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USP 37
NF 32

Volume 2

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USP
U.S. Pharmacopeial Convention

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2014

USP 37

THE UNITED STATES PHARMACOPEIA

NF 32

THE NATIONAL FORMULARY

Volume 2

By authority of the United States Pharmacopeial Convention
Prepared by the Council of Experts and its Expert Committees

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THE UNITED STATES PHARMACOPEIAL CONVENTION
12601 Twinbrook Parkway, Rockville, MD 20852

SIX-MONTH IMPLEMENTATION GUIDELINE

The *United States Pharmacopeia–National Formulary* and its supplements become official **six months** after being released to the public. The *USP–NF*, which is released on November 1 of each year, becomes official on May 1 of the following year. This six-month implementation timing gives users more time to bring their methods and procedures into compliance with new and revised *USP–NF* requirements.

The table below describes the official dates of the *USP–NF* and its supplements. The 2013 *USP 36–NF 31*, and its supplements, *Interim Revision Announcements (IRAs)* and *Revision Bulletins* to that edition, will be official until May 1, 2014, at which time the *USP 37–NF 32* becomes official.

Publication	Release Date	Official Date	Official Until
USP 37–NF 32	November 1, 2013	May 1, 2014	May 1, 2015 (except as superseded by supplements, *IRAs*, and *Revision Bulletins*)
First Supplement to the USP 37–NF 32	February 1, 2014	August 1, 2014	May 1, 2015 (except as superseded by *Second Supplement*, *IRAs*, and *Revision Bulletins*)
Second Supplement to the USP 37–NF 32	June 1, 2014	December 1, 2014	May 1, 2015 (except as superseded by *IRAs* and *Revision Bulletins*)
USP 38–NF 33	November 1, 2014	May 1, 2015	May 1, 2016 (except as superseded by supplements, *IRAs*, and *Revision Bulletins*)

The table below gives the details of the *IRAs* that will apply to *USP 37–NF 32*.

IRA	PF Posting Date	Comment Due Date	IRA Posting Date	IRA Official Date
40(1)	January 2, 2014	March 31, 2014	May 30, 2014	July 1, 2014
40(2)	March 3, 2014	May 31, 2014	July 31, 2014	September 1, 2014
40(3)	May 1, 2014	July 31, 2014	September 26, 2014	November 1, 2014
40(4)	July 1, 2014	September 30, 2014	November 26, 2014	January 1, 2015
40(5)	September 2, 2014	November 30, 2014	January 30, 2015	March 1, 2015
40(6)	November 3, 2014	January 31, 2015	March 27, 2015	May 1, 2015

Revision Bulletins published on the USP website become official on the date specified in the *Revision Bulletin*.

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Identification—

A: Mix 1 mL of Injection with 5 mL of alcohol, and evaporate on a steam bath with the aid of a current of air to dryness: the residue so obtained responds to *Identification* tests under *Ephedrine Sulfate.*

B: It responds to the tests for *Sulfate* ⟨191⟩.

Bacterial endotoxins ⟨85⟩—It contains not more than 1.7 USP Endotoxin Units per mg of ephedrine sulfate.

pH ⟨791⟩: between 4.5 and 7.0.

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

Assay—Transfer an accurately measured volume of Injection, equivalent to about 250 mg of ephedrine sulfate, to a separator, add water, if necessary, to make about 10 mL, and proceed as directed in the *Assay* under *Ephedrine Sulfate,* beginning with "Saturate the solution."

Ephedrine Sulfate Nasal Solution

» Ephedrine Sulfate Nasal Solution contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$.

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

USP Reference standards ⟨11⟩—
USP Ephedrine Sulfate RS

Identification—It responds to the *Identification* tests under *Ephedrine Sulfate Injection.*

Microbial enumeration tests ⟨61⟩ **and Tests for specified microorganisms** ⟨62⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

Assay—

Standard preparation—Weigh accurately about 26 mg of USP Ephedrine Sulfate RS, transfer to a 50-mL volumetric flask with the aid of 10 mL of water, add methanol to volume, and mix. Pipet 5 mL of the resulting solution into a 100-mL volumetric flask, dilute with water to volume, and mix.

