2009

# USP NF

The Official Compendia of Standards

## Volume 2

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2009

# USP 32 THE UNITED STATES PHARMACOPEIA

# NF 27 THE NATIONAL FORMULARY

Volume 2

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The designation on the cover of this publication, "USP NF 2009," is for ease of identification only. The publication contains two separate compendia: *The United States Pharmacopeia*, Thirty-Second Revision, and *The National Formulary*, Twenty-Seventh Edition.

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 change was adopted to give users more time to bring their methods and procedures into compliance with new and revised *USP–NF* requirements.

The table below describes the new official dates. The 2008 *USP31–NF26,* and the *Supplements* and *Interim Revision Announcements (IRAs)* to that edition, will be official until May 1, 2009, at which time the *USP32–NF27* becomes official.

| Publication | Release Date | Official Date | Official Until |
|---|---|---|---|
| *USP32–NF27* | Nov. 1, 2008 | May 1, 2009 | May 1, 2010 (except as superceded by *Supplements, IRAs,* and *Revision Bulletins*) |
| *First Supplement* | Feb. 1, 2009 | Aug. 1, 2009 | May 1, 2010 (except as superceded by *Second Supplement, IRAs,* and *Revision Bulletins*) |
| *Second Supplement* | June 1, 2009 | Dec. 1, 2009 | May 1, 2010 (except as superceded by *IRAs* and *Revision Bulletins*) |
| *USP33–NF28* | Nov. 1, 2009 | May 1, 2010 | May 1, 2011 (except as superceded by *Supplements, IRAs,* and *Revision Bulletins*) |

*IRAs* will continue to become official on the first day of the second month of the *Pharmacopeial Forum (PF)* issue in which they are published as final. For instance, *IRAs* published as final in the May-June *PF* (issue 3) will become official on June 1. This table gives the details of the *IRAs* that will apply to *USP31–NF26* and *USP32–NF27.*

| *IRA** | Release Date | Official Date | Revises |
|---|---|---|---|
| Jan. 1, 2009 *IRA, PF* 35(1) | Jan. 1, 2009 | Feb. 1, 2009 | *USP31–NF26* and its *Supplements* |
| Mar. 1, 2009 *IRA, PF* 35(2) | Mar. 1, 2009 | April 1, 2009 | *USP31–NF26* and its *Supplements* |
| May 1, 2009 *IRA, PF* 35(3) | May 1, 2009 | June 1, 2009 | *USP32–NF27* |
| July 1, 2009 *IRA, PF* 35(4) | July 1, 2009 | Aug. 1, 2009 | *USP32–NF27* and *First Supplement* |
| Sept. 1, 2009 *IRA, PF* 35(5) | Sept. 1, 2009 | Oct. 1, 2009 | *USP32–NF27* and *First Supplement* |
| Nov. 1, 2009 *IRA, PF* 35(6) | Nov. 1, 2009 | Dec. 1, 2009 | *USP32–NF27* and its *Supplements* |
| Jan. 1, 2010 *IRA, PF* 36(1) | Jan. 1, 2010 | Feb. 1, 2010 | *USP32–NF27* and its *Supplements* |
| Mar. 1, 2010 *IRA, PF* 36(2) | Mar. 1, 2010 | April 1, 2010 | *USP32–NF27* and its *Supplements* |

*NOTE—Beginning January 1, 2007, USP ceased identifying *IRAs* numerically (*First, Second,* etc.) and instead now designates them by the date on which they are published.

*Revision Bulletins* published on the USP website will continue to become official immediately upon publication, unless the *Revision Bulletin* specifies otherwise.

Revisions that contain a specific official date shall continue to become official upon such specified date, which supercedes the general official date for the publication.

For more information about the change in official dates, please visit the USP website at http://www.usp.org.

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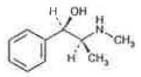
## Ephedrine



$C_{10}H_{15}NO$ 165.23
Benzenemethanol, α-[1-(methylamino)ethyl]-, [*R*-(*R**,*S**)]-.
(–)-Ephedrine [*299-42-3*].
Hemihydrate 174.24 [*50906-05-3*].

» Ephedrine is anhydrous or contains not more than one-half molecule of water of hydration. It contains not less than 98.5 percent and not more than 100.5 percent of $C_{10}H_{15}NO$, calculated on the anhydrous basis.

**Packaging and storage**—Preserve in tight, light-resistant containers, in a cold place.

**Labeling**—Label it to indicate whether it is hydrous or anhydrous. Where the quantity of Ephedrine is indicated in the labeling of any preparation containing Ephedrine, this shall be understood to be in terms of anhydrous Ephedrine.

