peak response of the individual impurity; and r_S is the peak response due to warfarin in the *Standard solution:* not more than 0.3% of any individual impurity and not more than 1.0% of total impurities is found.

Isopropyl alcohol content (*crystalline clathrate form*)**—**

Internal standard solution—Dilute 2 mL of *n*-propyl alcohol with water to 100.0 mL in a volumetric flask.

Standard preparation—Transfer an accurately weighed quantity of about 1.6 g of isopropyl alcohol to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, add 10.0 mL of the *Internal standard solution*, dilute with water to volume, and mix to obtain a *Standard preparation* having a known concentration of about 1.6 mg of isopropyl alcohol per mL.

Test preparation—Dissolve an accurately weighed quantity of about 1.85 g of Warfarin Sodium in about 50 mL of water in a 100-mL volumetric flask. Add 10.0 mL of the *Internal standard solution*, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 4-mm × 1.8-m column packed with 80- to 100-mesh support S2. The temperatures of the column, injector, and the detector are maintained at about 140°, 200°, and 250°, respectively. The carrier gas is nitrogen, flowing at the rate of about 40 mL per minute. The column temperature may be varied so that the following system suitability criteria are met: the resolution, *R,* between *n*-propyl alcohol and isopropyl alcohol is not less than 2.0; the tailing factor,