Assay preparation—Transfer an accurately measured volume of Nasal Solution, equivalent to about 26 mg of ephedrine sulfate, to a 50-mL volumetric flask, dilute with a 1 in 5 mixture of water in methanol to volume, and mix. Pipet 5 mL of the resulting solution into a 100-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Transfer 5-mL portions of the *Assay preparation* and the *Standard preparation* to separate glass-stoppered, 50-mL centrifuge tubes. Add 1 mL of saturated sodium carbonate solution and 2 mL of sodium metaperiodate solution (1 in 50) to each tube, mix, and allow to stand for 10 minutes. Pipet 20 mL of *n*-hexane into each tube, shake for 30 seconds, and allow the phases to separate. Concomitantly determine the absorbances of the *n*-hexane extracts in 1-cm cells at the wavelength of maximum absorbance at about 242 nm, with a suitable spectrophotometer, using *n*-hexane as the blank. Calculate the quantity, in mg, of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$ in each mL of the Nasal Solution taken by the formula:

$$(C / V)(A_U / A_S)$$

in which V is the volume, in mL, of Nasal Solution taken, C is the concentration, in µg per mL, of USP Ephedrine Sulfate RS in the *Standard preparation,* and A_U and A_S are the absorbances of the hexane extracts of the *Assay preparation* and the *Standard preparation,* respectively.

Ephedrine Sulfate Oral Solution

» Ephedrine Sulfate Oral Solution contains, in each 100 mL, not less than 360 mg and not more than 440 mg of ephedrine sulfate $[(C_{10}H_{15}NO)_2 \cdot H_2SO_4]$.

Packaging and storage—Preserve in tight, light-resistant containers, and avoid exposure to excessive heat.

USP Reference standards ⟨11⟩—
USP Ephedrine Sulfate RS

Identification, *Angular rotation* ⟨781A⟩—Use the 0.1 N sulfuric acid extract of the chloroform solution obtained as directed for *Assay preparation:* the angular rotation is levorotatory.

Alcohol content ⟨611⟩**:** between 2.0% and 4.0% of C_2H_5OH.

Assay—

Standard preparation—Dissolve an accurately weighed quantity of USP Ephedrine Sulfate RS in 0.1 N sulfuric acid to obtain a solution having a known concentration of about 20 µg per mL.

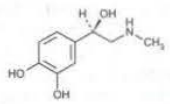
Assay preparation—Transfer 5 mL of Oral Solution to a separator, add 1 mL of 1 N sulfuric acid, and extract with 10 mL of chloroform. Discard the extract, and add 5 mL of potassium carbonate solution (1 in 5). After gas evolution has ceased, extract the solution with three 10-mL portions of chloroform, and combine the extracts in a second separator. Extract the chloroform solution with 50.0 mL of 0.1 N sulfuric acid. Filter the acid layer through paper, and dilute 5.0 mL of it with 0.1 N sulfuric acid to 100.0 mL.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Ephedrine Sulfate Capsules.* Calculate the quantity, in mg, of ephedrine sulfate $[(C_{10}H_{15}NO)_2 \cdot H_2SO_4]$ in the portion of Oral Solution taken by the formula:

$$C(A_U / A_S)$$

in which C is the concentration, in µg per mL, of USP Ephedrine Sulfate RS in the *Standard preparation;* and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation,* respectively.

Epinephrine



$C_9H_{13}NO_3$ 183.20

1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (*R*)-; (–)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol [51-43-4].

DEFINITION

Epinephrine contains NLT 97.0% and NMT 100.5% of $C_9H_{13}NO_3$, calculated on the dried basis.

IDENTIFICATION

• **A.** To 5 mL of pH 4.0 acid phthalate buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*) add 0.5 mL of a slightly acid solution of Epinephrine (1 in 1000) and 1.0 mL of 0.1 N iodine. Mix, and allow to stand for 5 min. Add 2 mL of sodium thiosulfate solution (1 in 40). **Acceptance criteria:** A deep red color is produced.

ASSAY

• **PROCEDURE**

Sample: 300 mg

Analysis: Dissolve the *Sample* in 50 mL of glacial acetic acid, warming slightly if needed to dissolve. Add crystal violet TS to the *Sample*, and titrate with 0.1 N perchloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 18.32 mg of epinephrine ($C_9H_{13}NO_3$).

Acceptance criteria: 97.0%–100.5% on the dried basis

IMPURITIES

• **RESIDUE ON IGNITION** ⟨281⟩: Negligible, from 100 mg

• **LIMIT OF ADRENALONE**

Sample solution: 2 mg/mL of Epinephrine in dilute hydrochloric acid (1 in 200)

Analysis: Determine the absorptivity of the *Sample solution* at 310 nm (see *Spectrophotometry and Light-Scattering* ⟨851⟩).