**USP Reference standards** ⟨11⟩—*USP Ephedrine Sulfate RS.*

**Identification**—Accurately weigh about 100 mg, and add by buret the exact volume of 0.1 N sulfuric acid, determined in the *Assay,* to neutralize it. Dilute with water in a volumetric flask to 25 mL. Mix 2 mL with 10 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* test *A* under *Ephedrine Sulfate*.

**Specific rotation** ⟨781S⟩: between –40.3° and –43.3°.

*Test solution:* 25 mg per mL, in 0.6 N hydrochloric acid.

**Water,** *Method Ib* ⟨921⟩: between 4.5% and 5.5%, for hydrated Ephedrine; not more than 0.5% for anhydrous Ephedrine.

**Residue on ignition** ⟨281⟩: not more than 0.1%.

**Chloride** ⟨221⟩—A solution of 500 mg shows no more chloride than corresponds to 0.20 mL of 0.020 N hydrochloric acid (0.030%).

**Sulfate**—Dissolve 100 mg in 40 mL of water, and add 1 mL of 3 N hydrochloric acid and 1 mL of barium chloride TS: no turbidity develops within 10 minutes.

**Ordinary impurities** ⟨466⟩—

*Test solution:* methanol.

*Standard solution:* methanol.

*Eluant:* a mixture of isopropyl alcohol, ammonium hydroxide, and chloroform (80 : 15 : 5).

*Visualization:* 1, followed by 4.

**Assay**—Dissolve about 500 mg of Ephedrine, accurately weighed, in 10 mL of neutralized alcohol, and add 5 drops of methyl red TS and 40.0 mL of 0.1 N hydrochloric acid VS. Titrate the excess acid with 0.1 N sodium hydroxide VS. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 0.1 N hydrochloric acid is equivalent to 16.52 mg of $C_{10}H_{15}NO$.

## Ephedrine Hydrochloride

$C_{10}H_{15}NO \cdot HCl$ 201.69
Benzenemethanol, α-[1-(methylamino)ethyl]-, hydrochloride, [*R*-(*R**,*S**)]-.
(–)-Ephedrine hydrochloride [*50-98-6*].

» Ephedrine Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_{10}H_{15}NO \cdot HCl$, calculated on the dried basis.

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

**USP Reference standards** ⟨11⟩—*USP Ephedrine Sulfate RS.*

**Identification**—

**A:** Dissolve 100 mg in 5 mL of water, add 1 mL of potassium carbonate solution (1 in 5), and extract with 2 mL of chloroform: the IR absorption spectrum of the chloroform extract so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Ephedrine Sulfate RS.

**B:** A solution of it responds to the tests for *Chloride* ⟨191⟩.

**Melting range,** *Class I* ⟨741⟩: between 217° and 220°.

**Specific rotation** ⟨781S⟩: between –33.0° and –35.5°.

*Test solution:* 50 mg per mL, in water.

**Acidity or alkalinity**—Dissolve 1.0 g in 20 mL of water, and add 1 drop of methyl red TS. If the solution is yellow, it is changed to red by not more than 0.10 mL of 0.020 N sulfuric acid. If the solution is pink, it is changed to yellow by not more than 0.20 mL of 0.020 N sodium hydroxide.

**Loss on drying** ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

**Residue on ignition** ⟨281⟩: not more than 0.1%.

**Sulfate**—Dissolve 50 mg in 40 mL of water, and add 1 mL of 3 N hydrochloric acid and 1 mL of barium chloride TS: no turbidity develops within 10 minutes.

**Ordinary impurities** ⟨466⟩—

*Test solution:* alcohol.

*Standard solution:* alcohol.

*Eluant:* a mixture of isopropyl alcohol, ammonium hydroxide, and chloroform (80 : 15 : 5).

*Visualization:* 1, followed by 4.

**Assay**—Dissolve about 500 mg of Ephedrine Hydrochloride, accurately weighed, in 25 mL of glacial acetic acid. Add 10 mL of mercuric acetate TS and 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid VS to an emerald-green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 20.17 mg of $C_{10}H_{15}NO \cdot HCl$.

## Ephedrine Sulfate

$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$ 428.54
Benzenemethanol, α-[1-(methylamino)ethyl]-, [*R*-(*R**,*S**)]-, sulfate (2 : 1) (salt).
(–)-Ephedrine sulfate (2 : 1) (salt) [*134-72-5*].

» Ephedrine Sulfate contains not less than 98.0 percent and not more than 101.0 percent of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$, calculated on the dried basis.

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

**USP Reference standards** ⟨11⟩—*USP Ephedrine Sulfate RS.*

**Identification**—

**A:** *Infrared Absorption* ⟨197K⟩.

**B:** A solution of it responds to the tests for *Sulfate* ⟨191⟩.

**Specific rotation** ⟨781S⟩: between –30.5° and –32.5°.

*Test solution:* 50 mg per mL, in water.

**Acidity or alkalinity**—Dissolve 1.0 g in 20 mL of water, and add 1 drop of methyl red TS. If the solution is yellow, it is changed to red by not more than 0.10 mL of 0.020 N sulfuric acid. If the solution is

pink, it is changed to yellow by not more than 0.20 mL of 0.020 N sodium hydroxide.

**Loss on drying** ⟨731⟩—Dry about 500 mg, accurately weighed, at 105° for 3 hours: it loses not more than 0.5% of its weight.

**Residue on ignition** ⟨281⟩: not more than 0.1%.

**Chloride** ⟨221⟩—A 200-mg portion shows no more chloride than corresponds to 0.40 mL of 0.020 N hydrochloric acid (0.14%).

**Ordinary impurities** ⟨466⟩—

*Test solution:* alcohol.

*Standard solution:* alcohol.

*Eluant:* a mixture of isopropyl alcohol, ammonium hydroxide, and chloroform (80 : 15 : 5).

*Visualization:* 1, followed by 4.

**Assay**—Transfer about 300 mg of Ephedrine Sulfate, accurately weighed, to a separator, and dissolve in about 10 mL of water. Saturate the solution with sodium chloride (about 3 g), add 5 mL of 1 N sodium hydroxide, and extract with four 25-mL portions of chloroform. Wash the combined chloroform extracts by shaking with 10 mL of a saturated solution of sodium chloride, and filter through chloroform-saturated purified cotton into a beaker. Extract the wash solution with 10 mL of chloroform, and add to the main chloroform extract. Add methyl red TS, and titrate with 0.1 N perchloric acid in dioxane VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 21.43 mg of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$.

## Ephedrine Sulfate Capsules

» Ephedrine Sulfate Capsules contain not less than 92.0 percent and not more than 108.0 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**—Macerate the contents of a sufficient number of Capsules, equivalent to about 200 mg of ephedrine sulfate, with 15 mL of warm alcohol for 20 minutes, filter, and evaporate the filtrate on a steam bath to dryness: the residue so obtained responds to the *Identification* tests under *Ephedrine Sulfate.*

**Dissolution** ⟨711⟩—

*Medium:* water; 500 mL.

*Apparatus 1:* 100 rpm.

*Time:* 30 minutes.

*Procedure*—Dilute filtered portions of the solutions under test with water to a concentration of about 25 µg per mL. Transfer 5.0-mL portions to suitable tubes. Add 1 mL of a saturated sodium carbonate solution and 2 mL of sodium metaperiodate solution (2 in 100) to each, mix, and allow to stand for 10 minutes. Add 20.0 mL of hexanes, shake for 30 seconds, and allow the phases to separate. Measure the absorbances of the hexanes extract in 1-cm cells at the wavelength of maximum absorbance, at about 242 nm, with a suitable spectrophotometer, using hexanes as the blank. Determine the amount of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$ dissolved by comparison with a similarly treated Standard solution having a known concentration of USP Ephedrine Sulfate RS in water. Remove the contents of 1 Capsule as completely as possible, with the aid of a current of air, dissolve the empty capsule shell in the *Medium*, determine the absorbance at the same dilution and in the same manner as for the Capsules, and make any necessary corrections.

*Tolerances*—Not less than 80% *(Q)* of the labeled amount of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$ is dissolved in 30 minutes.

**Uniformity of dosage units** ⟨905⟩: meet the requirements.

**Assay**—

*Standard preparation*—Weigh accurately about 25 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. Dilute 5.0 mL of this solution with water to 100.0 mL.

*Assay preparation*—Weigh accurately the contents of not less than 20 Capsules, and mix. Transfer an accurately weighed portion of the mixture, equivalent to about 25 mg of ephedrine sulfate, to a glass-stoppered conical flask, and add by pipet 50 mL of a 1 in 5 mixture of water in methanol. Shake by mechanical means for 10 minutes, and filter. Dilute 5.0 mL of the filtrate with water to 100.0 mL.

*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 the portion of Capsule contents 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 hexane extracts of the *Assay preparation* and the *Standard preparation*, respectively.

## Ephedrine Sulfate Injection

» Ephedrine Sulfate Injection is a sterile solution of Ephedrine Sulfate in Water for Injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$.

**Packaging and storage**—Preserve in single-dose or in multiple-dose, light-resistant containers, preferably of Type I glass.

**USP Reference standards** ⟨11⟩—*USP Endotoxin RS. USP Ephedrine Sulfate RS.*

**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.

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