Acceptance criteria: NMT 0.2

• **LIMIT OF NOREPINEPHRINE**

Standard stock solution A: 364 mg/mL of USP Epinephrine Bitartrate RS in formic acid

Standard solution A: 20 mg/mL of epinephrine in methanol, from *Standard stock solution A*

Standard stock solution B: 16 mg/mL of USP Norepinephrine Bitartrate RS in formic acid

Standard solution B: 1.6 mg/mL of USP Norepinephrine Bitartrate RS in methanol from *Standard stock solution B*

Sample solution: 20 mg/mL of Epinephrine. Dissolve 200 mg of Epinephrine in 1.0 mL of formic acid, and dilute with methanol to 10.0 mL.

Chromatographic system

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

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 5 µL

Developing solvent system: *n*-Butanol, water, and formic acid (7:2:1)

Spray reagent: Folin-Ciocalteu phenol TS

Analysis

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

In an unsaturated chamber, develop the plate in the *Developing solvent system* until the solvent front has moved three-fourths the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate in warm circulating air. Spray with *Spray reagent*, followed by sodium carbonate solution (1 in 10).

Acceptance criteria: The R_F value of the principal spot from the *Sample solution* corresponds to that of *Standard solution A*. Any spot from the *Sample solution* is not larger or more intense than the spot with the same R_F value from *Standard solution B*, corresponding to NMT 4.0% norepinephrine.

SPECIFIC TESTS

• **OPTICAL ROTATION,** *Specific Rotation* ⟨781S⟩: –50.0° to –54.0°

Sample solution: 20 mg/mL, in 0.6 N hydrochloric acid

• **LOSS ON DRYING** ⟨731⟩: Dry it in a vacuum over silica gel for 18 h: it loses NMT 2.0% of its weight.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Epinephrine Bitartrate RS

USP Norepinephrine Bitartrate RS

Epinephrine Inhalation Aerosol

» Epinephrine Inhalation Aerosol is a solution of Epinephrine in propellants and Alcohol prepared with the aid of mineral acid in a pressurized container. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of epinephrine ($C_9H_{13}NO_3$).

Packaging and storage—Preserve in small, nonreactive, light-resistant aerosol containers equipped with metered-dose valves and provided with oral inhalation actuators.

USP Reference standards ⟨11⟩—
USP Epinephrine Bitartrate RS

Identification—Place 10 mL of water in a small beaker, and deliver 2 sprays from the Inhalation Aerosol under the surface of the water, actuating the valve by pressing the tip against the bottom of the beaker. To 5 mL of the solution add 1 drop of dilute sulfuric acid (1 in 200), add 0.5 mL of 0.1 N iodine, allow to stand for 5 minutes, and add 1 mL of 0.1 N sodium thiosulfate: a red-brown color is produced.

Delivered dose uniformity over the entire contents: meets the requirements for *Metered-Dose Inhalers* under *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩.

PROCEDURE FOR DOSE UNIFORMITY—

Ferro-citrate solution and *Buffer solution*—Prepare as directed under *Epinephrine Assay* ⟨391⟩.

Standard preparation—Dissolve an accurately weighed quantity of USP Epinephrine Bitartrate RS in a freshly prepared sodium bisulfite solution (1 in 500), and dilute quantitatively and stepwise with the same sodium bisulfite solution as necessary to obtain a solution having a known concentration of about 18 µg per mL.

Test preparation—Discharge the minimum recommended dose into the sampling apparatus and detach the inhaler as directed. Rinse the apparatus (filter and interior) with four 5.0-mL portions of a freshly prepared sodium bisulfite solution (1 in 500), and transfer the resulting solutions quantitatively to a 50-mL centrifuge tube. Add 10 mL of chloroform, insert the stopper, shake vigorously for 1 minute, and centrifuge for 5 minutes. Use the clear supernatant as directed in the *Procedure*.

Procedure—Into three separate flasks, transfer the *Test preparation*, 20.0 mL of the *Standard preparation*, and 20.0 mL of water to provide the blank. To each flask add 100 µL of *Ferro-citrate solution* and 1.0 mL of *Buffer solution*, and mix. Concomitantly determine the absorbances with a suitable spectrophotometer, in 5-cm cells, of the solutions from the *Test preparation* and the *Standard preparation*, at the wavelength of maximum absorbance at about 530 nm, against the blank. Calculate the quantity, in µg, of $C_9H_{13}NO_3$ contained in the minimum dose taken by the formula:

$$(183.20 / 333.29)(20CN)(A_U / A_S)$$

in which C is the concentration, in µg per mL, of USP Epinephrine Bitartrate RS in the *Standard preparation*; N is the number of sprays discharged to obtain the minimum recommended dose; 183.20 and 333.29 are the molecular

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